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**Epidemiology of Diabetes  
Interventions and Complications  
Continuing Follow-Up**

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**PROTOCOL**

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CORE

**1st Edition November 2005**

Amended May 2007

Amended May 2008

Amended March 2009

Amended November 2010

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## **CHANGES TO THE EDIC PROTOCOL – November 15, 2010:**

### **Chapter 2**

Page 2-5 Cardiac Autonomic Neuropathy (CAN) testing Update: Based on R-R interval measurement, CAN testing will be repeated in years 16 & 17. CAN testing will serve to measure progression of autonomic neuropathy and as a risk factor for CVD.

### **Chapter 8**

Pages 8-5 & 8-6 (Section 8-4) Authorship Update:

#### DCCT/EDIC Publication and Authorship Policy

The DCCT/EDIC study has evolved since its inception from a randomized controlled clinical trial to an observational study of individuals with type 1 diabetes. We have successfully developed broad based collaborations with investigators outside of the DCCT/EDIC Research Group who are making unique contributions to our understanding of type 1 diabetes and its associated complications. In addition, a major component of our database, as well as study participant samples, are part of the NIH repository and many non-DCCT/EDIC affiliated groups are authoring papers based on the DCCT/EDIC data base. In this context, it is appropriate to reexamine our publication and authorship policies that have evolved with the following goals: 1. to maintain the rate of high-quality manuscripts reflecting the scientific output of DCCT/EDIC; 2. to provide the opportunity for as many members of the DCCT/EDIC group as possible to participate in the development and writing of papers; and 3. to provide appropriate attribution and recognition to those individuals who are responsible for the development, analyses, and writing of the manuscripts while not losing sight of the collective nature of the research efforts that underlie all of the clinical science advances from DCCT/EDIC. The paper categories are classified as follows.

- i. **Primary Manuscripts**: These papers address the major, i.e. primary, outcomes of the DCCT/EDIC study, e.g. effects of the DCCT randomly assigned interventions and/or glycemia and related mechanisms on major outcomes such as microvascular and cardiovascular disease.
- ii. **DCCT/EDIC Other Outcomes Manuscripts**: These papers report analyses of outcomes other than primary outcomes, and of metabolic intermediates and biomarkers, or epidemiologic analyses. These manuscripts would include analyses that use the database from all participating centers, as well as analyses of subsets or sub-cohorts of the complete cohort. They would also include sub-studies and ancillary studies conducted as additional initiatives beyond the initial DCCT/EDIC protocol.
- iii. **Methodology Manuscripts**: These papers focus on methodological issues, and do not include any new or original study outcome results. Such papers may include data generated from DCCT/EDIC to address a methodological objective that is not a DCCT/EDIC objective or outcome.

Responsibility for the category assignment for all manuscripts will rest with the Publications and Presentations Committee, in consultation with the Executive Committee, usually at the time that the manuscripts are planned.

The above classifications also apply to presentations, with the exception that classification occurs prior to abstract submission.

The following authorship principles will apply.

- I. Category 1 (Primary) Manuscripts: The authorship in the journal masthead will be the DCCT/EDIC Research Group. The complete list of Investigators appears as part of the manuscript, usually in an appendix at the end of the manuscript, as negotiated with the journal. The writing team for these papers will be identified in the manuscript in a footnote or as an entry in the appendix, according to individual journal requirements and style.
- II. Category 2 (Other Outcomes) Manuscripts: The authorship will be the writing team. For example, A Smith (Chairperson), A, B, C and the DCCT/EDIC Research Group.
- III. Category 3 (Methodologic) Manuscripts. Authorship Q, C, A, B+

+Acknowledge Research Group as appropriate (complete list of the Research Group can be found in Diabetes, 35:530-45, 1986).

## **CHANGES TO THE EDIC PROTOCOL – May 23, 2007:**

### Preface

The preface was updated with items 10–11.

### Chapter 3

Congestive Heart Failure was added to the Defined Events in Section 3.4.1.

### Chapter 5

Information concerning the Cardiac MRI study was added to Section 5.8 and Table 5.1. Appendix A and B to Chapter 5.

Information regarding the ANS study in EDIC Years 16/17 was added to Section 5.8 and Table 5.1.

### Chapter 7

The Study Organization was updated to reflect the addition of the Central MRI Reading Center to Section 7.2 and Figure 7.1.

## **Changes to the EDIC PROTOCOL May 15, 2008**

Add item 12 to Preface.

### Chapter 7

Page 7-1 item 7.2 Under structure change, 4<sup>th</sup> paragraph changed to (The External Evaluation Committee (EEC) appointed by the Director.

Page 7-6, Figure 7.1 changes: External Evaluation Committee, Follow-Up (AMC), Date Quality Assurance, Analytical Editorial (P&P).

### Chapter 8

Page 8-8 item 8.10 Implementation: third paragraph change EAC to EEC.

Page 8-9 item 8.13 Procedures, second line change: EAC to EEC

## **CHANGES TO THE EDIC PROTOCOL – Mar 5, 2009:**

### Preface

The preface was updated with items 13 & 14.

### Chapter 2

Page 2-3 (Table 2.1) changes: Use of the Dietary-7 day (Food Frequency) recall questionnaire was discontinued in January 2009. Cardiac Autonomic Neuropathy Testing will be done once in Years 13 or 14 and once in Years 16 or 17.

### Chapter 4

Page 4-5 (Figure 4.3) change: ANS tests with the autonomic symptom questionnaire (Autonomic Symptom Profile – ASP) will be repeated once in EDIC Year 16 or 17.

### Chapter 5

Page 5-3 (Section 5.7), Page 5-5 (Table 5.1), and Page 5-6 (Table 5.2) additions: Autonomic nervous system testing with the autonomic symptom questionnaire (Autonomic Symptom Profile – ASP) will be repeated once in Years 16 or 17.

Page 5-4 (Section 5.10), Page 5-5 (Table 5.1), and Page 5-6 (Table 5.2) additions: Use of The Food Frequency (Dietary-7 day) Recall Questionnaire was discontinued in January 2009.

## PREFACE

1. Introduction. This document contains the EDIC Continuing Follow-Up Protocol. This Protocol has been prepared by the EDIC Study Group. Protocols and procedures specified herein thus represent as thorough a review as possible of all major issues. Future revisions in this Protocol will introduce some heterogeneity in the data collection process; therefore, it is hoped that no changes will be necessary. However, there may be a need for revisions of varying degrees. The only changes to be permitted in this Protocol are those that will improve efficiency, enhance scientific validity and/or further ensure patient safety in this study.
2. Procedure for Revisions. During the conduct of the EDIC Continuing Follow-Up, proposed revisions should be discussed with the Principal Investigator at the clinical center and submitted to the Executive Committee. The Executive Committee will make judgment on all proposed changes as to the need for consideration by the Steering Committee and the Study Group.
3. Dissemination of Revisions. After any revisions have been approved, the Data Coordinating Center will be responsible for initial drafts and final retyping of the appropriate sections of the Manual of Operations. A cover letter along with the updated chapter of the Manual of Operations will be sent to each clinical center. The cover letter will describe the reason for the change and explain the change itself as well as the effective date. Any subsequent questions are to be directed to the Data Coordinating Center. Additionally, any revisions in this Manual of Operations will be discussed at the next EDIC meeting.
4. Final Disposition of the DCCT Manual of Operations. In May 1993, at the conclusion of data collection, the Manual of Operations and forms for the trial were put together in publishable form and registered with NTIS. Copies may be obtained from United States Department of Commerce, National Technical Information Service, 5285 Port Royal Road, Springfield, VA 22161, Telephone (703) 487-4650. The registration number is PB93-183382. Other protocols developed by the study, such as the Protocol for Closeout, are also available.
5. In July 1997, the NIDDK and Genentech, Inc. signed a Cooperative Research and Development Agreement (CRADA). The overall goals of the CRADA are: 1) to provide additional assessments of patients in the EDIC study regarding retinopathy, hypoglycemia and macrovascular disease; and 2) to accelerate the availability of a potentially beneficial therapeutic agent developed by Genentech, Inc. for treatment of Type 1 Diabetes (T1D) using EDIC data for comparison of safety outcomes resulting from an ongoing clinical trial of recombinant human insulin-like growth factor - I (rHIGF-I). At that time, the EDIC Protocol was changed to reflect the increased frequency of assessments of retinopathy, hypoglycemia, and macrovascular disease.  
  
These changes were reversed in 1998 when Genentech exercised its option to terminate the CRADA and the extra assessments of retinopathy and hypoglycemia were deleted from the Protocol.
6. In 2000, computed tomography of the heart was added to the tests at the 7th annual visit. The procedure to measure glomerular filtration rate was discontinued at the

biennial renal visits. The measurement of serum albumin was discontinued. The authorship policy was modified to name authors for the DCCT/EDIC Research Group for Category II publications.

7. In January 2002, the measurement of serum cystatin C was added on the serum collected annually.
8. In July 2002, the protocol was amended to do the following:
  - Extend EDIC from a ten-year follow-up to a twelve-year follow-up study
  - Add the URO-EDIC project in Year 10
  - Add the second round of fundus photographs in Year 10
  - Add "Markers and Mechanisms of Vascular Disease in Type 1 Diabetes" ancillary study on a biennial basis
  - Add the third round of carotid ultrasounds in Year 11
  - Add the second round of computed tomography of the heart in Year 12
  - Add the University of Washington Lipoprotein ancillary study on a biennial basis.
9. In January 2006, the DCCT/EDIC enters the 10-year extension of the follow-up of the cohort. The Core protocol is the same as the basic protocol followed for the first 12 years of EDIC. There are a few additions to the measurements; these are:
  - University of Washington Ancillary Studies
  - A repeat of the DCCT neurological procedures and additional quantitative sensory testing (QST), and two self-administered neurological quality-of-life questionnaires in EDIC years 13 and 14.
  - National Eye Institute Visual Functioning Questionnaire – 25 (NEI-VFQ-25)
  - Quality of Well Being Scale (QWB-SA)
  - The transfer of probands' biochemical saved samples to the NIDDK-sponsored Central Repositories.
10. In 2007, the Cardiac MRI and the Gadolinium test were added to the annual exam and they are expected to be performed once on all participants by April 2009. Because of the safety issue with respect to the contrast agent, gadolinium, the GFR estimated from serum creatinine must be measured locally within 1 – 2 months before the Gadolinium test. (See appendix to chapter 5.)
11. Congestive Heart Failure was added as an outcome. A simple screening for congestive heart failure was added to Section H.3. (Verification of Events) on the Form 002.7 (Annual Medical History and Physical Examination).
12. In 2008 EAC renamed EEC
13. In March 2009, additional Autonomic Nervous System (ANS) tests (including the Autonomic Symptom Profile (ASP) questionnaire) were added to the EDIC Protocol. ANS and the ASP will be repeated in EDIC Years 16 or 17.
14. Use of The Food Frequency Recall Questionnaire was discontinued in January 2009.

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**Note from RTI/NIDDK Repository:**

**The Manual of Operations (MOO) and accompanying Table of Contents begins after Chapter 8.**

## 1. INTRODUCTION

### 1.1 Summary of Rationale

The long-term microvascular, neurologic, and macrovascular complications of insulin-dependent (Type 1 Diabetes; T1D) and non-insulin dependent diabetes mellitus (Type 2 Diabetes; T2D) cause major morbidity and mortality. (1) Despite major advances in the treatment of diabetic retinopathy with photocoagulation (2,3) and vitrectomy (4), it remains the major cause of new onset blindness in adults in the U.S. (1) Diabetic nephropathy is the most common cause of end-stage renal disease in adults. (5) Diabetes increases the risk of amputation by more than forty-fold compared with the non-diabetic population and accounts for more amputations in the U.S. than any other cause. (1) Finally, the major cause of mortality in diabetes is cardiovascular disease. Diabetes is associated with a two- to seven-fold increase in cardiac and cerebral vascular disease. (6-8) The estimated cost of these complications in the aggregate was in excess of 20 billion dollars per year in 1987. (9)

Despite the recognized cost in human suffering, loss of productivity, and expense associated with medical care and disability attributable to these complications, there is a remarkable paucity of data on T1D, other than for retinopathy, regarding their occurrence, pathogenesis, associated risk factors, interactions (including co-occurrence) and effective treatments. Many of the studies that have attempted to describe the epidemiology of long-term complications of diabetes mellitus have suffered from the following shortcomings:

1. Failure to separate T1D from T2D populations;
2. Reliance on cross-sectional analysis prone to prevalence bias;
3. Relatively brief follow-up often with significant attrition when prospective studies have been conducted;
4. Inclusion of small, selected populations with limited generalizability,
5. Failure to follow populations of diabetic patients from early in the course of their disease and, consequently, absence of baseline measurements independent of the presence of complications;
6. Failure to use objective, reliable outcome measurements;
7. Failure to measure established or putative risk factors, including level of glycemia, with acceptable methods and/or frequency.

Although the Wisconsin Epidemiologic Study of Diabetic Complications and the Pittsburgh Epidemiologic Study of Diabetic Complications have rectified some of these deficiencies, a study of a large cohort of T1D patients from early in their disease with serial quantitative measurements of renal and macrovascular complications and of potential risk factors is necessary.

The shortcomings noted above have been particularly problematic with regard to our understanding of nephropathy and macrovascular disease in T1D. Nephropathy is the most pernicious diabetes-specific long-term complication, leading to end-stage renal disease (ESRD) in 35-45% of the T1D population. (10) The evolution of nephropathy from normal renal function to ESRD is now recognized to proceed through a number of indistinct stages including elevated albumin excretion ("microalbuminuria"), which precedes ESRD by 15-20 years. (11-13) These predictors of clinical nephropathy have been established by several small retrospective studies. (12,13) Unfortunately, no study has prospectively examined the course of diabetic nephropathy in a population of T1D patients for a period long enough to characterize its progression and

examine risk factors, including glycemia, diabetes treatment, blood pressure, and dietary and genetic factors. The majority of recent studies examining interventions has been of short (<2 years) duration and has utilized surrogate outcomes, such as microalbuminuria, rather than the development of clinical (>300 mg albuminuria per 24 h) proteinuria or a decline in glomerular filtration rate. (14-16) Thus, our current understanding of the development and progression of diabetic nephropathy is predicated on cross-sectional and retrospective analyses and brief interventional studies that have examined short-term surrogate outcomes rather than the hard outcomes of clinical nephropathy. These limited studies have provided incomplete understanding of diabetic nephropathy and its development and risk factors.

While our understanding of nephropathy in T1D is limited by the paucity of long-term studies with carefully measured, reliable outcomes and risk factors, our understanding of macrovascular disease is compromised by the virtual absence of detailed studies in T1D. Almost the entire data base with regard to macrovascular disease and diabetes is based on studies in T2D patients such as the Framingham (6), Bedford (7), Rancho Bernardo (17), WHO (18), and NHANES (19) studies. Despite the major impact of macrovascular diseases on the T1D population, almost no long-term, large-scale studies have been performed in T1D. Specifically, almost no direct data exist regarding macrovascular diseases' occurrence, progression, associated risk factors, and relationship to other diabetic complications. (20) The relatively few long-term studies of T1D patients, such as the Steno hospital-based report on "Prognosis of diabetics with diabetes onset before age thirty-one" (21), are either too old to reflect contemporary medical/cardiac care, incomplete with regard to collection of outcome and risk factor data, and/or based on such a limited and selected population that the data's relevance is uncertain. In any case, there are no current studies to determine whether risk factors for macrovascular disease identified in studies of non-diabetic and T2D populations pertain in T1D. In addition to the risk factors identified in studies of non-diabetic and T2D populations (including increased LDL-cholesterol and triglyceride levels, decreased HDL-cholesterol, hypertension, smoking, obesity and a sedentary life-style), glycemic level, diabetes treatment, uremia, autonomic neuropathy, altered lipoprotein composition, and genetic and other factors specific to T1D may play a role in the pathogenesis of macrovascular disease in T1D. The interaction of such risk factors in promoting the increased occurrence of cardiovascular disease in T1D with resulting profound morbidity and mortality is obviously unknown. In the absence of understanding the true roles of traditional and T1D specific risk factors in the pathogenesis of cardiovascular disease in T1D, designing appropriate interventions and strategies for prevention is problematic.

The Diabetes Control and Complications Trial (DCCT) and the Epidemiology of Diabetes Interventions and Complications (EDIC) follow-up study have established the short-term and longer-term impact of intensive diabetes therapy on retinopathy, nephropathy, neuropathy, and cardiovascular disease (CVD). In addition, they have defined the roles of hyperglycemia and other risk factors on the development and progression of complications. The previous results of DCCT/EDIC have been seminal in developing the modern-day therapy of Type 1 diabetes that has been adopted worldwide. The DCCT/EDIC cohort has been followed with consistent, validated methods for a mean of 16 (13-20) years with 94% retention and represents the most carefully studied group of Type 1 diabetic patients in history. The current protocol describes further follow-up of the DCCT/EDIC cohort with the goals of: determining the very long-term effects of the original interventions on advanced complications; exploring the longevity of the imprinting ("metabolic memory") phenomenon; delineating the modern-day clinical course of diabetic complications including the interactions among complications and co-occurrence of complications; examining the long (er)-term effects of intensive vs. conventional therapy on cardiovascular events; exploring the pathophysiologic mechanisms that underlie the

development and progression of microvascular, neurologic, and cardiovascular complications; and defining the long-term quality of life and economic impacts of intensive therapy.

## 1.2 Summary of the DCCT/EDIC Study

The Diabetes Control and Complications Trial (DCCT, 1982-93) and the Epidemiology of Diabetes Interventions and Complications (EDIC, 1994-2006) follow-up study have been ongoing for more than twenty years. (22-25) After a mean follow-up of approximately 16 years, the cohort remains remarkably complete with 94% of the original cohort being actively followed. In concert, the clinical trial and subsequent follow-up have provided more information regarding the relationship among glycemia, other risk factors and long-term complications, and the effects of glycemic therapy, than any other study.

The DCCT was a multicenter, randomized clinical trial designed to compare intensive with conventional diabetes therapy with regard to their effects on the development and progression of the early vascular and neurologic complications of insulin-dependent diabetes mellitus.

The goal of the EDIC follow-up was to examine the longer term effects of the original DCCT interventions, especially as they apply to complications, such as cardiovascular and more advanced stages of retinal and renal disease, that require a longer period of time to develop. (24) The EDIC study has been remarkably fruitful in discovering the long term “imprinting” effects (metabolic memory) of the previous intensive and conventional therapies, and in delineating the interactions among risk factors, with regard to microvascular complications. (25-27) In addition, EDIC established, for the first time, the role of intensive therapy and chronic glycemia with regard to atherosclerosis. (28,29)

The following is a summary of the DCCT/EDIC Study results.

**Background.** Long-term microvascular and neurologic complications cause major morbidity and mortality in patients with insulin-dependent diabetes mellitus (T1D). We examined whether intensive treatment (IT) with the goal of maintaining blood glucose concentrations close to the normal range could decrease the development and progression of these complications.

The DCCT (1983-93, mean follow-up of 6.5 years) demonstrated the beneficial effects of IT, aimed at achieving glycemic levels as close to the non-diabetic range as safely possible, compared with CT on retinopathy, nephropathy, and neuropathy. (23, 30-35) (Table 1.1) In addition, the relative costs and risks of intensive therapy (36,37) and its effects on neurocognitive function (38), quality of life (39), and cardiovascular disease (40) were delineated. The relationship among glycemic levels, other risk factors, and diabetic complications were also established. (41,42)

The DCCT represented a landmark study in many ways. Not only did the DCCT clearly define the role of glucose control in the development and progression of the long-term complications of diabetes mellitus, it demonstrated the strength of the randomized controlled clinical trial. The DCCT established the metabolic goals of diabetes care and the means to achieve those goals.

The primary goal of the EDIC study was to determine the long-lasting effects of the previously assigned therapies, based on an intention-to-treat analysis, on diabetic complications. Those complications that require longer time to develop than the original DCCT period of follow-up, including more advanced microvascular complications and cardiovascular disease, were of particular interest.

**Table 1.1**  
**Reduction in Risk for Microvascular Complications with Intensive Therapy,**  
**Compared with Conventional Therapy, during DCCT and EDIC (Combined Primary**  
**Prevention and Secondary Intervention Cohorts)**

Complication	Percent Reduction	
	During DCCT	During EDIC
Retinopathy		
3-step change	63	72
Proliferative	47	76
Macular edema	26*	77
Laser therapy	51	77
Nephropathy		
Microalbuminuria (> 28mg/min)	39	53
Clinical albuminuria (> 208mg/min)	54	82
Neuropathy+	60	

\*P< 0.001 for all reductions, except for macular edema during DCCT, which was ns.  
 +EDIC assessment of neuropathy different than DCCT assessment, precluding comparison of DCCT and EDIC results

**Methods.** The DCCT studied a cohort of 1,441 subjects between 13 and 39 years old with type 1 diabetes mellitus (T1DM) for 1-15 years. (22,23) All participants were relatively healthy except for diabetes and were free of severe diabetes-related complications. The Primary Prevention cohort consisted of 726 subjects with T1DM for 1-5 years and no diabetes-related complications (no microaneurysms on fundus photography and urine albumin excretion <40 mg/day). The Secondary Intervention Cohort consisted of 715 subjects with T1DM for 1-15 years and mild to moderate nonproliferative retinopathy and a urinary albumin excretion rate <200 mg/day. Subjects were randomized to conventional (CT) or intensive diabetes therapy (IT). The intent of IT was to achieve blood glucose levels of 70-120 mg/dL in the morning and before meals, <180 mg/dL after meals, and an HbA1c in the non-diabetic range (<6.05%). Although it was not feasible to achieve these glycemic targets consistently in the majority of the subjects assigned to the IT group (fewer than 5% maintained an average HbA1c <6.05%), there was a substantial difference in glycemic control between the IT and the CT groups. The CT group maintained an average HbA1c of about 9.0% (similar to their baseline value) throughout the 3-9 (mean 6.5) years of follow-up. Those in the IT group lowered their HbA1c to about 7.0% and maintained this for the duration of the study (Figure 1.1).

Following the end of the DCCT in 1993, and a transitional period during which the conventional treatment group was taught intensive therapy and the clinical care of all of the subjects was transferred to their own health care providers, an observational study of the DCCT cohort, entitled Epidemiology of Diabetes Interventions and Complications, was launched. (24) During the transition from the DCCT clinical trial to the EDIC observational study, the difference in glycemic control, measured by HbA1c, that had been approximately 2% during the DCCT (7.2% in the intensive treatment group compared with 9.1% in the conventional treatment group) narrowed (7.9% vs. 8.1% in IT and CT groups, respectively). (23,25) The difference in mean HbA1c between the two original treatment groups has become statistically indistinguishable during the most recent six years of EDIC follow-up. (Figure 1.1)

Phase 1 of the EDIC follow-up study spanned twelve years. The total mean follow-up of the original cohort was approximately 16 (range 13-20) years. Retention of the DCCT cohort

remained outstanding. Ninety-six percent of the surviving DCCT cohort joined EDIC in 1994 and 94% of the original cohort (n= 1357 of 1441) remained active throughout the first phase of EDIC. The demographics of the EDIC study population at closeout are shown in Table 1.2.

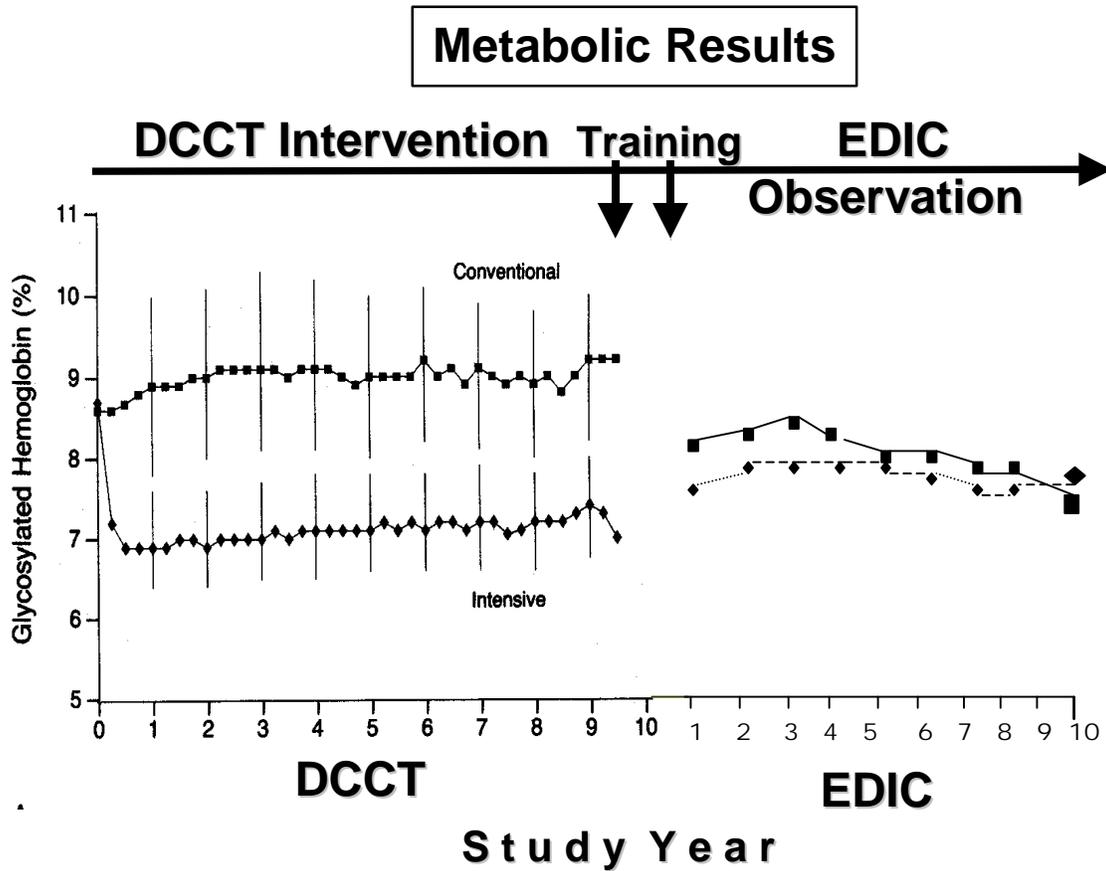


Figure 1.1: Glycemic Levels during DCCT/EDIC as measured by glycosylated hemoglobin (HbA1c). Medians with 25th to 75th percentiles shown.

**Table 1.2**  
**Characteristics of DCCT/EDIC Study Population 2003 (EDIC 10 year followup)**  
**Original Cohorts**

	<u>Primary Prevention</u> n= 638	<u>Secondary Intervention</u> n= 638	<u>All</u> 1276
Attained age (years)	43	45	44
Gender (% males)	52	53	53
Diabetes Duration (years)	19	26	22
Race (% Caucasian)	96	97	97
Retinopathy (%)			
None	2	0	1
Mild NPDR or Worse	55	77	63
Moderate NPDR or Worse	25	44	34
Severe NPDR or Worse	9	30	19
Proliferative DR or Worse	8	27	18
HRC <sup>#</sup> or Worse	7	20	13
CSME <sup>#</sup>	13	25	19
Laser therapy (all)	8	21	8
For macular edema	7	11	15
For proliferative DR	7	18	8
VA < 20/200 (both eyes)	0	0	0
Nephropathy (%)			
No microalbuminuria	70	55	62
> 40 mg/24 h	30	45	38
> 300 mg/24 h	7	13	10
Severe renal*	2.1	2.5	2.3

\*Cr > 2.0, dialysis, or renal transplant.

<sup>#</sup>NPDR—nonproliferative diabetic retinopathy.

CSME—clinically significant macular edema.

HRC—high risk characteristics.

**Results.** In the primary-prevention cohort, intensive therapy reduced the adjusted mean risk for the development of retinopathy by 76 percent (95 percent confidence interval, 62 to 85 percent), as compared with conventional therapy. In the secondary-intervention cohort, intensive therapy slowed the progression of retinopathy by 54 percent (95 percent confidence interval, 39 to 66 percent) and reduced the development of proliferative or severe non-proliferative retinopathy by 47 percent (95 percent confidence interval, 14 to 67 percent). In the two cohorts combined, intensive therapy reduced the occurrence of microalbuminuria (urinary albumin excretion of  $\geq 40$  mg per 24 hours) by 39 percent (95 percent confidence interval, 21 to 52 percent), that of albuminuria (urinary albumin excretion of  $\geq 300$  mg per 24 hours) by 54 percent (95 percent confidence interval, 19 to 74 percent), and that of clinical neuropathy by 60 percent (95 percent confidence interval, 38 to 74 percent). In addition, there was a 41% decrease (95 percent confidence interval, -10 to 68) in macrovascular events although not statistically significant in the intensive treatment group. The chief adverse event associated with intensive therapy was a two- to three-fold increase in severe hypoglycemia.

The EDIC follow-up has demonstrated that the differences in outcomes between the IT and CT groups persist for as long as ten years, despite the narrowing of glycemic differences that appeared to explain the vast majority of the treatment differences during the DCCT. (25-27)

The prolonged salutary effects of IT and prolonged deleterious effects of CT have been named “imprinting” or “metabolic memory”. During the DCCT, the frequency of cardiovascular events was too low to determine whether the interventions had significantly different effects. (40) During EDIC, two measures of atherosclerosis were employed, ultrasound measurement of carotid intima-media wall thickness (IMT) (28,43) and electron beam (or multidetector) computed tomography of the heart to measure coronary artery calcification. (29) The progression of IMT during EDIC was decreased in the former IT group compared with the former CT group. (28) Similarly, the prevalence of coronary calcification was less in the former intensive treatment group. (29) Both measures were associated with the level of glycemia during the DCCT, independent of other established cardiovascular risk factors. The frequency of major CVD clinical events (defined as any one of the following: fatal and non-fatal myocardial infarctions and stroke, silent myocardial infarctions, angina confirmed by a positive stress test or catheterization, and PTCA or CABG) has increased during EDIC. Preliminary analysis of the clinical events has shown differences between the two original treatment groups that support a benefit of IT on clinical disease as was previously demonstrated for atherosclerosis. Collaboration with investigators centered at Medical University of South Carolina, and supported by an independent Program Project from NHLBI, has explored inflammatory, lipid, hemorheologic and other risk factors for micro- and macrovascular disease during EDIC.

Conclusions. In summary, the DCCT/EDIC Research Group has established the following:

1. Intensive therapy aimed at achieving glycemic levels as close to the non-diabetic range as safely possible reduces the development and progression of all diabetes-specific complications by as much as 76%.
2. Intensive therapy reduces measures of atherosclerosis over time, and probably reduces CVD events as well.
3. Intensive intervention is most effective when implemented early in the course of diabetes; if intensive intervention is delayed, the momentum of complications is harder to slow, as shown by the results of the secondary intervention group.
4. The salutary effects of a 6.5-year mean period of intensive therapy persist for at least 10 years after differences in glycemia between the original intensive and conventional therapy groups have disappeared (metabolic memory).
5. Chronic glycemia and duration of diabetes are the major factors in the pathogenesis of microvascular complications in Type 1 diabetes and play a role in the development of atherosclerosis

### **1.3 Study Goal**

In planning the future study of the DCCT/EDIC cohort, the most extensively phenotyped (and genotyped) population with Type 1 diabetes, we have carefully selected those clinical and scientific questions that can be addressed uniquely through further study, or with additional analyses of collected data, of the DCCT/EDIC cohort. New tools such as imaging methods, proteomics and metabolomics, that have the potential to advance our understanding of Type 1 diabetes and its complications have become available since we added genomic studies to the DCCT/EDIC five years ago.

The studies in the core follow-up described in this protocol continue methods that have been used consistently during DCCT/EDIC and utilize new studies and analyses to address remaining clinical and scientific questions regarding Type 1 diabetes and its complications. The ability to perform the proposed studies in the multicenter environment of DCCT/EDIC and the projected burden on our research volunteer partners has been included in our planning. The success of DCCT/EDIC has largely been predicated on the extraordinary cooperation of our cohort over the past twenty years, and we will not do anything to jeopardize that special relationship.

The core protocol has been designed to provide the resources necessary to continue follow-up of the DCCT/EDIC cohort on an annual basis, as during the past 12 years of EDIC. The core study will include an annual physical examination, interval history, standard questionnaires, and biochemical measurements, as performed previously during EDIC, with the expectation that the retention of participants will remain at the high levels experienced in the past. In addition, those specialized studies that have been central to the DCCT and EDIC, including assessment of retinopathy, nephropathy, neuropathy, and cardiovascular disease are included as part of this core. Continuation of identical, or comparable, methods is a focus of the protocol with the goal of providing a continuous series of interpretable observations and analyses over time.

## 2. OBJECTIVES AND DESIGN

### 2.1 Study Objectives

Numerous important clinical research questions remain regarding long-term complications in Type 1 diabetes. The DCCT/EDIC cohort, the largest and best characterized group of Type 1 diabetic subjects, is uniquely able to answer many of these clinically important questions.

The clinical research questions that need to be addressed and that the DCCT/EDIC Research Group and Cohort can address include the following:

1. What are the long(er) term effects of the original interventions on advanced complications that affect health status?
2. What is the longevity of the imprinting (metabolic memory) phenomenon?
3. What is the modern-day clinical course of diabetic complications including the interactions among complications and co-progression of complications (triopathy)? Does intensive therapy only delay the development of advanced complications, or are they truly prevented?
4. What are the pathophysiologic mechanisms that underlie the development and progression of microvascular and neurologic complications (the genetics studies are included in an accompanying protocol, and the new biochemical measurements of inflammation and other putative pathogenetic factors are included in the accompanying CVD protocol)?
5. What are the long(er)-term effects of intensive vs. conventional therapy on cardiovascular events (addressed in this protocol and accompanying protocol)?
6. What are the pathophysiologic mechanisms that underlie the development and progression of cardiovascular disease (the genetics studies are included in an accompanying protocol, and the new biochemical measurements of inflammation and other putative pathogenetic factors are included in the accompanying CVD protocol)?
7. What is the impact of intensive compared with conventional therapy on quality of life?
8. What are the economic (cost:benefit) implications of intensive therapy in the long-term?

These major areas of investigation have been considered in the context of the four major complications (outcomes) of the DCCT/EDIC: retinopathy, nephropathy, neuropathy, and cardiovascular disease. There is considerable overlap between the resources necessary to address the major questions in the four different complications; moreover, the specific methods to study each of the microvascular and neuropathic complications have been used in the past. Although some new measurement and analytic techniques are included for retinopathy, nephropathy, and neuropathy, the major new methods proposed are for cardiovascular disease. Therefore, for planning purposes, the microvascular complications that have been the more traditional areas of research during DCCT/EDIC—as they are more specific to diabetes—are

included in the core protocol. The requirements for continued followup and retention of the cohort that are necessary for overall conduct of the studies are included in this core protocol.

## 2.2 Operational Objectives

In addition to the primary study objectives, there are the following operational objectives:

1. To follow as many as possible of the 1357 living patients who were studied in the DCCT.
2. To maintain acceptable levels of adherence to the visit and data collection schedule.
3. To monitor and maintain the precision, quality and accuracy of the assessments.
4. To analyze and disseminate the data promptly.

## 2.3 Design

### Subjects

All DCCT/EDIC subjects will be invited to continue followup. Although the EDIC followup of the original DCCT cohort has been somewhat open-ended, the most recent informed consent included a 12-year term for EDIC followup. Therefore, new informed consents (see Section 4.1 for a template) will be administered. On the basis of our previous recruitment and retention results (see Table 2.2), we anticipate that between 95 and 100% of the current cohort will elect to continue in the study. The demographic and clinical characteristics will be very similar to those shown in Table 1.2.

### Recruitment

Although retention of the original DCCT cohort has remained very high during the previous 11 years of EDIC (see Table 2.2), with no appreciable loss to followup, the Research Group will not take re-enrollment for the next ten years for granted. A set of patient-directed information sheets will be developed that describe the past progress of DCCT-EDIC, the remaining scientific and clinical questions that we hope to answer with further followup, and the ongoing and new procedures that are included in the protocol. The new procedures in the protocol will be highlighted.

**Table 2.1**  
**Core Evaluations**

<b><u>Evaluation</u></b>	<b><u>Content/Method</u></b>	<b><u>Frequency</u></b>
Standardized history		Annual
Standardized physical exam		Annual
Questionnaires	Health Insurance	Annual
	Health Status Questionnaire	Alternate years*
	Diabetes QOL	Alternate years
	Dietary-7 day recall	Alternate years
		Discontinued in Jan 2009
	QWB-SA	Once
Retinopathy	7-field stereoscopic Fundus photography	Quadrennial
	Fundus exam, Visual Acuity, and IOP	Quadrennial
	NEI-VFQ-25 <sup>&amp;</sup>	Quadrennial
Nephropathy	4 hour urine <sup>@</sup> for albumin excretion and creatinine clearance, serum creatinine serum cystatin C	Alternate years
Neuropathy <sup>‡</sup>	Michigan Neuropathy Screening Instrument	Annual
	Quantitative sensory test	Once
	Cardiac Autonomic Neuropathy Testing	Once in Years 13 & 14
	NeuroQOL	Once in Years 16 & 17
		Once
Cardiovascular disease	Ankle:brachial BP	Annual
	EKG	Annual
	Fasting lipid profile	Alternate years

\*Performed in one-half of the entire cohort every other year. Fasting studies such as lipid profiles and autonomic neuropathy testing will be synchronized.

‡ Cardiac autonomic neuropathy (R-R intervals), quantitative sensory testing, and the Neuropathy Quality of Life (NeuroQOL) survey will be added (see neuropathy section)

<sup>&</sup> NEI-VFQ-25 is a quality of life measure specific to eye disease.

<sup>@</sup> Spot urine samples, corrected for creatinine, are being evaluated in the EDIC population as a measure of albuminuria. If they prove to be an acceptable measure, they will replace 4-hour collections.

QWB-SA—Quality of Well Being Scale (self-administered).

IOP—intraocular pressure.

Quadrennial—randomization anniversary divided by 4, i.e., 16, 20, 24, 28, 32, 36, etc.

**Table 2.2**  
**History of Subject Retention in DCCT/EDIC**

Year	Phase	Subjects (#)	Retention* (%)
1983-90	DCCT	1441	100
1993	DCCT end	1422	99
1994	EDIC beginning	1387	96
2004	End of first 10 y of EDIC	1357	94 <sup>+</sup>

\*Percent of original DCCT cohort remaining in study. Loss to followup includes 11 deaths during DCCT and 31 deaths during EDIC followup as of 10/1/04.

<sup>+</sup>Of the 1399 surviving members of the original cohort, 1357 (97%) remain active in EDIC.

The consent process will include provision of written information followed by a face-to-face discussion with potential volunteers to discuss the project further and address any questions or concerns. These meetings may be carried out in a group format or individually, depending on local clinic factors. Since the elements of the Core protocol are very similar to the DCCT and EDIC tasks that the study cohort has been performing for as long as 21 years, this process should be relatively straightforward. Clinic staff, including the PI and Program Coordinator, will participate in this process.

The Informed Consent will be mailed to potential participants so that they can read it and formulate questions prior to providing consent. We expect that the majority of participants will be consented at a face-to-face meeting either prior to or at the time of their scheduled evaluation. The three part process (printed material, group and/or individual meetings, and the informed consent itself) will continue the long-standing DCCT/EDIC tradition of including our cohort as fully informed partners in the study and should result in a similarly high level of retention and adherence as we have seen in the past.

As with the informed consent process during the past 20 years of DCCT/EDIC, volunteers will be able to decline participation in specific elements of the study, but continue to participate in the Core study.

### Design

The EDIC study will continue as a non-interventional, observational followup of the DCCT cohort. Study personnel will not administer diabetes or any other medical care as part of the study. All medical care will be provided by the subjects local care providers. Of note, as of September 2004, approximately 48% of the study cohort receives diabetes care at a prior DCCT site, but not as part of the study, and not necessarily from prior DCCT or EDIC staff.

The annual visits that have been the standard followup during EDIC will continue to be the major time during which study data will be obtained. Annual visits, based on the DCCT randomization date, will be scheduled for all volunteers at the clinical centers. Table 2.1 shows the routine annual tests that will be performed as part of the Core study. The methods have been described in detail in previous publications (22-25,44,45) and are described in brief below.

The core methods have been selected with the aim of being able to complete the annual visit in a single day visit. Although local and individual factors, such as travel distances, may occasionally require an overnight stay, we expect this to be the exception. The more time-consuming and/or laborious elements of the protocol will be staggered, for example in alternate

years, when possible, to distribute the workload for participants and staff. Similarly, the major elements of the accompanying CVD protocol will be incorporated into the test schedule to reduce the burden at any one visit. When possible, self-administered questionnaires will be sent to the participants before their scheduled visits to reduce the amount of time needed at the visit.

Standardized history and physical examination—The information collected annually through the standardized history and physical examination addresses general health and diabetes-specific outcomes. The same questionnaire and physical examination, with minor modifications, have been employed throughout the DCCT and EDIC, facilitating longitudinal study. The history is completed by the participants with help, as needed, from DCCT/EDIC staff. The physical examination is performed by a DCCT/EDIC physician-investigator. (22,44,45)

Questionnaires—The questionnaires, directed at measuring overall health status (SF36) and insurance status, quality-of-life (DQOL), and dietary and nutritional data have been used during DCCT and EDIC and have been described in detail. (44,45) A new questionnaire to measure quality of life—the Quality of Well-Being, SA (QWB-SA)—will be added as part of the health economics evaluations.

Retinopathy evaluation—Seven-field stereoscopic fundus photography and an evaluation of intraocular pressure and visual acuity have been performed by DCCT/EDIC certified ophthalmologists and photographers from the outset of the DCCT. (30,31) The grading of the fundus photography will be conducted, as in the past, at the Central Ophthalmologic Reading Center (CORU).

Nephropathy—As with retinopathy, the nephropathy evaluation has been consistently applied using standardized methods throughout DCCT and EDIC. Serum Cystatin-C measurements have been added during EDIC.

Neuropathy—Michigan Neuropathy Screening Instrument (MNSI)—The MNSI, a history and physical examination-based instrument, has been validated as a reliable index of peripheral neuropathy in other studies. (46) It was introduced during EDIC to take the place of the more extensive neuropathy evaluation (history and physical examination by neurologist, nerve conduction studies, and autonomic neuropathy testing) that was used two to three times during DCCT. (33-35) The simultaneous performance of the MNSI and complete neuropathy protocol will allow a direct comparison of these methods and facilitate longitudinal followup with continuous and comparable methods through DCCT and EDIC. In addition, quantitative sensory neuropathy testing will be added to refine the measurement of peripheral neuropathy, and the NeuroQOL survey included to determine the impact of neuropathy on quality of life.

**Cardiac Autonomic Neuropathy (CAN) testing—Based on R-R interval measurement, CAN testing will be repeated in years 16 & 17. CAN testing will serve to measure progression of autonomic neuropathy and as a risk factor for CVD.**

Cardiovascular Disease (CVD)—The Core elements of the CVD outcomes will remain the same as during DCCT/EDIC, including annual historical and physical data addressing the occurrence of intercurrent events (validated and confirmed by the morbidity/mortality committee), annual ankle:brachial index and EKG, and alternate year fasting lipids (Table 2.1).

### 3. BIOSTATISTICAL CONSIDERATIONS

#### 3.1 Subject Population

The DCCT was comprised of 1441 T1D research subjects recruited between 1983 and 1989 to participate in a randomized clinical trial to examine the effects of intensive compared with conventional diabetes treatment on the development and progression of early microvascular, neurologic and other complications. (47-49) The adherence of the research volunteers to the highly complex protocol was extraordinary over the 10 years of the study with less than 3% loss to follow-up and less than 3% non-study mandated deviation from assigned therapy.

The DCCT population, aged 13-39 at entry in 1983-89, included two cohorts selected to answer two separate questions. The primary prevention cohort was selected to determine whether intensive diabetes treatment, designed to achieve glucose goals as close to the non-diabetic range as possible, would prevent the development and subsequent progression of retinopathy in T1D patients with short (1-5 y) duration, no retinopathy and < 40 mg albuminuria/24 h at baseline. The secondary intervention cohort was selected to determine whether intensive therapy would affect the further progression of retinopathy in T1D patients with 1-15 y duration, minimal to moderate retinopathy and < 200 mg albuminuria/24 h at baseline. Thus, the two cohorts were selected to have either no or minimal complications at baseline. In addition, the entry criteria eliminated patients with hypertension (>140/90), hyperlipidemia (total cholesterol >3SD over LRC age and gender specific norms), known cardiovascular disease, and patients who were unlikely to accept randomization or comply with the highly complex protocol.

After a mean follow-up of approximately 16 years, the cohort remains remarkably complete with 94% of the original cohort being actively followed.

#### 3.2 Generalizability

A collaboration between the DCCT and the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) (50) examined the similarities and differences between the DCCT cohort and a population-based T1D cohort (51). Compared with the population-based T1D cohort, the DCCT cohorts have a limited age span (age at entry to the long-term follow-up 16 to 50) and are healthier without clinically significant diabetes-specific or macrovascular complications.

Comparison of the conventionally treated DCCT primary prevention and secondary intervention cohorts at baseline with the respective WESDR groups revealed older age and older age at diagnosis, lower HbA1c and more frequent injections and monitoring in the DCCT cohorts, but relatively few other substantive differences between the populations. The 4-year progression of retinopathy and its association with baseline HbA1c were similar for the DCCT and WESDR cohorts, except for a lower rate of progression in the DCCT secondary intervention cohort than its WESDR counterpart, perhaps because of the lower HbA1c.

DCCT patients were generally similar to the population-based T1D cohort in WESDR. There were differences in HbA1c that diminished over time as the HbA1c in the WESDR cohort decreased. The demographic similarities between the DCCT and WESDR cohorts, the similar rates of progression of retinopathy in conventionally treated patients and the similar

associations between HbA1c and retinopathy progression in the DCCT and WESDR support the validity of generalizing the DCCT results to T1D in the non-research population.

### 3.3 Analytic Strategies

The study objectives broadly fall into three areas: 1) assessment of outcomes where an effect was established during the DCCT (e.g., retinopathy) and including the imprinting phenomenon; 2) assessment of the long-term effects for outcomes where no effect was definitively established during the DCCT (e.g., macrovascular events); and 3) assessment of the pathophysiology of progression of complications. The general epidemiologic and statistical strategies to be employed to address these objectives are as follows.

1) *Assess the effect of an initial average period of 6.5 y of DCCT intensive versus conventional therapy on subsequent outcomes during EDIC for which a significant treatment effect had been established during the DCCT.* This includes analyses of all of the microvascular complications for which significant benefit was demonstrated over the period of follow-up during the DCCT. The question is then whether the initial period of DCCT treatment has effects on the pathophysiology of these complications that persist beyond the DCCT. However, since the treatment groups differed during the DCCT, some of these apparent long-term effects could be attributable to this initial DCCT effect. Thus, these analyses will attempt to remove the effect manifest during the DCCT by adjusting for the status of the complication at the end of the DCCT or at EDIC baseline, either through a stratified analysis or through the use of an appropriate regression model. These analyses could also adjust for DCCT baseline covariates that could affect the status of the complication and their values during or at the end of the DCCT.

This strategy was employed to address the prolonged effect of DCCT therapy on the risk of *further* progression of retinopathy and nephropathy over 4 and 8 years, respectively, of follow-up in EDIC. In each case, the persistence of the group effect was assessed after eliminating the initial DCCT effect. For retinopathy (26), *further* progression from the level at the end of the DCCT was described among those who had not yet progressed to the need for laser therapy, and for nephropathy (27), *new* onset of albuminuria was described among those without such at the end of the DCCT. In both cases, the initial DCCT effect was removed and then the difference between groups was tested during EDIC.

Since the DCCT consisted of two distinct cohorts for the Primary Prevention and Secondary Intervention Trials, treatment effects will be assessed either separately within each cohort or in the combined cohorts if no treatment group by cohort interaction is detected, i.e., if the treatment effect within the two cohorts is similar. Models will also test for interactions between treatment group and other relevant covariates.

If a long-term DCCT treatment group effect is observed (i.e., *imprinting*), additional analyses will be conducted to attempt to identify the mechanisms of that effect. For example, the analysis could adjust for the mean level of HbA1c during the DCCT to evaluate the percentage of the DCCT group imprinting effect that is attributable to the initial group differences in HbA1c. For the analysis of the EDIC 8 year renal outcomes (27), such an analysis that also adjusted for differences in the incidence of hypertension during the DCCT and during EDIC did not explain the long-term imprinting effects on the further progression of albuminuria.

Further analyses would also be conducted along the lines described in 3) below.

2) Assess the **cumulative** effect of an initial average period of 6.5 y of DCCT intensive versus conventional therapy on subsequent outcomes during EDIC for which a significant treatment effect had **not** been established during the DCCT. This would include analyses of the incidence of macrovascular events or mortality or of advanced complications for which significant benefit was not demonstrated definitively over the period of follow-up during the DCCT. This is equivalent to the long-term pragmatic effect of an initial therapy where a treatment is administered for a period of time and long-term effects are examined over a period that extends beyond the period of initial therapy. In this case, since the period of follow-up was too short, relative to the natural history of the evolution of the outcome events, there is no need to restrict the analysis only to events observed after the period of active treatment (intensive versus conventional) during the DCCT.

Such analyses would compare the DCCT intensive and conventional groups adjusting only for DCCT baseline covariates. While there are minimal covariate imbalances at baseline in the complete randomized cohort, there might be a small imbalance within the EDIC subset, and thus these analyses would also adjust for age on entry, gender, primary vs. secondary cohort, diabetes duration, and known risk factors including smoking, blood pressure, lipid levels, and AER, all at DCCT baseline. Analyses would also assess whether the results within the primary prevention and secondary intervention trials are homogeneous in which case an analysis within the combined cohorts will be presented.

If a cumulative effect is observed, then additional analyses will assess the effect over the period of the DCCT and the period of EDIC separately. The former will adjust only for DCCT baseline factors. The latter will also adjust for factors evaluated during and up to the end of the DCCT, such as body weight, lipids, and other risk factors.

Similar considerations apply to an outcome that was not assessed during the DCCT, such as carotid artery intima-media thickness (IMT) or coronary artery calcification (CAC) by computed tomography. Each was initially assessed during EDIC, carotid IMT at years 1 and 6, and CAC at year 9. In the analyses of the IMT at year 6 (28), the DCCT group effect (Table 1.2 therein) was assessed relative to the year 1 value, adjusting only for DCCT covariates age and sex. The year 1 value during EDIC (that showed no difference between groups) and factors inherent in the measurement, such as the scanning site effects, were used as covariates. Thus, the analysis described the difference between groups in the change in IMT over the 5 year period during EDIC.

If a long-term DCCT group effect is established, then further analyses would assess the mechanism of the effect by examining the group effect after adjusting for other factors during DCCT, such as HbA1c, or during EDIC such as smoking or hypertension. In this case, the objective would be to see whether adjustment for any of these factors eliminates or diminishes, not enhances, the DCCT group effect. Analyses will also be conducted as in #3 below using both DCCT and EDIC covariates.

3. For all EDIC outcomes, microvascular and macrovascular, identify antecedent factors that are associated with onset or progression of outcomes during EDIC. The above analyses focus specifically on the evaluation of a long-term DCCT treatment group effect on outcomes. Regardless of whether a group effect is established, additional analyses will be performed to assess the association between the history of all factors (cross-sectional and longitudinal) observed during DCCT and EDIC on the pathophysiology of disease progression as reflected by

specific outcomes. This would entail models containing covariates measured at DCCT baseline, during the DCCT, at EDIC baseline, and during EDIC.

If a DCCT group effect is observed on long-term outcomes, either then the analyses will be performed separately within each DCCT GROUP, or DCCT GROUP would be used as an adjusting covariate—the same way primary/secondary cohort could be an adjusting covariate. However, once EDIC covariates are included in the model, the DCCT group no longer has a prospective population effect interpretation and should not be a covariate of primary interest in the analyses. Further, interactions between DCCT group and other factors, as well as interactions among the other factors, will be assessed.

For example, in the assessment of the carotid IMT at 6 years (28), additional analyses assessed the influence of DCCT and EDIC factors on carotid IMT (Table 2.1 therein). That analysis showed that smoking during EDIC and attained age, but not blood pressure or lipids, were significantly associated with the degree of progression in IMT. Analysis also showed that the effect of attained age differed significantly between the DCCT groups, i.e., there was a DCCT group by attained age interaction. Thus attained age is the principal determinant of the degree of atherosclerosis, measured by the year 6 common carotid IMT, identified thus far, and more so in the DCCT conventional than intensive treatment group.

In addition to known risk factors, such analyses will also evaluate in particular the history of hyperglycemia and its effect on risk of microvascular and macrovascular complications. In analyses conducted to date, the outcomes have been significantly associated with the cumulative mean HbA1c over DCCT and EDIC, combined within both DCCT groups. During EDIC there is only a ~0.2% difference in HbA1c between the former DCCT intensive and conventional treatment groups, and as expected, this small difference explains only a small fraction of the long-term DCCT group effect. However, when examined separately within *either* DCCT treatment group, the effect of the EDIC HbA1c on outcomes could ultimately exceed that of the effect of the DCCT HbA1c.

### **3.4 Defined Analytical Outcomes**

#### **3.4.1 Defined Events**

At each visit, a variety of measurements will be obtained. In this section, we list those events that we are interested in ascertaining at the annual visits.

Cardiovascular disease: death secondary to cardiovascular disease or sudden death; acute myocardial infarction or confirmed non-acute myocardial infarction; coronary artery disease requiring bypass surgery or angioplasty; angina confirmed by angiography or by ischemic changes on non-invasive testing; stroke either fatal or nonfatal; and congestive heart failure. Additional tests for the presence of CAD may be used as outcome variables depending on future availability.

Hypercholesterolemia: persistent calculated LDL-cholesterol  $\geq$  130 mg/dl.

Hypertriglyceridemia: persistent serum triglyceride > 500 mg/dl.

Cerebrovascular disease: fatal or non-fatal stroke. TIA confirmed by angiography or non-invasive testing.

Peripheral vascular disease: amputation of a lower extremity, arterial events requiring bypass or angioplasty or claudication with exercise testing or angiography evidence of vascular disease.

Lower extremity ulcer: a traumatic or non-traumatic excavation or loss of subcutaneous tissue in the foot or leg with evidence of inflammation and/or infection that requires medical or surgical treatment by a health professional in an office or hospital setting.

Hypertension: sitting systolic blood pressure  $\geq 130$  and/or diastolic  $\geq 85$ .

Microalbuminuria: urinary albumin excretion, of  $\geq 28$   $\mu\text{g}/\text{min}$ .

Albuminuria: urinary albumin excretion, of  $\geq 208$   $\mu\text{g}/\text{min}$ . In addition, in the absence of a 4-hour renal collection, procedures have been developed which may be carried out locally (see Chapter 14 in the Manual of Operations).

Renal Insufficiency: serum creatinine of  $\geq 2$  mg/dl, or GFR of  $\leq 70$  ml/min/1.73m<sup>2</sup>, or the need for dialysis or transplant.

Advanced retinopathy: proliferative diabetic retinopathy, measured by fundus photographs and graded by the final ETDRS grading scales at the Central Ophthalmologic Reading Unit.

Blindness: loss of vision, in one or both eyes, defined as visual acuity of 20/200.

Photocoagulation type: (focal or pan-retinal) and indication (macular edema or PDR).

Hypoglycemia: hypoglycemic events that require assistance from another individual will be ascertained at the annual visits. All accidents will be reviewed with the patient for the possible association with hypoglycemia.

DKA: glycemc event associated with a constellation of typical symptoms in the presence of ketonuria and acidemia. Treatment within a health care facility is necessary for the event to qualify as DKA.

### **3.4.2 Statistical Methods**

All data entry, management, and analysis will be performed at the DCCT/EDIC Data Coordinating Center located at The Biostatistics Center of The George Washington University (GWU) using SAS. (52) The statistical methods previously employed to assess the effects of intensive versus conventional treatment during the DCCT will again be employed to assess differences between groups during EDIC. Additional methods will be employed to assess covariate effects on outcomes, and to conduct longitudinal analyses of changes within subjects over time.

All results that are nominally significant at the 0.05 level will be indicated. Hochberg's (53) improved Bonferroni procedure will be used to adjust for multiple comparisons where appropriate. All analyses comparing the original DCCT treatment groups will be conducted under the principle of intention-to-treat, with all patients included in their originally assigned DCCT treatment group.

All analyses will be conducted separately within the primary prevention and secondary intervention cohorts because these samples were drawn from different subgroups of the type 1 diabetic population. The cohorts will be combined if the effects of DCCT group and covariates are similar between cohorts, i.e., no statistical interaction with cohort exists.

Binary Outcomes. Examples of such a binary outcome include the presence or absence coronary artery calcification at EDIC year 8, or of definite confirmed clinical neuropathy at the EDIC 12 year evaluation. Such analyses typically describe the *prevalence* of an outcome at a specific point in time. For the analysis of a binary variable at a specific point in time, Pearson's contingency chi-square test will be employed and the difference expressed as an estimated odds ratio (OR) with large sample confidence limits. (54) For an analysis stratified by other categorical factors, such as primary or secondary cohort, the Mantel-Haenszel test and estimate of the adjusted odds ratio, with 95% confidence limits, will be employed (54). A preliminary test of homogeneity will be conducted and if heterogeneity is detected, results will be reported within strata rather than a single stratified-adjusted test and odds ratio.

Logistic regression models (54) will be employed to examine the effects of various covariates on the odds of the binary outcome at a specific point in time, such as at EDIC year 12. In these models, likelihood ratio tests of effects will be employed and the strength of the effect measured by a partial entropy R<sup>2</sup> for each covariate. (54) Value-added plots (55) will be employed to explore whether transformations or polynomial covariate effects are warranted rather than a simple linear effect. Goodness of fit will be assessed by the Hosmer-Lemeshow test and over-dispersion using the tolerance limits on the ratio of the Pearson Chi-square to its df. (54,56) If the model assumptions are violated, the robust estimate of the covariance matrix of the estimates will be employed as the basis for confidence intervals and tests of significance. (54) For example, among those without neuropathy at EDIC baseline, logistic regression analysis will be used to calculate the odds ratio for developing clinical signs of neuropathy or any diagnosable level of peripheral neuropathy at the EDIC year 12/13 examination, and to compare the effects of former DCCT conventional versus intensive treatment.

Generalized estimating equations (57) with a logit link will be employed to assess the effects of covariates on the odds of an outcome over repeated points in time, allowing for the correlation among the repeated measures. Partial Wald or score tests will be used to test covariate effects and Madalla's R<sup>2</sup> (54) used to describe the strength of effect for each covariate.

In some cases it will be of interest to compare the agreement among various binary measures, such as albuminuria at a point in time as assessed by the AER obtained from a timed urine collection versus albuminuria as assessed by an albumin/creatinine ratio from a spot urine. In such cases, the Kappa statistic (58) will be used to quantify the percent of agreement above that expected by chance for two specific assessments, or for the set of all assessments. A regression model can also be used to estimate the magnitude of Kappa adjusting for other covariates (59).

Ordinal Outcomes. An ordinal outcome is a nominal assessment with multiple (> 2) categories with an implied ordering, such as no nephropathy, microalbuminuria only, albuminuria only, or end-stage renal disease at a point in time. Simple proportions in each category will be used to describe the prevalence within each category at a given point in time, and differences between groups tested using the 1 df Mantel-Haenszel test of mean scores (59), or using the Wilcoxon signed rank test with the adjustment for tied ranks (74). A

proportional odds model (59) will be used to examine covariate effects on the prevalence within each ordered category. If the test of the proportional odds assumption is rejected, then that implies the need to model covariate effects on each category separately. In this case, the odds of each category versus a designated reference category (e.g., no neuropathy) at a specific point in time will be assessed using a multinomial logit model (59). In essence, this model simultaneously fits a logistic model for C-1 comparisons of each positive category versus the reference category. The results of these models will be summarized as above for a logistic regression model. For a longitudinal analysis of repeated assessments over time, separate GEE logit models for each positive category versus the reference category will be conducted.

Time-to-Event Outcomes. For a right-censored time-to-event outcome, such as the day of a cardiovascular event, a Kaplan-Meier survival function curve (54), and its complement the cumulative incidence function, over time will be employed in descriptive analyses. The Mantel-logrank test will be used to conduct a test of differences between groups, without adjustment for covariates. Covariate effects will be assessed using the Cox proportional hazards model. (59). The model assumptions will be tested using Lin's test (61). If the PH model assumptions are violated, remedial action will be taken such as using the robust estimate of the covariances, or incorporating covariate by time effects or using a different class of models such as an accelerated failure proportional odds model (62).

Many of the observations during EDIC are interval-censored, meaning that it is known that an event occurred during an interval, but the exact day is not known. This applies to all observations for which a procedure is required in order to diagnose the event, e.g., fundus photographs, renal examination, neurologic examination, etc. For an interval-censored time to event outcome, analyses will employ a Weibull proportional hazards accelerated failure time model, if the Weibull model assumptions are met. (62) For the assessment of time-dependent covariate effects on such an outcome, the generalized Weibull model (63) will be employed with the same caveat as above.

Rates of Events. In some cases, the observed data consists of a number of events reported to have occurred over an interval of time, such as the number of hospitalizations or episodes of hypoglycemia reported by each subject at the annual examination. In this case, the data are summarized as a rate of events per 100 patient years and differences between groups as a relative risk, with 95% confidence limits. (54) If the distribution of events violates the usual Poisson assumptions, as did hypoglycemia during the DCCT, robust methods for inference will be employed. (54)

Poisson regression models will be employed to assess covariate effects on the rate of such events (54) and robust methods for inference employed if the model Poisson assumptions are violated. (54)

Numerical (Quantitative) Outcomes. For numerical variables with no point of truncation, the AER in mg/24 h, simple differences between groups will be assessed by a Wilcoxon test (60). Models adjusting for covariate effects will be conducted using normal errors regression models. (64) Partial residual or value-added plots will be employed to determine whether a transformation or a polynomial best represents a covariate effect rather than a simple linear term. The homoscedastic normal errors assumptions will be tested using the Shapiro-Wilks test of normality of residuals and White's test of homoscedasticity of error variances. (65) If violations are detected, then an appropriate transformation will be sought. If still violated, all inferences will be based on White's robust estimate of the covariances of the estimates (65) that provides consistent estimates of the variances of the coefficient estimates.

The normal errors mixed model will be employed for an analysis of covariate effects on repeated quantitative measures over time using an “unstructured” covariance matrix for the repeated measures. (57) Such “marginal” analyses provide an assessment of covariate effects on the average of values over time, or at specific points in time when covariate by time effects are employed. For example, these models will be used to evaluate the interaction between group and time to determine if previous intensive care was associated with persistent changes in albumin excretion rates over time.

Alternately, mixed models with a random time and covariate by time effects (57) allow the assessment of covariate effects on the average rate of change in the outcome over time, such as testing whether the mean slope of change in AER over time differs between groups.

Numerical Outcomes with Truncation. Some numerical measures are truncated, such as a coronary artery calcification that is immeasurably small and reported as “zero”, or a nerve conduction velocity where no response is elicited. In such cases, it is inappropriate to treat the truncated values as missing, and also inappropriate to treat the values as zero. Analyses of such measures at specific points in time will be conducted using a “worst rank” analysis. (66) In such an analysis, all values below the limit of truncation are assigned a rank that is less than that of all observed values, and then a rank analysis conducted using the Wilcoxon rank test. For the analysis of multiple or repeated measures, the Wei-Lachin multivariate rank test will be employed. (67,68) The Mann-Whitney statistic will be used to describe the magnitude of group differences in the distribution of the outcome. (68) A stratified analysis can also be conducted to adjust for covariate effects. (68) In prior analyses of such data in the DCCT, the N-weighted Wei-Lachin test of stochastic ordering was used to assess group differences. (68) This procedure tests whether the majority of the measures show differences in a single direction, therefore favoring one group over the other.

A TOBIT regression model (69) will be used to assess covariate effects on such truncated measures obtained at a specific point in time. This method simultaneously assesses a covariate effect on the probability of having a measurable value (above the limit of truncation) and the quantity of the measurement. The TOBIT regression model was used in the analyses of the coronary calcification measurements obtained in EDIC. (29)

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## 4. PATIENT ORIENTATION AND INFORMED CONSENT

### 4.1 Patient Orientation

The template letter introducing the EDIC continuing followup to the patients is presented in Figure 4.1.

The template patient directed information summary for the EDIC Continuing Follow-Up study is presented in Figure 4.2.

### 4.2 Informed Consent

In order to be eligible for the continuing follow up study each participant must be willing to sign a statement of informed consent prior to participation, in order to document that subjects understand the study and its procedures and agree to participate in the study activities. The Informed Consent must be signed and a copy returned to the Data Coordinating Center for a patient to be considered officially enrolled in the EDIC. The Informed Consent must be signed before any data may be collected on that patient. The basic informed consent form for EDIC is presented in Figure 4.3.

The basic elements of the informed consent are:

1. A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;
2. A description of any reasonably foreseeable risks or discomforts to the subject;
3. A description of any benefits to the subject or to others which may reasonably be expected from the research;
4. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;
5. A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;
6. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;
7. An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject;
8. A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled;

9. A statement that a particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;
10. Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;
11. Any additional costs to the subject that may result from participation in the research;
12. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;
13. A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject; and
14. The approximate number of subjects involved in the study.

Additionally, EDIC will send saved specimens to the NIDDK Central Repositories. The informed consent will contain a description of the repositories' purpose and the measures taken to protect the identity of the individual participants.

In accordance with DHHS policy on informed consent, it is necessary to recognize that each subject's mental and emotional condition is important, and that in discussing the element of risk a certain amount of discretion must be employed consistent with full disclosure of facts necessary to any informed consent.

Individual clinical centers may require that the recommended Informed Consent Form be amended to include additional statements or be reworded based on local institutional requirements.

**Figure 4.1**  
**EDIC CONTINUING FOLLOW-UP LETTER TO PATIENTS**

Dear PATIENT,

Thank you again for participating in the first phase of EDIC, the follow-up study to DCCT. We are finishing data collection and are ready to begin the next 10 years of follow-up.

As we continue to learn about the complications associated with diabetes and differing levels of intervention, we want to stay in touch with you and know how you are doing. To help us, there are a few simple things you can do.

1. Take a few minutes to read the enclosed introduction page and new informed consent form
2. If you would like to continue your participation in EDIC, sign the informed consent and return it with the enclosed stamped and self-addressed envelope.
3. If you do not wish to help us at this time, please return the unsigned informed consent form to us so we may know your decision.

Thank you again for all of your cooperation with this very important research! If you have any immediate questions or concerns, please feel free to contact me at PHONE NUMBER, or via e-mail at EMAIL.

Sincerely,

COORDINATOR

**Figure 4.2**  
**PATIENT DIRECTED INFORMATION FOR THE EDIC CONTINUING FOLLOW UP STUDY**

With your help and support, the Diabetes Control and Complications Trial (DCCT) and Epidemiology of Diabetes Intervention and Complications (EDIC) have made major contributions to our understanding type 1 diabetes mellitus and how it is best treated. The DCCT was a landmark study which was the first to demonstrate conclusively that treating diabetes intensively and controlling blood glucose protected people with diabetes from eye, kidney and peripheral nervous system complications. The DCCT results changed the approach to diabetes treatment around the world. In EDIC, we have learned that intensive treatment has long lasting effects on diabetes complications. EDIC has also demonstrated that intensive diabetes treatment retards atherosclerosis, the process that causes heart attacks and strokes. Both carotid artery wall thickness and coronary artery calcification were less in DCCT participants who were treated intensively than in those who were not. This is the first such demonstration available in the medical literature.

Although we have learned a great deal in DCCT/EDIC, there is still much to be learned about type 1 diabetes and its management. Accordingly, the National Institutes of Health has approved a plan to extend EDIC ten additional years, until approximately the year 2015. In this extension, EDIC tests and procedures would be much as they have been. Participants would be asked to come to their EDIC center for an annual evaluation. Eye examinations would be performed every fourth year. Kidney evaluations and blood cholesterol testing would also be performed every second year. This will be the core EDIC study. As in the past, results of all tests would be made available to participants and their physician.

Extending EDIC ten additional years will establish the longest study of diabetes in history. We hope to learn more about how treatment of diabetes influences eye, kidney, and peripheral nervous system complications. We also hope to learn how diabetes influences atherosclerosis, the process that causes heart attack and stroke. Such information will benefit not only participants in DCCT/EDIC, but also other people with diabetes now and in the future.

Attached is a copy of the consent form for the ten year EDIC extension. The form describes in some detail all of the tests and procedures to be performed.

The track record of research participants in DCCT/EDIC has been extraordinary. Of the 1,441 volunteers who enrolled in DCCT, 99% completed the study. After completing DCCT, 96% of you volunteered for EDIC and 94% of you completed the first ten years of EDIC. No other research study in medical history has had such an altruistic and committed group of volunteers. We hope you will choose to continue your participation in EDIC. Both the Trial Coordinator and the Principal Investigator at your center will be happy to answer any questions you may have about ongoing participation in EDIC.

**Figure 4.3**  
**INFORMED CONSENT FOR PARTICIPATION IN THE EDIC CONTINUING FOLLOW-UP**

Participant \_\_\_\_\_ IRB Approval Number \_\_\_\_\_

Principal Investigator \_\_\_\_\_

Title of Project: Epidemiology of Diabetes Intervention and Complications Continuing Follow-Up

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**1. You are invited to participate in a study conducted by *Name of Principal Investigator* and/or colleagues. The overall purpose of this research is:**

To assess the development of long-term complications of diabetes among people who participated in the Diabetes Control and Complications Trial (DCCT) between 1983 and 1993 and the Epidemiology of Diabetes Intervention and Complications (EDIC) investigational study between 1994 and 2005. Approximately 1,400 volunteers will be asked to participate in the EDIC continuing follow-up in up to 28 centers in North America. The overall goal of the study is to help determine factors that are associated with the development of eye, kidney, nerve, and large blood vessel complications in diabetes.

**2. Your participation will involve:**

- a. Approximately every year for up to ten years you will undergo a medical examination to check your overall health, diabetes control, and the presence of diabetes related complications. During these visits some of the tests of eye, kidney, nerve, and heart function performed during the DCCT and EDIC will be repeated according to a pre-arranged schedule. Questionnaires will be performed every year and blood for hemoglobin A1c measurements will be collected every year. The ophthalmologic (eye) exams will include fundus photographs, which are photographs of the retina, a visual acuity examination, and a visual function questionnaire. The eye exams and Fundus photographs will be performed every fourth year. Blood and urine for kidney tests and blood cholesterol measurements will be collected on alternate years.

Tests to evaluate your nervous system will be done in Years 13 or 14. These tests are repeats of those that were performed during DCCT (nerve conduction studies and cardiac autonomic nervous system (ANS) tests) and will also include some tests that were not done during the DCCT. These are a vibration perception tests and two questionnaires, one focused on peripheral neuropathy and the other asking about symptoms of autonomic neuropathy. The ANS test and that questionnaire about autonomic symptoms will be repeated once either in Year 16 or Year 17.

- b. Unlike your prior participation in the DCCT but like your participation in EDIC, routine diabetes and health care will not be provided in the EDIC continuing follow-up. This study will also not routinely supply insulin, insulin administration supplies or supplies to monitor blood glucose levels except as they are made available without charge to the study by contributions from industry.
- c. Unlike your participation in the DCCT but like your participation in EDIC, the results of medical examinations and tests obtained during the EDIC continuing follow-up study will

be made available to you and to your physician(s) or health care providers. These results will include your hemoglobin A1c concentration, blood pressure, and tests for diabetes related complications of the eyes, kidneys, nerves, and large blood vessels.

- d. The information gathered during EDIC continuing follow-up will be added to the information already gathered during DCCT and EDIC. Some of this information may be combined or compared with data from other patients with diabetes as part of cooperative research projects with diabetes researchers in North America and other countries. If you move, you will be given a list of centers in North America that may be more convenient for your yearly exams.
- e. The EDIC study includes the collection of blood for lipid analysis on alternate years. An additional study of lipoproteins, proteins that transport fat in the blood, will be done during the same years as the lipid collection. The lipoprotein study involves the additional drawing of three 7mL tubes of blood (about 4 teaspoons). Dr. John Brunzell, of the University of Washington, is the principal investigator of the lipoprotein study.

Do you consent to participating in the lipoprotein study? (Please place your initials in the space in front of your response.):

\_\_\_\_\_Yes

\_\_\_\_\_No

- f. With your permission, we would like to store the collected samples of your blood and urine in the NIDDK Central Repositories at the conclusion of the study. The Repository is a research resource supported by the National Institute of Health. The Repository collects, stores, and distributes biological samples and associated data from people with many kinds of disorders, from unaffected family members, and from other healthy people. The purpose of this collection is to make samples available for use in research for the study of Type 1 Diabetes after the EDIC Genetic Studies project has ended. Sending samples to the Repository may give scientists valuable research material that can help them to develop new diagnostic tests, new treatments, and new ways to prevent diseases.

The Repository will take measures to protect your privacy, although no guarantee of confidentiality can be absolute. Before EDIC sends samples to the Repository, your name, and all personal identifying information, such as address, social security number, and date of birth, will be removed. Therefore, the Repository will not be able to give out your name, or other information that identifies you to the scientists who receive the samples. However, the Repository and scientists will have some data about you, such as age, sex, diagnosis, race, and outcomes from the DCCT/EDIC studies.

You will not receive any direct benefit or payment for participating, but your samples may benefit the future health of the community at large or some particular group. Because other researchers will not have access to your identity, neither you nor your physician will get the eventual results of studies that might be performed using your samples or data. It is possible that research findings resulting from use of your samples or data will eventually be used in a research publication. In that event, your name or other identifying information will not be included, as this information will not be available to the researchers.

It is important for you to understand that there is a small chance that some research may yield results that may indirectly have a negative impact on insurability, employability, and/or family relationships of some individuals or groups of people.

Sometimes, research results in findings or inventions that have value if they are made or sold. These findings or inventions may be patented or licensed, which could give a company sole right to make and sell products or offer testing based on the discovery. Some of the profits from this may be paid back to researchers and the organizations doing this study, but you will not receive any financial benefits.

Your donation is voluntary, and if you choose not to participate, there will be no penalty or loss of benefits to which you are entitled. Once you agree to have your samples stored in the Repository, you will not be able to withdraw your samples because the Repository will not know which ones are yours. The samples will stay in the Repository indefinitely.

Do you consent to participating in the NIDDK Biosample Repository? (Please place your initials in the space in front of your response.):

\_\_\_\_ Yes

\_\_\_\_ No

**3. There are certain risks and discomforts that might be associated with this research:**

- a. Blood sampling may cause local pain, discomfort, and an occasional bruise. The total amount of blood drawn at any yearly visit will be approximately four ounces, less than the amount drawn during a routine blood bank donation.
- b. Urine collections have no side effects except the inconvenience of collection.
- c. During the measurement of eye pressures (part of the ophthalmologic examination), an instrument will touch your eyes. Drops are put in each eye to dilate (widen) the pupil and numb the surface. Once numb, pressure can be measured without discomfort. Drops placed in the eyes sometimes sting and burn or cause blurred vision. On rare occasions, dilating the pupil may cause an attack of glaucoma if you have a tendency for glaucoma (even if you did not know about it). More rarely, local allergic reactions, such as redness or swelling, may develop.
- d. For the nerve conduction studies, the neurologist will measure the temperature of the surface of your skin and may warm or cool your limbs to make sure the skin temperature is in the ideal range for testing, and comparable to the temperature used at your last DCCT nerve conduction studies. This part of the examination is not painful, and not generally thought of as uncomfortable, but may take some time. Once at the right temperature, small electrodes will be placed at specific spots on one arm and on one leg. These electrodes stick on the surface of the skin, much like those used for your EKG, and they do not penetrate the skin. A small current of electricity is passed through the electrode to stimulate a specific nerve. You may feel a sensation like you have received a static electricity shock (like a "carpet shock"), and your arm or leg may twitch in response to the current. Most people describe the sensation as uncomfortable, but not painful.
- e. Only minimal discomfort may be experienced during the ANS and vibration perception tests. If you have proliferative retinopathy, (a type of eye damage related to diabetes) or if you have had proliferative retinopathy treated by LASER or vitrectomy, the Valsalva portion of the test will not be done.

- f. Participation in this study will involve a commitment of up to one or two days per year to undergo tests. You will ordinarily not be paid for travel expenses to the clinic conducting the examinations. You will not be paid for time lost from work. You will also not be provided with free medical care for any diabetes complications discovered during yearly visits. You will, however, be counseled as to what care would be appropriate and where and how to obtain it.
  - g. **We will keep information that could identify you separate from your coded medical information and will not release this information to third parties.** Data from the medical records will be sent to our data coordinating center at The Biostatistics Center of The George Washington University for statistical analysis. Medical records will be kept in restricted areas at *[name of center]*. A code number will be used on your medical information and investigators outside your clinical center who look at your medical information will not be able to identify you.
  - h. The NIDDK Central Repository will take measures to protect your privacy, although no guarantee of confidentiality can be absolute. Before EDIC sends samples to the Repository, your name, and all personal identifying information, such as address, social security number, and date of birth, will be removed. Therefore, the Repository will not be able to give out your name, or other information that identifies you to the scientists who receive the samples. However, the Repository and scientists will have some data about you, such as age, sex, diagnosis, race, and outcomes from the DCCT/EDIC studies. It is important for you to understand that there is a small chance that some research may yield results that may indirectly have a negative impact on insurability, employability, and/or family relationships of some individuals or groups of people.
- 4. The possible benefits to you and/or society from this research are:**  
Because you have diabetes, you may benefit from the tests being conducted in this study because they may detect problems that would benefit from early treatment. All of the tests conducted in this study will be performed free of charge. The information gathered during this study may also be of benefit to society at large and other patients with diabetes in particular.
- 5. You may choose not to participate in this research study. Your choice will not at any time affect the commitment of your health care providers to administer care.**
- 6. The following alternatives to your participation are available:**  
Participation in this project is strictly voluntary. You have the option not to participate. If you decide at a later date that you do not want future specimens collected from you to be used for research, you may notify *Name of Principal Investigator*.
- 7. The University will take all reasonable measures to protect the confidentiality of your records and your identity will not be revealed in any publication that results from this study. The confidentiality of all study related records will be maintained in accordance with applicable state and federal laws. There is a possibility that your medical record, including identifying information, may be inspected and/or photocopied by federal or state government agencies during the ordinary course of carrying out their functions. Representatives of the sponsor, The National Institutes of Health, may also inspect your research records.**

8. Participation is voluntary and you may refuse to participate or withdraw consent to participate at any time. There will, of course, be no penalty or loss of benefits to which you are otherwise entitled.
  
9. If you have any questions or concerns regarding EDIC continuing follow-up, or if any problems arise, you may call the Principal Investigator at \_\_\_\_\_. You may also ask questions or state concerns regarding your rights as a research subject to the Chairman of your University's Human Studies Committee or Institutional Review Board at \_\_\_\_\_.
  
10. The University will provide immediate medical treatment in the event that a physical injury results because of your participation in this project. You will be responsible for the cost of such medical care not reimbursable through your health insurance. No compensation will be provided to you for such an injury.
  
11. IF YOU ARE PREGNANT, BREASTFEEDING, OR BECOME PREGNANT WHILE PARTICIPATING IN THIS RESEARCH STUDY, IT IS IMPORTANT THAT YOU INFORM THE PRINCIPAL INVESTIGATOR.
  
12. You will be informed of any significant new finding during the course of participation in this research that may have a bearing on your willingness to continue in the study or to seek treatment that may be of benefit to you. The investigator may choose to withdraw you from this research study if at any time circumstances arise which warrant doing so.

I have read this consent form and have been given the opportunity to ask questions. I will be given a copy for my records. I hereby consent to my participation in the research described above.

\_\_\_\_\_  
Participant's Signature/Date

\_\_\_\_\_  
Witness' Signature/Date

This form is valid only if the Human Studies Committee or local Institutional Review Board stamp of approval is shown above. Approval is for one year unless otherwise stated.

## 5. PROCEDURES FOR FOLLOW-UP VISITS

### 5.1 General Principles

During the course of the study, participants will be asked to undergo a set of regularly scheduled standardized procedures. All visits will be scheduled to coordinate these procedures and examinations with other requirements in order to optimize convenience for the study participants and to minimize costs.

A standardized follow-up history and physical examination will be scheduled yearly for each subject. The schedule for other follow-up procedures is discussed in the following sections. Table 5.1 presents the follow-up schedule. Table 5.2 lists the EDIC core evaluations. Table 5.3 is an outline of the visit organization and time windows for scheduling visits. Table 5.4 is a list of the equipment and supplies needed to carry out the EDIC protocol.

### 5.2 Guidelines for EDIC Staff and Patient Interactions in the Course of Outcome Determinations

Although official recording and interpretation of outcome measurements are carried out in the central units, in some instances the process of data collection makes it unavoidable that certain EDIC staff will see outcome data before it is transmitted centrally. Examples include visual acuity testing, inspection of fundus photographs for quality prior to submission to the Central Ophthalmologic Reading Unit, etc. In these circumstances, patients (and possibly other EDIC staff members) will naturally be curious as to the results. It is therefore important that by neither manner nor speech, information should not be provided unnecessarily or inappropriately. If in the process of data collection a staff member is asked for information by a patient, he/she should respond by reminding the patient that all data collected is sent to a central source for analysis and interpretation and that no information is available locally. The patient should be reassured that outcome data will be examined promptly at central units and that all results will be immediately transmitted to the EDIC center.

It is equally important that other EDIC staff members, including the Principal Investigator, should not be informed spontaneously of any perceived change in results from inspection of data by a technician or by the M.D. /PhD. in charge. Incomplete data or incomplete assessments transmitted casually to some or all other staff members can only generate rumors and speculation that may impact adversely on carrying out the EDIC protocol.

On the other hand, if a patient complains of visual symptoms, for example, to the technician, that technician should promptly report such symptoms to the ophthalmologist. In addition, the Study Coordinator should be informed of the patient's complaints.

A decrease in visual acuity (the ophthalmologist will decide if the visual acuity change is real) not perceived by the patient should be immediately communicated to the ophthalmologist. If the latter decides that the loss of vision is not due to diabetic retinopathy, he/she will inform the patient and appropriate EDIC staff, and will recommend treatment. If loss of visual acuity is thought to be due to diabetic retinopathy, the ophthalmologist will recommend treatment. Neither the patient nor the appropriate EDIC staff should be informed until an ophthalmological course of action has been agreed upon.

After a patient's data has been analyzed centrally and the results have been returned to the Data Coordinating Center, all data will be made available to the patient, excluding those

regarding DNA tests. After each annual visit, a report will be prepared by the Data Coordinating Center documenting the results of the examinations. (See Chapter 23 of the EDIC Manual of Operations). This report will be sent to the clinic, which will then pass the results on to the patient and the patient's physician.

### **5.3 Preparation**

In preparation for each annual visit, the clinic staff will arrange a date and time appropriate for the patient and assure the availability of any staff or laboratory personnel required for that visit. Any necessary appointments will be arranged with the ophthalmologist or sonographer at least two weeks in advance. After the necessary arrangements have been made, the visit will be confirmed by mail with the patient. This written confirmation should be sent two weeks before the visit, and should include the date and time of the visit, the estimated time needed to complete the visit, and a specific schedule for the visit including times and locations for seeing various study team members. This written confirmation should be followed by phone contact with the patient two to three days prior to the scheduled visit.

At the same time, the staff person responsible for visit scheduling should make certain that the various clinic team members are aware of the date and time of the visit, and have the necessary forms to complete during that visit.

### **5.4 General**

1. Standardized follow-up history and physical examination for cardiovascular disease performed yearly.
2. Current Medications Form completed yearly.

### **5.5 Ophthalmologic**

1. The standardized history will occur annually.
2. The ophthalmologic exam, visual acuity, IOP, NEI-VFQ-25, and stereo fundus photography will be performed every four years. Original fundus photographs will be sent to the Central Ophthalmologic Reading Unit for analysis. Copies of the photographs may be maintained at the clinical centers. The fundus photographs will be graded using the final ETDRS grading scale.

### **5.6 Renal**

Renal examination will be performed every 2 years on alternate years from the lipid assessments. However, serum cystatin C will be measured annually. At this examination, urine and serum will be sent to the Central Biochemistry Laboratory for the following:

1. Random urine
2. Microalbuminuria (in-clinic four-hour timed collection)
3. Creatinine excretion based on four-hour timed collection
4. Serum creatinine
5. Calculate creatinine clearance based on 2 and 3.

6. Dipstick to screen for bacteriuria
7. Serum Cystatin C annually

### 5.7 Neurologic

The Quantitative sensory test, Cardiac Autonomic Neuropathy Testing, and Neuro Quality of Life questionnaire will be performed in Years 13 and 14. The neurological history and examination, nerve conduction studies and autonomic nervous system testing performed during the DCCT will be repeated during EDIC in years 13 or 14 to evaluate the development and progression of distal symmetrical peripheral neuropathy and autonomic neuropathy in the EDIC. In addition, subjects will undergo quantitative sensory testing (QST) and will be asked to complete two questionnaires: a neurology symptom-specific quality of life questionnaire (NeuroQOL) and the autonomic symptom questionnaire (Autonomic Symptom Profile – ASP). **Autonomic nervous system testing and the ASP will be repeated in Years 16 or 17.** Subjects will continue to have the Michigan Neuropathy Screening Instrument administered annually.

### 5.8 Cardiovascular

1. Triglycerides, total cholesterol, and high density lipoprotein cholesterol measured every 2 years on serum collected after an overnight fast (low density lipoprotein cholesterol will be calculated from the above measurements). In addition, at this time, an extra aliquot of .5 ml of serum will be collected in order for the CBL to obtain a serum creatinine measure. A saved specimen will also be aliquoted, frozen and forwarded to the CBL for central storage.
2. Resting electrocardiograms performed yearly and coded at the Central ECG Reading Unit.
3. Ankle-brachial blood pressure will be measured every year.
4. In EDIC year 14 and 15 Cardiac MRI and the Gadolinium test will be performed and read at the Central MRI Reading Unit. See appendix A to Chapter 5 for Inclusion and Exclusion Criteria for the MRI. Gadolinium, a contrast agent, will be used to help identify presence of scarring of the heart. See appendix A to Chapter 5 for exclusion criteria for the Gadolinium test. If a patient is excluded from the Gadolinium test they may be eligible for the MRI if they meet the criteria for that portion of the exam. See appendix B for Cardiac MRI Informed Consent.

### 5.9 Health Care

1. The Health Status and Diabetes Quality of Life questionnaires will be completed every two years. In EDIC years 13 and 14, they will not be completed because other Quality of Life questionnaires will be used.
2. The QWB-SA will be filled out by the entire cohort once.
3. The Healthcare Delivery questionnaire will be completed annually.

### 5.10 Dietary

The Harvard Food Frequency Recall Questionnaire will be completed every 2 years in conjunction with the lipids. **Use of The Harvard Food Frequency Recall Questionnaire was discontinued in January 2009.**

### **5.11 Blood Glucose Control**

Annual HbA1c measurements will be conducted at the Central Biochemistry Laboratory.

### **5.12 Examination Results**

All the results of the preceding examinations will be recorded on standardized forms and mailed to the EDIC Data Coordinating Center. The timely submission of results of all examinations is the responsibility of the individual clinical center. All results of the centrally determined measurement will be mailed to the staff of the clinical center and it is their responsibility to inform the patient and if necessary the patient's personal physician.

### **5.13 Missed Visits**

The importance of the visit schedule will be stressed to both the subject and the staff of the clinical center. Ideally, no visits should be missed; however, if a visit is missed, the visit should be rescheduled as soon as possible. The Follow-Up Committee will develop incentive programs and other activities to promote high adherence to the data collection schedules.

### **5.14 Make-Up Visits**

Make-up visits are visits scheduled for annual assessments outside the allowable (8 month) time windows for those visits. When an annual visit cannot be scheduled within the proper time window, a make-up visit must be scheduled as soon as possible within the allowable time window for make-up visits (see Table 5.1).

If an illness or other condition occurs close to or at the time of an annual visit to assess complications, the visit may be rescheduled. For example, if a patient has a renal event near the time of the renal studies assessment, that portion of the visit may be rescheduled to a time when the assessment may be more valid. A Missed Visit Form should be filed for that assessment to document the reason for the rescheduled visit. However, the assessments for other complications could be scheduled within the time window if the patient is willing and able to undergo them.

### **5.15 Transfer**

Every effort will be made to follow all study subjects even when they make temporary or permanent moves to another city or section of North America.

When a subject moves into a geographic area served by a clinical center other than the one in which he/she was originally enrolled or is currently being served, the subject will be reassigned to the new center. Regular direct communication between the center and the subject should be maintained by telephone, letter, newsletter, and other adherence techniques.

Outcome measurements may be performed at the subject's "home" center or the nearest center.

**Table 5.1  
SCHEDULE OF FOLLOW-UP EXAMINATIONS**

<b><u>EXAMINATIONS (Outcomes)</u></b>	<b><u>YR13</u></b>	<b><u>YR14</u></b>	<b><u>or</u></b>	<b><u>YR15</u></b>	<b><u>YR16</u></b>	<b><u>YR17</u></b>	<b><u>YR18</u></b>	<b><u>YR19</u></b>	<b><u>YR20</u></b>	<b><u>YR21</u></b>	<b><u>YR22</u></b>
<b>CARDIOVASCULAR (CABG, Angioplasty, MI, Angina, CHF, Stroke, TIA, Foot ulcer, Amputation)</b>											
Standardized History (Including Family) and Physical Exam	X	X		X	X	X	X	X	X	X	X
Electrocardiogram	X	X		X	X	X	X	X	X	X	X
Ankle/Arm Index by Doppler	X	X		X	X	X	X	X	X	X	X
Cardiac MRI			x								
Gadolinium Test			x								
<b>LIPOPROTEIN LEVELS (Hypercholesterolemia, Hypertriglyceridemia)</b>	SCHEDULING OF VISITS IS A FUNCTION OF RANDOMIZATION DATE-Alternate Years-										
Total Cholesterol											
HDL Cholesterol											
Triglycerides											
Calculated LDL											
<b>ANCILLARY STUDIES</b>	--IN CONJUNCTION WITH LIPIDS--										
Univ. of Washington Ancillary Studies											
<b>NEPHROPATHIC (Renal Failure, Transplant, Dialysis, Elevated Serum Creatinine)</b>	X	X	X	X	X	X	X	X	X	X	X
Standardized History and Physical Exam	SCHEDULING OF VISITS IS A FUNCTION OF RANDOMIZATION DATE--Alternate Years--										
Albumin Excretion Rate											
4 Hour Standard Creatinine Clearance	X	X	X	X	X	X	X	X	X	X	X
Serum Creatinine	X	X	X	X	X	X	X	X	X	X	X
Serum Cystatin C	X	X	X	X	X	X	X	X	X	X	X
<b>NEUROPATHY</b>											
Michigan Neuropathy Screening Instrument	X	X	X	X	X	X	X	X	X	X	X
10 gm Filament Examination	X	X	X	X	X	X	X	X	X	X	X
ANS Testing with the Autonomic Symptom Profile (ASP)	X		X								
Nerve Conduction Studies	X										
Quantitative Sensory Testing	X										
NeuroQOL	X										
<b>RETINOPATHIC (Photocoagulation, Vitrectomy, Blindness, Vitreous Hemorrhage)</b>	X	X	X	X	X	X	X	X	X	X	X
Standardized History	--EVERY 4 YEARS--										
Ophthalmological Exam											
Visual Acuity											
Fundus Photographs											
NEI-VFQ-25											
<b>HYPOGLYCEMIA (Accidental Mortality/Morbidity)</b>	X	X	X	X	X	X	X	X	X	X	X
Standardized History	X	X	X	X	X	X	X	X	X	X	X
<b>METABOLIC (DKA, Chronic Glycemia)</b>	X	X	X	X	X	X	X	X	X	X	X
Standardized History	X	X	X	X	X	X	X	X	X	X	X
HbA1c	X	X	X	X	X	X	X	X	X	X	X
<b>PSYCHOLOGICAL</b>											
Quality of Life Questionnaire			X		X		X		X		X
Health Status Questionnaire			X		X		X		X		X
QWB-SA			X		X		X		X		X
	--COMPLETED ONCE BY THE ENTIRE COHORT--										
<b>HEALTH CARE DELIVERY</b>	X	X	X	X	X	X	X	X	X	X	X
Standardized Questionnaire	X	X	X	X	X	X	X	X	X	X	X
<b>DIETARY</b>											
Food Frequency Recall Questionnaire	--IN CONJUNCTION WITH LIPIDS. DISCONTINUED IN JANUARY 2009--										

**Table 5.2**  
**Core Evaluations**

<u>Evaluation</u>	<u>Content/Method</u>	<u>Frequency</u>
Standardized history		Annual
Standardized physical exam		Annual
Current Medications		Annual
Questionnaires		
	Health Insurance	Annual
	Health Status Questionnaire	Alternate years*
	Diabetes QOL	Alternate years
	Dietary-7 day recall	Alternate years – Discontinued in Jan 2009
	QWB-SA	Once
Retinopathy	7-field stereoscopic Fundus photography	Quadrennial
	Fundus exam, Visual Acuity, and IOP	Quadrennial
	NEI-VFQ-25 <sup>&amp;</sup>	Quadrennial
Nephropathy	4 hour urine <sup>@</sup> for albumin excretion and creatinine clearance, serum creatinine, and cystatin C	Alternate years
Neuropathy <sup>‡</sup>	Michigan Neuropathy Screening Instrument	Annual
	Quantitative sensory test	Once
	Autonomic Nervous System Testing	Once in Years 13 or 14 Once in Years 16 or 17
	NeuroQOL	Once
Cardiovascular disease	Ankle:brachial BP	Annual
	EKG	Annual
	Fasting lipid profile	Alternate years

\*Performed in one-half of the entire cohort every other year. Fasting studies such as lipid profiles will be synchronized.

<sup>‡</sup> Cardiac autonomic neuropathy (R-R intervals), quantitative sensory testing, and the Neuropathy Quality of Life (NeuroQOL) survey will be added (see neuropathy section)

<sup>&</sup> NEI-VFQ-25 is a quality of life measure specific to eye disease.

<sup>@</sup> Spot urine samples, corrected for creatinine, are being evaluated in the EDIC population as a measure of albuminuria. If they prove to be an acceptable measure, they may replace 4-hour collections.

QWB-SA—Quality of Well Being Scale (self-administered).

IOP—intraocular pressure.

Quadrennial—randomization anniversary divided by 4, i.e., 16, 20, 24, 28, 32, 36, etc.

## 5.16 Temporary Inactive Status

Transfer to inactive status is defined as a temporary or permanent moratorium on subject participation in the study. Transfer to inactive status is allowable in the following situations:

1. When in the judgment of the Principal Investigator and Study Coordinators, any manner of participation in the study would be directly injurious to the subject's well-being or could no longer be considered informed, e.g., catastrophic injury or illness resulting in coma, dementia.
2. Complete inaccessibility to monitoring of outcomes (for example, long-term imprisonment).
3. Subject withdraws consent for continuing participation in the trial.

## 5.17 Lost to Follow-Up

This is a category of patient status that can be determined only at the conclusion of the study. It is important, however, to realize that the number of patients who are lost-to-follow-up should be kept to a minimum.

## 5.18 NIDDK Central Repositories

The Biosample, Genetics, and Data Repositories have been established to store biosamples and data collected in designated NIDDK-funded clinical studies. The purpose of the NIDDK Central Repositories is to expand the usefulness of these studies by allowing a wider research community to access these materials beyond the end of the study. Sending samples to the NIDDK Repositories may provide valuable research material that can help other investigators to develop new diagnostic tests, new treatments, and new ways to prevent diseases. The clinics will not be directly involved in these activities, except for informing the patients and getting their consent that the specimens can be sent to a central repository.

**Table 5.3**  
**Visit Organization and Windows for Scheduling Visits**

Type of Visit	Visit Name	Window
I. ROUTINE PROTOCOL VISITS	A. Annual .....	Plus or minus 4 months
	B. Biennial.....	Plus or minus 4 months
II. MAKE-UP VISITS	A. Annual .....	Up to the opening of the next annual window
	B. Biennial.....	Up to the opening of the next annual window

**Table 5.4**  
**Equipment and Supplies**

**Blood Pressure for Hypertension**

- Sphygmomanometer, cuffs, and bladder (standard and large adult cuff sizes)
- Stethoscope

**Ankle/Arm Doppler**

- Medasonic Model BF4B
- Standard or large adult cuff
- Blood pressure gauge that goes up to 300 mm Hg
- Acoustical gel (NOT ECG gel)
- Table

**Ophthalmic**

- Zeiss FF series camera (Topcon used with CORU approval)
- 6 mm diameter opaque disk (Zeiss "black dot")
- Kodak Wratten filter, #81A (option suggested)
- Power supply modified to allow recharging within 1 to 2 seconds
- Haag-Streit 900 slit-lamp
- Film
  - Kodachrome (ASA25 or 64)
  - Ektachrome (ASA100)
  - Fujichrome (ASA50 or 100)
- Standard cardboard 2x2" readymounts
- 20-pocket 9x11" transparent plastic sheets. Stock number 62022C – 20 slide sideload clear page. 1-800-223-1357.
- Tonometer
- Head-mounted indirect ophthalmoscope and hand held condensing lens (14 or 20D Nikon Aspheric lens recommended)

**Acuity**

- ETDRS Visual Acuity Charts
-

**Table 5.4**  
**Equipment and Supplies**  
**(Continued)**

**Specimen Collection/Shipment - CBL**

- 10 ml red-topped serum tubes
- alcohol swabs
- tourniquet
- labels and barcodes
- refrigerator
- freezer (-20 C) [NOT autodefrost model]
- EDTA lavender topped tubes, 7 ml (T204Q, 13 x 100 mm)
- Trasylol for EDTA tubes
- 5 ml plastic cryotubes NUNC #1086-1
- Centrifuge
- Shipping containers, Polyfoam Packers Corp Model #355

**ECG**

- ECG machine, any modern with any number of channels
- ECG paper
- ECG gel

**Height/Weight**

- Height measure, either metal or wood mounted on the wall with a horizontal board to sit atop head
- Standard scale with regular calibration throughout the year

**Neurology**

- reflex hammer
- tuning fork
- 10 gm monofilament
- Vibratron II
- ANS 2000

**Waist-to Hip**

- tape measurement
-

## Appendix A

**Inclusion and Exclusion Criteria for Cardiac MRI** [amend according to local MRI inclusion/exclusion criteria].

Inclusion Criteria: Anyone who is a participant in the EDIC study may take part in the EDIC CMRI study UNLESS any of the CMRI exclusion criteria listed below is present.

Exclusion Criteria: [amend to include any local exclusion criteria not listed]

The patient cannot take part in the EDIC CMRI study if the;

- patient is pregnant.
- patient has a history of any metal in head or eyes.
- patient has a pacemaker, an implanted defibrillator or certain other implanted electronic or metallic devices.

The patient cannot take part in the Gadolinium test if the;

- patient is on dialysis, had a kidney transplant, or ever had a GFR < 60.
- patient had an allergic reaction to Gadolinium in the past.

**For safety purposes, it is critical that the GFR that is estimated be from a serum creatinine measured locally within 1 – 2 months before the Gadolinium test. The locally determined serum creatinine must be sent to the Data Coordinating Center where the GFR will be recalculated and sent to the study coordinator who will complete the screening process.**

## Appendix B

**Informed Consent for Participation in the Cardiac MRI in EDIC Continuing Follow-Up***(To be modified to meet local IRB Requirements)*

*The purpose of this document is to provide your site with some guidelines for submission of your site-specific consent form. You may choose to utilize a portion of this consent form language for inclusion in an existing consent form or you may choose to utilize the entire document for submission of a separate consent form. This language should only be considered a guideline.*

.....

**RESEARCH PARTICIPANT INFORMED CONSENT AND PRIVACY AUTHORIZATION FORM**

**Protocol Title:** Epidemiology of Diabetes Interventions and Complications Cardiac Magnetic Resonance Imaging (MRI) Study (EDIC CMRI)

**Application No.:**

**Principal Investigator:**

**Date:**

---

**A. PURPOSE AND BACKGROUND:**

*The purpose of Epidemiology of Diabetes Interventions and Complications (EDIC) is to examine the long-term effects of conventional vs. intensive diabetes treatment received during the DCCT on the development and progression of eye, kidney, nerve, and large blood vessel complications in diabetes. The EDIC study also examines factors, such as blood glucose control, blood pressure, cholesterol levels, smoking and medication use that may be associated with the risk for development and progression of diabetes complications.*

*Because you are a participant in the EDIC study, you are being asked to have a test called a Cardiac Magnetic Resonance Imaging (CMRI) study. People with type 1 diabetes may have greater risk for heart disease, blood vessel disease (atherosclerosis, sometimes called "hardening of the arteries") and "silent" heart attacks (that is, heart damage that occurs without any of the typical symptoms such as chest pain, arm pain, or chest pressure). The CMRI study in EDIC will provide information about the frequency and severity of these types of problems in people with type 1 diabetes.*

*The EDIC CMRI study is being done in collaboration with the Johns Hopkins University Magnetic Resonance Imaging Reading Center, (JHU MRI RC). If you agree to participate in this study, you will have a CMRI here at the [Local Institution] and the study itself will be sent to the JHU MRI RC for analysis. The JHU MRI RC will work closely with the EDIC study staff to analyze the information from all participants at all EDIC sites.*

This consent form explains the CMRI study and your part in the study. Please read it carefully and take as much time as you need. Please ask questions at any time about anything you do not understand.

**B. VOLUNTARY:**

Your participation in the EDIC CMRI study is voluntary. While you are in this CMRI study, the study team will tell you any new information that could affect whether you want to stay in the study. You may refuse to participate or even withdraw from the study at anytime. If you leave the EDIC CMRI study before it is finished, there will be no penalty to you and you will not lose any benefits to which you are otherwise entitled. If you choose not to participate in this study, it will not affect your participation in any other aspects of EDIC.

## Informed Consent for Participation in the Cardiac MRI in EDIC Continuing Follow-Up

### C. STUDY PROCEDURES:

The EDIC CMRI study will be done one time during EDIC years 14-15. This study uses magnetic resonance imaging (MRI) to make detailed images of your heart. Before having the CMRI done, you'll be asked to complete a questionnaire to make sure that you are able to safely enter the MRI area. This questionnaire is given to all people having CMRI performed at [site]. If you have a history of any metal in your head or your eyes, or if you are pregnant, you cannot have CMRI performed. Not taking part in the EDIC CMRI will not affect your participation in other parts of the EDIC study. If you are a woman, you will be tested for pregnancy with a urine test. If you are a woman and are breast feeding, it is recommended that you discontinue breast feeding for 24 hours after the test.

#### Serum Creatinine measurement of Glomerular Filtration (GFR):

Serum Creatinine measurement of Glomerular Filtration Rate (GFR): A small blood specimen for serum creatinine and calculated GFR will need to be obtained prior to the Gadolinium scan. (5 ml, or less than a teaspoon of blood, will need to be drawn in a lab either at your clinic on the day of test, or locally 1-2 months before the visit). GFR is estimated from serum creatinine using an equation that varies if the participant is a woman, non-Caucasian, and older. Therefore, if you are on dialysis or had a kidney transplant or ever had a GFR < 60 during DCCT or EDIC you will not complete the Gadolinium portion of this test. However, you may still participate in the remaining portions of the CMRI study

#### MRI Examination:

The effects of magnetic fields in a CMRI scanner have been extensively studied, and there are no known significant risks with an MRI exam. However, you may not participate in this study if you have a pacemaker, an implanted defibrillator or certain other implanted electronic or metallic devices. It is important for you to advise the EDIC MRI staff if you have had brain surgery for a cerebral aneurysm, or if you have implanted medical or metallic devices, shrapnel, or other metal, such as metal in your eye.

If you use an insulin pump or continuous glucose pens you will be asked to remove these devices during the CMRI scanning procedure. The study coordinator will work with you to minimize any impact this may have on your diabetes control.

The CMRI scanner is a long, narrow tube, and even though ends of the tube are open, you may be bothered by feeling confined (claustrophobia). If this is significant to you, please notify the CMRI staff. You may end your participation in this study at any time by telling the MRI staff.

If you are able to have CMRI testing, you will be asked to lie on a padded table. A device called an imaging coil will be placed on your body in the area where the images will be taken. The coil is necessary to help the MRI machine take pictures. The table on which you are lying will be moved to the center of a CMRI magnet, which looks like a long narrow tube.

When CMRI pictures are taken it is normal for the CMRI machine to make loud banging and clicking noises. You will be asked to wear earplugs or earphones for your comfort during the test.

#### Contrast Agent (Gadolinium)

Gadolinium is used routinely for CMRI exams to help identify the presence of scarring of the heart. You will be given a contrast agent call Gadolinium. This will be given as an injection through a vein in your arm. The Gadolinium contrast agent is used to make any cardiac scarring that is present easier to identify. Cardiac scarring occurs following heart attacks, and so this test will be useful especially for identifying "silent" heart attacks.

Insertion of the needle may cause minor pain, bruising and/or infection at the injection site. The Gadolinium itself does not cause pain but you may feel discomfort, tingling or warmth in the lips, a metallic taste in the mouth, tingling in the arm, nausea, or headache. These symptoms occur in less than 1% (less than 1 in 100) of people and go away quickly. Very rarely allergic reactions to Gadolinium have occurred, but the risk of severe allergic reaction is less than one in 300,000. There will be emergency personnel and equipment on hand for your safety. A physician will be

## Informed Consent for Participation in the Cardiac MRI in EDIC Continuing Follow-Up

available during the procedure to administer any necessary care if side effects do occur, and to determine when or if the injection of the contrast agent should be stopped.

Please notify the EDIC staff and CMRI technologist if you are allergic to gadolinium or experience any of these effects or other symptoms that concern you.

\*Special Note\* - In June 2006, the FDA released a public advisory regarding contrast agents containing gadolinium. They are investigating a potential relationship between gadolinium and the development of Nephrogenic Systemic Fibrosis/Nephrogenic Fibrosing Dermopathy (NSF/NFD) in patients with renal failure. The clinical picture of NSF/NFD involves the skin with hardening and plaque formation, flexion contractures of the joints, the liver, lungs kidneys and heart. There have been a few fatalities. Gadolinium is excreted by the kidney so people with chronic renal insufficiency have greater degrees of exposure through longer retention times.

GFR is estimated from serum creatinine using an equation that varies if the participant is a woman, non-Caucasian, and older. Therefore, if you are on dialysis or had a kidney transplant or ever had a GFR < 60 during DCCT or EDIC you will not complete the Gadolinium portion of this test. However, you may still participate in the remaining portions of the CMRI study. Also note that the GFR will be estimated from a Serum Creatinine that is measured locally within 1 – 2 months before the Gadolinium test.

During the exam, the CMRI staff is able to see and hear you. You will be able to hear the CMRI staff. The CMRI staff will be talking to you throughout your CMRI exam and may give you simple instructions regarding holding your breath, maintaining position, etc. You will generally be requested to lie perfectly still through out the exam. In most cases, the CMRI procedure can be completed within 1 to 2 hours.

The results of the CMRI exam will be made available to you and your own physician (s) or health care professional after they have been analyzed. The results will be added to the other data that have been collected in DCCT and EDIC.

### **What might interfere with the completion of your CMRI test?**

We may take you out of the study early or reschedule your study if you are unable to tolerate the CMRI examination for whatever reason or if the equipment malfunctions.

### **Inclusion and Exclusion Criteria [amend according to local CMRI inclusion/exclusion criteria].**

Inclusion Criteria: Anyone who is a participant in the EDIC study may take part in the EDIC CMRI study UNLESS any of the CMRI exclusion criteria listed below is present.

Exclusion Criteria: [amend to include any local exclusion criteria not listed]

You cannot take part in the EDIC CMRI study if;

- You are pregnant.
- You have a history of any metal in your head or eyes.
- You have a pacemaker, an implanted defibrillator or certain other implanted electronic or metallic devices.

You cannot take part in the Gadolinium test if;

- You are on dialysis, had a kidney transplant, or ever had a GFR < 60.
- You have had an allergic reaction to Gadolinium in the past.

**For safety purposes, it is critical that the GFR that is estimated be from a serum creatinine measured locally within 1 – 2 months before the Gadolinium test. The locally determined serum creatinine must be sent to the Data Coordinating Center where the GRF will be calculated and sent to the study coordinator who will complete the screening process.**

### **D. RISKS AND/OR DISCOMFORT:**

Time Commitment:**Informed Consent for Participation in the Cardiac MRI in EDIC Continuing Follow-Up**

Participation in this CMRI study will involve a commitment of up to several hours. The study coordinator will work with you and the local CMRI staff to help find a time that best fits your schedule. If possible, the study will be done on the same day that you come to the EDIC center for your other yearly tests.

You will ordinarily not be paid for travel expenses to the clinic conducting the examinations. You will not be paid for time lost from work. You will also not be provided with free medical care for any diabetes complications discovered during yearly visits. You will, however, be counseled as to what care would be appropriate and where and how to obtain it.

Risk of Loss of Privacy:

Your CMRI study will be identified using your EDIC study identification number, and not by information that personally identifies you. Information that could link your EDIC study identification number to your personal identity will not be

given to anyone outside of the EDIC study and will not be available to the staff at the JHU MRI RC or other third parties unless they have a legal right to view that information. Information about you collected for the EDIC study, including results from your CMRI are sent to the EDIC data coordinating center at The Biostatistics Center of The George Washington University for statistical analysis. Research records will be kept in restricted areas at **(name of center)**. Please review section G of this document for further details about the confidentiality of research information collected about you.

**WHAT SHOULD YOU DO IF YOU ARE INJURED OR ILL AS A RESULT OF BEING IN THIS CMRI STUDY?**

Call **(Institution PI, SC) at (Institution PI and SC Phone #)**, if you have an urgent medical problem or if you think you injured or ill because of your participation in this study.

Medical care at **(Institution)** is open to you as it is to all sick or injured people. **(Institution)** does not have a program to pay you if you are hurt or have other bad results from being in the study. The costs for any treatment or hospital care would be charged to you and/or your insurance company.

**E. BENEFITS:**

Because you have diabetes, you may benefit from the tests being conducted in this study because they may identify problems that would benefit from early detection and treatment. The results of the CMRI exam will be made available to you, and if you choose, to your personal health care professional, once they have been analyzed. The information gathered during this study will also continue to be of great benefit to society at large and other patients with diabetes in particular.

**F. COST/PAYMENT:**

All of the tests conducted in this CMRI study will be performed at no cost to you or to your insurance carrier. However, if any of the tests performed for CMRI reveal a condition that may require additional testing or evaluation, you or your insurance carrier will be responsible for those charges. You, or your insurance company, will still be responsible for the costs associated with any procedures that were ordered by your health care professional as part of your routine care.

**Will you be paid if you join this study?**

You will not be paid if you participate in this study.

**G. CONFIDENTIALITY:****How will your privacy be protected?**

## Informed Consent for Participation in the Cardiac MRI in EDIC Continuing Follow-Up

**(Institution)** has rules to protect information about you. Federal and state laws also protect your privacy. This part of the consent form tells you what information about you may be collected in this study and who might see or use it.

Generally, only people on the EDIC research team will know that you are in the study and will see your information. However, there are a few exceptions that are listed later in this section of the consent form. Unless you give permission or the board that reviews research studies approves it, no one else will be able to see or use your information.

The people working on the study will collect information about you. This includes things learned from the tests described in this consent form. They may collect other information including your name, address, date of birth, and other details.

Sometimes other people at **(Institution)** may see or give out your information. These include people who review the research studies, their staff, lawyers, or other **(Institution)** staff.

People outside of **(Institution)** may need to see your information for this study. Examples include government groups, safety monitors, other hospitals in the study, and organizations that sponsor the study.

We cannot do this study without your permission to use and give out your information. You do not have to give us this permission. If you choose to not provide your permission, you may not be able to participate in CMRI study.

We will use and share your information only as described in this consent form and in our Notice of Privacy Practices. However, people outside **(Institution)** who receive your information also will be asked to not share your information.

We try to make sure that everyone who needs to see your information keeps it confidential – but we cannot guarantee this.

The use of your information has no time limit. You can cancel your permission to use and disclose your information at any time by calling the **(Institution)** IRB at \_\_\_\_\_ or by sending a letter to:

### **(Institution) IRB Address**

Your cancellation would not affect information already collected in this study.

### **Will the study require any of your other health care providers to share your health information with the researchers of this study?**

By participating in this study, you are providing researchers involved with this study permission to access your medical records. If you do not want researchers involved in this study to have access to your medical records, you should not participate in this study.

*What is the Institutional Review Board (IRB) and how does it protect you?*

The **(Institution)** IRB is made up of:

- Doctors
- Nurses
- Ethicists
- Non-scientists
- People from the local community.

The IRB reviews human research studies. It protects the rights and welfare of the people taking part in those studies. You may contact the IRB if you have questions about your rights as a participant or if you think you have not been treated fairly. The IRB office number is **(Institution IRB phone #)**. You may also call this number for other concerns or questions about the research.

## Informed Consent for Participation in the Cardiac MRI in EDIC Continuing Follow-Up

### H. CONTACT INFORMATION:

6. WHAT ARE THE ORGANIZATIONS THAT ARE PART OF (INSTITUTION)?

(Institution) includes the following:

- The (Institution) University
- The (Institution) Hospital
- Etc...

**What do you do if you have questions about the study?**

Call the principal investigator, (Institution PI) or study coordinator (Institution SC) at (Institution SC Phone #). If you cannot reach the principal investigator study coordinator or wish to talk to someone else, you may call the IRB office at (Institution IRB Phone #)

### I. RECORD OF INFORMATION PROVIDED:

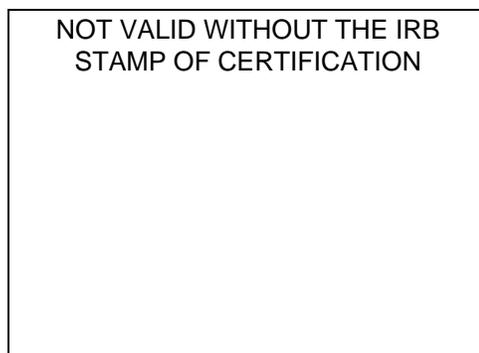
**What does your signature on this consent form mean?**

Your signature on this consent form means that:

- you understand the information given to you in this form
- you accept the information contained in this form
- you agree to participate in the EDIC CMRI study

You will not give up any legal rights by signing this consent form.

**WE WILL GIVE YOU A COPY OF THIS SIGNED AND DATED CONSENT FORM**



*Do not sign after the expiration date of: \_\_\_\_\_*

\_\_\_\_\_  
Signature of Participant

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature of Person Obtaining Consent

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature of Witness to Consent Procedures (optional unless IRB or Sponsor required)

\_\_\_\_\_  
Date

**NOTE: A COPY OF THE SIGNED, DATED CONSENT FORM MUST BE KEPT BY THE PRINCIPAL INVESTIGATOR; A COPY MUST BE GIVEN TO THE PARTICIPANT; AND IF APPROPRIATE A COPY OF THE CONSENT FORM MUST BE PLACED IN THE PARTICIPANT'S MEDICAL RECORD**

## 6. INTERNAL MONITORING

### 6.1 General Principles

The Study Group will institute mechanisms for continuous performance monitoring of all study units. In any long-term longitudinal study, maintaining a high rate of patient follow-up is difficult but essential. An overall study rate of follow-up of at least 90% will be the goal. Remedial efforts will be mandated for any clinic that consistently fails to meet this goal. These efforts include site visits for any clinic that is achieving less than 60% of expected data, and has required 2 contacts per year. External quality control surveillance will be instituted to assess the precision of all measurements made by the Central Biochemistry Laboratory (CBL), Central Ophthalmologic Reading Unit (CORU), Central ECG Reading Unit, and the Central ANS Reading Unit. Appropriate tabulations of indices of performance will be reported periodically to the appropriate study committee and to the individual study unit.

### 6.2 Responsibility for Monitoring

Performance monitoring of each study unit will be conducted by working committees of the Study Group. The Data Coordinating Center will participate in monitoring all study units by preparing tabulations of performance indices, by participating in site visits, and by maintaining permanent records of the performance of each study unit. Responsibilities of the working committees are as follows:

- a) Quality Assurance
  - i) History and physical data; doppler measurements
  - ii) Central Biochemistry Laboratory
  - iii) Central Ophthalmologic Reading Unit
  - iv) Central ECG Reading Unit
  - v) Central ANS Reading Unit
  - vi) **Central CMRI Reading Unit**
- b) Follow-Up Committee-- Clinical Centers and patient retention and adherence to the outcome schedule.

### 6.3 Performance Monitoring

#### 6.3.1 Clinical Centers

The Follow-Up Committee will monitor all aspects of clinical center performance regularly. The Follow-Up Committee established the Adherence Monitoring Committee to monitor adherence to follow-up schedules and standardization of study procedures. The Adherence Monitoring Committee holds a conference call every six weeks to evaluate the timeliness of the data and the completion of study visits. Review of performance data shall be conducted with sufficient frequency to allow timely detection of deviations from expected

performance. Such deviations shall be investigated by the Adherence Monitoring Committee and corrective actions recommended to the clinical center.

Each central unit has established mechanisms by which the standardization of procedures performed by the individual clinical centers can be assessed and monitored. The Quality Assurance Committee and the Executive Committee will review these periodically.

### **6.3.2 Central Units**

#### **Central Biochemistry Laboratory**

External quality control surveillance programs have been established to monitor the performance of the CBL. This will entail the masked submission of duplicate specimens from the clinics for analysis by the laboratory. The resulting data will allow an assessment of the on-going precision of the laboratory test results. Bench quality control assessment, though useful, is insufficient because laboratory performance alone is but one step in a chain of activities that could influence the test results. A program of external duplicate surveillance will allow assessment of the total system starting with the collection of a specimen in the clinic and ending with the entry of the data into the Data Coordinating Center computer. The duplicate quality control data are analyzed periodically by the Data Coordinating Center and presented to the Data Quality Assurance Committee for review. Any deficiencies detected will be investigated and corrected.

#### **Central Ophthalmologic Reading Unit**

Likewise, an external quality control surveillance program has been established for the CORU that entails the duplicate masked evaluation of fundus photographs estimating the reproducibility of the grading system. These data are analyzed periodically by the Data Coordinating Center and presented to the Quality Assurance Committee for review. Any deficiencies detected will be investigated and corrected. In addition, the quality of the photographs is reviewed periodically to determine if there are any clinic-specific problems with the photographs. If any quality problems are detected, the photographer is contacted and made aware of the problem and the photographing procedures are reviewed with the photographer.

#### **Central ECG Reading Unit**

An external quality control surveillance program has been established for the Central ECG Reading Unit that entails the duplicate masked evaluation of ECGs estimating the reproducibility of the grading system. In addition, the Quality Assurance Committee reviews the quality of the ECGs. If any clinic-specific problems are discovered, the ECG technician is contacted and a memo reviewing the proper procedures is sent.

#### **Central ANS Reading Unit**

Quality control measures will be developed for the Central ANS Reading Unit

#### **Central CMRI Reading Unit**

Quality central measurements will be developed for the unit.

#### **Forms**

The Quality Assurance Committee also monitors certain data from the EDIC forms on a regular basis. For example, blood pressure data, ankle/arm index data, and overall error rate on the form. As the EDIC progresses, any other data that is determined to be critical to the study will also be monitored very closely.

#### **6.4 Correction of Deficiencies**

If monitoring procedures detect deficiency in the performance of any study unit, the matter will be investigated by the Quality Assurance Committee and then considered by the Executive Committee and/or Steering Committee. Expert consultants will be used as necessary. Steps will then be instituted to correct the deficiency. If, after a reasonable period, deficient performance persists, the matter will be referred to the External Advisory Committee.

## 7. STUDY ORGANIZATION

### 7.1 Introduction

The organizational structure of the EDIC has been developed to coordinate the activities of the necessary committees, laboratories, units and review groups, and to facilitate the conduct of this study by ensuring careful and uniform adherence to the Protocol and Manual of Operations. In Figure 7.1, the organization of EDIC is depicted.

### 7.2 Structure

The Director of the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK) is responsible for the use of institute funds and the management of Institute programs. He bears ultimate responsibility for the conduct of the EDIC and serves as the final decision-maker for all major issues affecting the EDIC. The Institute Director appoints the Chair and members of the oversight group.

The Director, Division of Diabetes, Endocrinology and Metabolic Diseases (DEMD), is the principal representative of the Director of NIDDK and is responsible for ensuring that the scientific, and technical goals of the study are consistent with the mission and responsibilities of the NIDDK.

Within the Diabetes Program Branch of the DEMD Division, the Diabetes Epidemiology Program Office provides liaison between the EDIC Study Group and the NIDDK. This office represents the Institute in all matters that concern the administrative, scientific, and technical direction of the study. A program representative is a member of the study's Executive and Steering Committees and Study Group and an ex-officio member of each of the working committees.

The **External Evaluation Committee (EEC)** appointed by the Director, NIDDK, will consist of experts in clinical diabetes, epidemiology, data management, and statistics to periodically review the progress of the study and advise the NIDDK and the study group. This committee will comprise individuals who are independent of the conduct of the study, and it will be chaired by an individual selected by the Director, NIDDK who is also independent of the operational events of the study group. The committee may be augmented with ad hoc members as necessary. The committee will meet at least every two years, or more often if needed, with representatives of the NIDDK, the study group, the clinical coordinating center, the data coordinating center, and such others as necessary. The committee will review statistical and narrative reports prepared by the NIDDK and/or the study group addressing the progress and operational aspects of the study.

Responsibilities of this committee will include the following:

1. If the study group believes that an objective of the study has been reached, this committee will review the evidence for that conclusion and recommend to the NIDDK whether or not early release of this information is prudent.
2. Review of all activities that affect the operational and methodological aspects of the trial, including quality control procedures and performance of clinical centers, data and clinical coordinating centers, and central facilities.
3. Review of study data to ensure the quality of the data and procedures for analysis. The committee may request specific data analyses needed for clarification of specified

questions; they may advise the study group on the content of study reports and manner of data display; and they may provide advice to the Director, NIDDK, and the study group regarding interpretation and implications of the results.

4. Review of all proposed major modifications to the protocol or Operations Manual in order to advise the NIDDK and the study group as to the appropriateness, necessity, and impact of the proposed modification on the overall objectives of the study.
5. Preparation of reports to the NIDDK and the study group on the progress of the study following each meeting with particular attention to important issues or problems identified and recommendations for appropriate actions.

The Study Group/Steering Committee is the representative body of all study participants. It is comprised of a Chair, the Principal Investigator and Study Coordinator from each of the clinical centers, one representative from the NIDDK Clinical Studies Program Office, and one representative from the Data Coordinating Center. It provides overall scientific direction for the study through consideration of recommendations from the working committees. The business of the Study Group is conducted in accordance with customary parliamentary procedures. Members unable to attend a meeting may designate an alternate to act on their behalf.

The Executive Committee acts on behalf of the Study Group during the intervals between Study Group meetings and makes the day-to-day management decisions needed for the study to proceed in a smooth, efficient, and orderly way. The Executive Committee is comprised of the Chair of the Study Group and Chair of the Steering Committee (the study co-chairs), the Principal Investigator and Director of the Data Coordinating Center, Principal Investigator of the Clinical Coordinating Center, and the Program Officer from the Diabetes Clinical Studies Program Office. A Vice-Chairman, who will also assume leadership of the Analytical/Editorial Committee, has recently been added to the Executive Committee. Actions taken by the Executive Committee will be reported at the next meeting of the Study Group and major decisions (e.g., those that in the opinion of any member of the Executive Committee may affect the integrity of the study or require a Protocol change) will be made only after consideration by the Study Group and approval by the majority of voting members present.

The working committees that support the Study Group are: Follow-Up, Data Quality, Analytical/Editorial, and Research Review. These committees are appointed by the Study Group Chair from among the professional personnel from each of the clinical centers, the Data Coordinating Center staff, the NIDDK staff, and necessary consultants. The members of the Executive Committee are ex-officio members of each of the working committees.

More description is provided below regarding the nature of the activities of the clinical centers, the working committees, the Clinical Coordinating Center, the Data Coordinating Center, and the central study units.

1. Clinical Centers. The clinical centers are staffed by a Study Coordinator and other necessary personnel under the supervision of a Principal Investigator. The Principal Investigator will work with the Coordinating Center, Chair of the EDIC Study Group, and NIDDK staff assigned to this project to conduct the study in accordance with the Protocol and Manual of Operations. The clinical centers are expected to perform the following functions:
  - a) Obtain informed consent from all patients.
  - b) Maintain contact with all patients.
  - c) Schedule, perform and arrange for performance of all procedures within specified times.

- d) Collect and ship properly all specimens.
- e) Receive results from central labs and reading units and transmit them promptly to patients and their physicians.
- f) Maintain files of results for response to interval requests for information.
- g) Obtain validating information on all patient-reported outcome events.
- h) Provide advice and support to patients regarding adequacy of glycemic control and need for specialty consultation, but without providing direct diabetes management unless by physician-patient contract.
- i) Keep patients up to date on pertinent advances in diabetes research and diabetes care.
- j) Prepare yearly budgets.

See Table 7.1 for a list of the 28 clinical centers.

2. Working Committees. All working committees have specific responsibilities as outlined below and will assume such other responsibilities as requested by the Study Group or Executive Committee(s).

- a) **The Follow-Up Committee** will assist the Data Coordinating Center in monitoring the completeness of the data being collected and will develop strategies intended to optimize patient adherence. Specifically:
  - monitor adherence of volunteers,
  - monitor completeness and promptness of data collection,
  - develop strategies to maintain adherence, and
  - recommend methods for remediation of problems.
- b) **The Quality Assurance Committee** will assist the Data Coordinating Center in monitoring the performance of the central units (Central Biochemistry Laboratory, Central Ophthalmic Reading Unit, Central ECG Reading Unit and the Central Ultrasound Reading Unit) and will consider any proposals for changes in procedures as specified in the Protocol and the Operations Manual. Specifically:
  - monitor quality of data collection,
  - monitor performance of central units, and
  - review and recommend proposals for addition or change of procedures.
- c) **The Analytical/Editorial Committee** will review the accumulating data, the appropriate analyses thereof, and will decide on the timing and content of publications and presentations. Specifically:
  - review accumulating data,
  - review and develop analyses of the data,
  - recommend what and when to present and publish, and
  - oversee the activities of the manuscript writing teams.
- d) **The Research Review Committee** will review all research requests for use of study patients, study specimens or accumulating study data. Specifically:
  - review requests for the use of study volunteers,
  - review requests for use of study specimens,
  - assist NIDDK in reviewing requests for use of stored DCCT specimens, and
  - review proposals for expansion or contraction of EDIC.

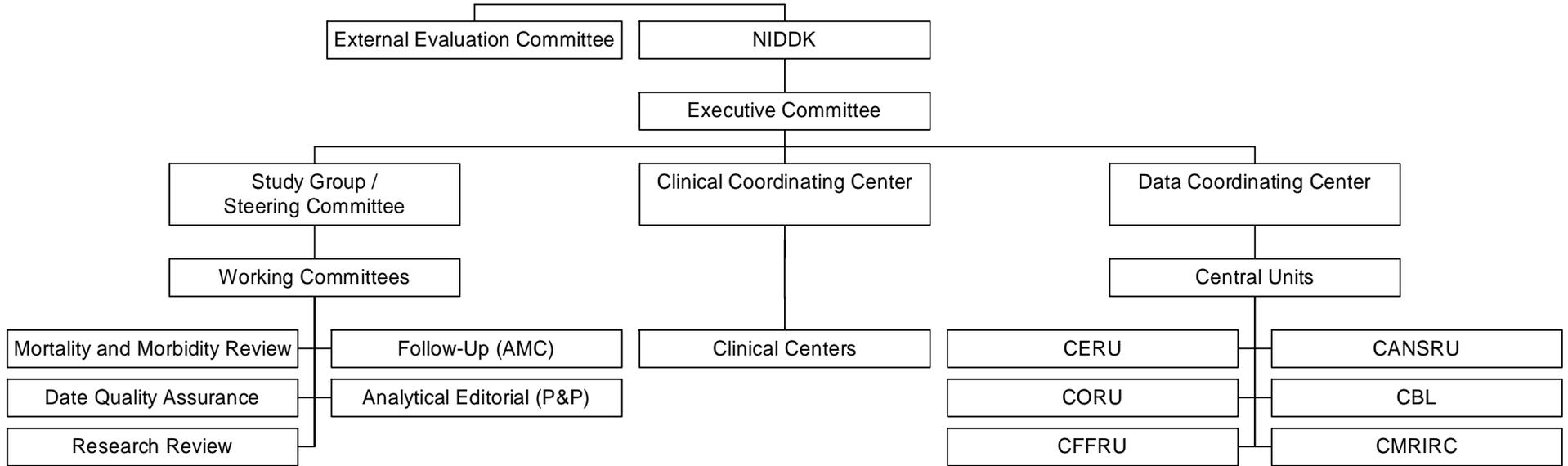
- e) **The Mortality and Morbidity Review Committee (MMRC)** will review pertinent materials documenting all identified deaths and reported non-fatal cardiovascular outcome events in the EDIC cohort, specifically:
- myocardial infarction (as a result of a procedure or not),
  - coronary artery disease (as defined by documented atherosclerotic disease resulting in the need for or actual coronary artery bypass or angioplasty),
  - angina resulting in hospitalization (confirmed by angiography and/or ischemic changes on testing or unconfirmed)
  - peripheral artery bypass or revascularization,
  - amputations,
  - strokes, and
  - transient ischemic attacks.

The materials will be forwarded to the Data Coordinating Center from the clinical centers where they are masked to the participants' identities, clinic center, and randomization group. The MMRC, which consists of individuals with appropriate clinical and methodological expertise, will review each reported outcome against established criteria. The reviews will be returned to the Data Coordinating Center, where the results will be tabulated. If a majority of the reviewers agree, the review is judged as complete. If there is no agreement, the event is adjudicated by discussion at a meeting of the committee.

3. Clinical Coordinating Center: The Clinical Coordinating Center (CCC) will provide overall coordination of all fiscal aspects of the study. The Center will manage protocol implementation and oversee all aspects of the 28 clinical centers' performance. The CCC will prepare the annual report and budget request. The Director of the Coordinating Center will serve on the EDIC Executive Committee. He will interact with the Director of the DCC weekly to review progress and problems. Together they will create the agenda for the Executive Committee's conference calls. If any clinic experiences problems that require a site visit, the CCC will arrange the visit.
4. Data Coordinating Center. The Data Coordinating Center will participate in all aspects of the design and implementation of the EDIC. The Principal Investigator and the Director of the Coordinating Center are members of the Steering Committee and the Executive Committee. Coordinating Center personnel will provide scientific, technical and staff services to the Study Group and each of its working committees/groups. The Data Coordinating Center has the responsibility for implementing the systems necessary for data collection, editing, management, and statistical analysis and for the maintenance of permanent study records and files. They have the responsibility of providing appropriate and timely data reports to the Executive Committee, the oversight committee, and to the NIDDK Director. They are responsible for all aspects of intrastudy communication and will work with the Analytic/Editorial Committee in providing appropriate statistical analyses of study data in a timely fashion for use in approved publications and presentations. The Data Coordinating Center will implement its responsibilities as specified in its internal procedures manual, ensuring that study data are safely maintained and not released in an unauthorized manner. The following five central units are the responsibility of the Data Coordinating Center. In general, these units provide scientific and technical guidance to the Study Group, specific working committees, and the Data Coordinating Center.

- a) **Central Ophthalmologic Reading Unit:** The Central Ophthalmologic Reading Unit will receive and evaluate the quality of all photographs of the eye; utilize the final ETDRS classification system for evaluating the grading of fundus photographs and maintain study records of all photographic data.
- b) **Central Biochemistry Laboratory:** The laboratory will provide baseline and repeated measurements of HbA1c, lipids, and serum and urine constituents.
- c) **Central ECG Reading Unit:** The Central ECG Reading Unit will provide baseline and follow-up coding of all ECG tracings from eligible patients.
- d) **Central Food Frequency Recall Unit:** The Central Food Frequency Recall Unit will code the food frequency recall questionnaire that the patients complete every year.
- e) **Central ANS Reading Unit:** The Central ANS Reading Unit will read and analyze the ANS data recorded for each eligible patient.
- f) **Central CMRI Reading Center:** The Central MRI Reading Center will collect and analyze all images and data, and assess the categories of disease ((cardiac dysfunction, accelerated atherosclerosis, and myocardial scar (silent MI)) that can readily be probed by MRI.

**Figure 7.1**  
**Organization Chart for the Epidemiology of Diabetes Interventions and Complications**



*CERU* = Central ECG Reading Unit  
*CORU* = Central Ophthalmologic Reading Unit  
*CBL* = Central Biochemistry Laboratory  
*CANSRU* = Central ANS Reading Unit  
*CFFRU* = Central Food Frequency Reading Unit  
*CMRIRC* = Central MRI Reading Center

**Table 7.1**  
**List of Clinical Centers by Clinic Number**

Case Western Reserve University (01) Cleveland, OH	University of Washington (17) Seattle, WA
University of Pennsylvania (02) Philadelphia, PA	University of Western Ontario (18) London, Ontario, Canada
Cornell University Medical College (03) New York, NY	Vanderbilt University (19) Nashville, TN
Henry Ford Medical Center-New Center One (04) Detroit, MI	Washington University at St. Louis (20) St. Louis, MO
Joslin Diabetes Center, Inc. (05) Boston, MA	Yale University School of Medicine (21) New Haven, CT
Massachusetts General Hospital (06) Boston, MA	Albert Einstein College of Medicine (22) Bronx, NY
Mayo Clinic (07) Rochester, MN	Northwestern University (23) Chicago, IL
Medical University of South Carolina (08) Charleston, SC	University of California - San Diego (24) La Jolla, CA
International Diabetes Center (09) Minneapolis, MN	University of Maryland (25) Baltimore, MD
University of Iowa (10) Iowa City, IA	University of New Mexico School of Medicine (26) Albuquerque, NM
University of Minnesota (11) Minneapolis, MN	University of South Florida College of Medicine (27) Tampa, FL
University of Missouri (12) Columbia, MO	University of Michigan (41) Ann Arbor, MI
University of Pittsburgh (13) Pittsburgh, PA	
University of Tennessee (14) Memphis, TN	
University of Texas (15) Dallas, TX	
University of Toronto (16) Toronto, Ontario, Canada	

## 8. POLICY MATTERS

### 8.1 Editorial Policy

The Editorial/Analytic Committee will coordinate, monitor, review, and assume responsibility for arranging the preparation of all press releases, interviews, presentations, and publications relating to the study. Recommendations will be presented to the Executive Committee or Study Group for approval.

### 8.2 Duties of the Editorial/Analytic Committee

Specifically, the Committee shall:

1. Recommend policy and procedures for review and approval of all communications (written and spoken) regarding the long-term follow-up to outside groups.
2. Identify publications to be written during the course of the study, with target dates for each.
3. Propose policy guidelines for authorship of publications, and/or recommend to the Study Group senior authors and co-authors for each paper.
4. Monitor the writing of each paper to ensure publication in a timely fashion.
5. Establish standards of excellence for publications.
6. Review, edit and approve all publications and presentations prior to submission, enlisting the special assistance of the appropriate committees whenever appropriate. The review will be conducted pursuant to the following editorial policy:
  - a) To ensure that all publications preserve the scientific integrity of the study.
  - b) To correct factual and conceptual inaccuracies if necessary.
  - c) To safeguard the rights of volunteer participants.
  - d) To prepare comments to assist collaborating scientists in publishing papers of the highest quality and clarity.
  - e) To inform the Study Group, NIDDK, and advisory groups of all public dissemination of information about the study and coordinate press releases with the NIDDK.
  - f) To avoid conflict with and/or duplication of other publications.
  - g) To coordinate all major releases of study data with NIDDK.
7. Review, suggest necessary revisions, and approve any publications arising from approved ancillary studies prior to their submission for publication. In addition to the issues cited in the editorial policy above, proposed publications of ancillary

studies will be scrutinized to ensure that their presentation will not threaten the viability of EDIC.

8. Suggest appropriate journals for publications and monitor the process of publication.
9. Perform other writing, reviewing, or editing tasks assigned by the EDIC Study Group or its Executive Committee (EC).

### **8.3 Specific Definitions and Policies**

#### **8.3.1 Press Releases and Interviews**

A press release is defined as a document given to radio, television, newspapers, popular periodicals, or scientific journals not indexed in the Index Medicus. An interview is any discussion with a member of the press, a science writer, or a radio or television commentator, which in turn provides information for public dissemination.

Press releases and interviews will not be initiated by clinical centers. Centrally prepared press releases will be reviewed by the Editorial/Analytic Committee and distributed to the centers. It is suggested that these prepared releases be given to the media when interviews are requested. This procedure will help ensure uniformity and accuracy in the information disseminated through the media. In this instance, use of such press releases and interviews need not have received prior approval from the Editorial/Analytic Committee. If a center is solicited for a press release or interview, then such may be given without prior review and approval by the Editorial/Analytic Committee provided that the substantive content is limited to information available either in the final Protocol, the Manual of Operations, or in papers already published as peer reviewed articles, with no added interpretations or inferences.

Should a clinical center be solicited for information other than that detailed above, then the clinical center should refer the soliciting party to the Chairman of the Editorial/Analytic Committee.

#### **8.3.2 Presentations**

A presentation is the delivery of information to scientific, professional, or public groups, such that public dissemination might ensue through publications, press releases, etc.

A presentation may be given without prior review and approval by the Editorial/Analytic Committee provided that the content is limited to substantive information available in either the final Protocol, the Manual of Operations, or other published data, with no added interpretations or inferences.

All EDIC presentations involving any "new" data (not published as peer reviewed article) must be reviewed by the Editorial/Analytic Committee as described below:

1. Forum Identification: The Editorial/Analytic Committee will identify scientific and professional forums where presentations about EDIC should be made on behalf of the group. Suggestions for such forums and topics for presentations will be sought from the Editorial/Analytic Committee itself and individual investigators and brought to the Study

Group for approval. The Editorial/Analytic Committee will identify one or more persons from a list of volunteer investigators to prepare and present the material.

2. Invited Presentations: If members of the EDIC Research Group are personally invited to present EDIC data or represent the EDIC Study Group the invitation must be forwarded to the Editorial/Analytic Committee as soon as possible. The Editorial/Analytic Committee reserves the right to accept or not accept the invitation and suggest a presenter other than the EDIC Research Group member who received the original invitation.
3. Preparation and Review Schedule:
  - a) Requests for additional data from the Data Coordinating Center must be made sufficiently early to allow for delivery of the data requested (at least 60 days).
  - b) An abstract for a proposed presentation must be received by the Editorial/Analytic Chairman at least 14 days prior to the scientific society's deadline for receipt of abstract to provide time for review, possible revision, and rewrite.
  - c) A copy of the abstract is to be distributed by the Editorial/Analytic Chairman to each EDIC center and the NIDDK at least 60 days before presentation.
  - d) A presentation script (talk copy) with tables (bibliography not required) must be sent to the Editorial/Analytic Chairman at least 4 weeks prior to the scheduled presentation.

For an invited presentation for which there is no scientific society abstract review, an abstract should be prepared and submitted to the Editorial Board at least 60 days plus 2 weeks prior to the presentation to allow Editorial/Analytic Committee review and distribution of the abstract to the EDIC centers 60 days prior to presentation. Data requests and presentation scripts for invited presentations have the same deadlines as indicated in a) and b) from above.

### **8.3.3 Publications**

A publication is any document submitted to a professional journal listed in the Index Medicus or any popular periodical with national circulation. All publications of results of the EDIC will be prepared under the overall review of the Editorial/Analytic Committee. Publication of results of ancillary studies by individual investigators will be allowed with approval by the Editorial/Analytic Committee. It must be recognized that approval of publications or presentation of ancillary studies that may jeopardize the outcome of the EDIC may be withheld until such time as is deemed appropriate by the Editorial/Analytic Committee.

1. Journal Identification: The Editorial/Analytic Committee will suggest (or endorse) the choice of an appropriate journal for the publication of each proposed manuscript so that the manuscript can be prepared according to the guidelines of a specific journal and be direct towards its known leadership.
2. Preparation and Review Schedule: The Editorial/Analytic Committee will select a writing group of three to seven individuals for each proposed manuscript. One individual will be designated as Chairman and will be responsible for ensuring that the first draft of the publication is written. The first draft should be produced within 6 months following approval by the Study Group.

A reasonable number of data tabulations will be prepared by the Coordinating Center to assist the writing group for each manuscript. The Co-Directors of the Coordinating Center will designate one of their staff to work with each writing group in order to provide liaison and resource material for their particular manuscript.

The final manuscript will be reviewed by the Editorial/Analytic Committee and distributed to each EDIC center (each sub-specialty paper will be sent to the designated specialists in the clinic) and the NIDDK.

Fourteen days after distribution to the EDIC centers and the NIDDK, a paper approved by the Editorial/Analytic Committee may be submitted for publication. Any member of the EDIC Study Group wishing to comment on the paper must communicate his/her concerns to the Editorial/Analytic Chairman within the 14 days. The Editorial/Analytic Chairman will delay the submission until resolution is reached.

#### **8.3.4 Standards of Excellence**

In addition to the review system established for the critique of publications and presentations as described in the previous section, the following guidelines are suggested for maintaining the highest standards of excellence for EDIC publications and presentations.

If, in the opinion of the members of the Editorial/Analytic Committee, there is no member of the EDIC who has sufficient scientific background to review the pertinent material, then outside expert consultants will be selected by the Editorial/Analytic Committee and asked to critique the material. However, it is expected that sufficient expertise will be available from the members of the Study Research Group to provide a review of all publications and presentations.

For the major publications and presentations, the completeness or adequacy of the reports may be assessed by the following criteria:

1. Purpose of the report should be clearly stated.
2. Selection of the population exclusion criteria should be explicitly delineated.
3. Information on the loss of subjects during the study including reasons for loss to followup. Data should be presented to demonstrate comparability of the subjects who participated and who exited from each treatment group throughout the followup.
4. Information regarding the efforts made to achieve masking to defend against the introduction of additional bias.
5. Information on the exact statistical tests should be presented as well as a presentation of the actual data.
6. Information on the estimated range of treatment effects, i.e., use of confidence intervals in reporting results.
7. Information on the power to assure the reader of the strength of the conclusion, if a negative conclusion is reached.

8. Significance testing should be used in conjunction with an empirical review of the data.

## 8.4 Authorship

### DCCT/EDIC Publication and Authorship Policy

The DCCT/EDIC study has evolved since its inception from a randomized controlled clinical trial to an observational study of individuals with type 1 diabetes. We have successfully developed broad based collaborations with investigators outside of the DCCT/EDIC Research Group who are making unique contributions to our understanding of type 1 diabetes and its associated complications. In addition, a major component of our database, as well as study participant samples, are part of the NIH repository and many non-DCCT/EDIC affiliated groups are authoring papers based on the DCCT/EDIC data base. In this context, it is appropriate to reexamine our publication and authorship policies that have evolved with the following goals: 1. to maintain the rate of high-quality manuscripts reflecting the scientific output of DCCT/EDIC; 2. to provide the opportunity for as many members of the DCCT/EDIC group as possible to participate in the development and writing of papers; and 3. to provide appropriate attribution and recognition to those individuals who are responsible for the development, analyses, and writing of the manuscripts while not losing sight of the collective nature of the research efforts that underlie all of the clinical science advances from DCCT/EDIC. The paper categories are classified as follows.

- i. Primary Manuscripts: These papers address the major, i.e. primary, outcomes of the DCCT/EDIC study, e.g. effects of the DCCT randomly assigned interventions and/or glycemia and related mechanisms on major outcomes such as microvascular and cardiovascular disease.
- ii. DCCT/EDIC Other Outcomes Manuscripts: These papers report analyses of outcomes other than primary outcomes, and of metabolic intermediates and biomarkers, or epidemiologic analyses. These manuscripts would include analyses that use the database from all participating centers, as well as analyses of subsets or sub-cohorts of the complete cohort. They would also include sub-studies and ancillary studies conducted as additional initiatives beyond the initial DCCT/EDIC protocol.
- iii. Methodology Manuscripts: These papers focus on methodological issues, and do not include any new or original study outcome results. Such papers may include data generated from DCCT/EDIC to address a methodological objective that is not a DCCT/EDIC objective or outcome.

Responsibility for the category assignment for all manuscripts will rest with the Publications and Presentations Committee, in consultation with the Executive Committee, usually at the time that the manuscripts are planned.

The above classifications also apply to presentations, with the exception that classification occurs prior to abstract submission.

The following authorship principles will apply.

- I. Category 1 (Primary) Manuscripts: The authorship in the journal masthead will be the DCCT/EDIC Research Group. The complete list of investigators appears as part of the manuscript, usually in an appendix at the end of the manuscript, as negotiated with the journal. The writing team for these

papers will be identified in the manuscript in a footnote or as an entry in the appendix, according to individual journal requirements and style.

- II. Category 2 (Other Outcomes) Manuscripts: The authorship will be the writing team. For example, A Smith (Chairperson), A, B, C and the DCCT/EDIC Research Group.
- III. Category 3 (Methodologic) Manuscripts. Authorship Q, C, A, B+

+Acknowledge Research Group as appropriate (complete list of the Research Group can be found in Diabetes, 35:530-45, 1986).

## 8.5 Research Review

Ancillary studies will be evaluated with careful consideration of their potential impact on the objectives and performance of the EDIC. Ancillary studies that complement the objectives and thereby enhance the value of the study are to be encouraged. Such studies should augment and promote the continued interest of both subjects and investigators. To protect the integrity of the major study, a proposal to conduct an ancillary study must be reviewed and approved by the Research Review Committee before its initiation. Ancillary studies must also be approved by the Study Group. All approved ancillary studies will be reviewed yearly by the Research Review Committee for progress and impact on the study as a whole.

### 8.5 Definition of an Ancillary Study

An ancillary study is defined as research or data collection involving study subjects or specimens, using any technique, medication, procedure, questionnaire, or observation other than those set forth in the Protocol.

The investigator responsible for the conduct of an ancillary study must be a member of the Study Group. If an external research request is made by an individual who is not a member of EDIC, a member of the Study Group must be a co-investigator.

#### 8.5.1 Reason for Requirement of Approval

Investigators and subjects are entitled to prior assurance that all ancillary studies are of high scientific merit and that no ancillary study will:

1. Cause a deviation from the Protocol.
2. Confound interpretation of the study results.
3. Adversely affect subject cooperation.
4. Jeopardize the public image of the study.

5. Create a significant diversion of the study resources locally or at the Coordinating Center or any other unit.
6. In any way negatively influence the cooperative spirit of the collaborating investigators.
7. Otherwise compromise the scientific integrity of the study.

### **8.6 Levels of Approval Required for Ancillary Studies**

There are two levels of approval for ancillary studies:

Level I: Approval by the Research Review Committee

Level II: Further approval by the Study Group.

In general, Level I approval will suffice if the ancillary study involves analyzing available data from the study for questions not addressed in the major study, and no additional tests or observations will be made on the subjects. Other types of ancillary research will customarily require both Level I and Level II approval. The decision regarding the necessary level of approval will be made on a case-by-case basis by the Chair of the Research Review Committee in consultation with the Executive and/or Study Groups.

After approval by the Research Review Committee and the Study Group, final approval is contingent upon the Research Review Committee receiving a letter signed by the principal and all collaborating investigators in which they agree to abide by the policies for ancillary studies herein described including that regarding publication or presentation of results.

### **8.7 Funding of Ancillary Studies**

The study will not provide funds for ancillary studies. In particular, no funds are provided for Central Laboratory or other units or for the Data Coordinating Center activities or services in support of ancillary studies. If funds are needed, the investigator must explore other avenues such as: (1) submission of a research grant application; or (2) use of other sources of funds (i.e., a foundation, drug company, etc.) The anticipated source of funds must always be identified.

### **8.8 Publication of Ancillary Study Results**

All manuscripts, abstracts, or presentations for scientific meetings based on ancillary study data must be reviewed and approved by the Editorial Committee before publication or presentation.

### **8.9 Implementation**

The request for approval of an ancillary study should be in narrative form. It should contain a brief description of the objectives, methods, significance of the study, plans for analysis and publications, and information regarding funding level and source. If a proposal is being submitted elsewhere for funding (e.g., a grant application), the source of funding should be identified and the application may be used as the basis for the request. Full details should be given concerning any procedures or tests to be carried out on a study patient including: any

ophthalmologic, renal, cardiovascular, neurologic, psychological, or other evaluation to be performed; any substances to be injected or otherwise administered to the patients; any observations to be made or procedures to be conducted on patients outside of the clinic; any extra clinic visits required of the patient or any prolongation of the patient's usual clinic visits; and any additional specimens (blood, urine, etc.) to be obtained or additional procedures to be done on specimens collected according to the EDIC Protocol. The proposal should discuss the measures to be taken to ensure patient safety and confidentiality and an assessment by the investigator(s) of the potential impact of the ancillary study on EDIC. Prior approval by the appropriate Human Subjects Review Committee should be demonstrated. The proposal should also specify whether Level I or both Levels I and II approval is requested.

The investigator should send his/her ancillary study proposal to the Data Coordinating Center, which will distribute it to all members of the Research Review Committee. The proposal should be written in sufficient detail so that the Research Review Committee can assess the study's scientific merit and potential impact on the EDIC. To ensure thorough scientific review, the Chair of the Research Review Committee may elect to seek outside expert opinion in advance of the Committee meeting. Within 30 days of receiving the proposal, the Chairman of the Research Review Committee will summarize the questions and objections (if any) raised by members of the Committee and refer this summary to the applicant so that he/she may amplify, clarify, and/or withdraw the request. The members of the Research Review Committee will have another opportunity to review the request and the Chair will then prepare a statement of the Committee consensus, including any remaining reservations or objections. This statement will be sent to the investigator requesting approval for the ancillary study. If only Level I approval is required and the study has been approved by this Committee, the investigator may proceed with the study when it has been approved and authorized by NIDDK. Approval or disapproval is based on majority opinion.

If Level II approval is also needed, the approval statement of the Research Review Committee will be forwarded to the Study Group. Each member should respond to the Chair of the Research Review Committee within 1 month. No response will be considered approval. Recommendations of the Research Review Committee and Study Group will be forwarded to the EEC for assessment of impact on the EDIC. Approved Research Review will then be forwarded to NIDDK for final authorization. The investigator may proceed with the ancillary study once it has been authorized by the NIDDK.

In the event that the Research Review Committee disapproves of a proposed ancillary project, the investigator can appeal to the Study Group, whose decision may override that of the Research Review Committee. If the Study Group also disapproves of the ancillary study, the proposed study will not be undertaken.

## **8.10 Protocol Changes**

The objectives of the EDIC are most likely to be achieved if the Protocol does not require alteration. Any changes in the Protocol may result in some degree of heterogeneity of the data, which complicates the analyses and may compromise the scientific integrity of the study. However, occasions may arise in which Protocol changes are desirable or necessary, such as technological advances.

## **8.11 Study Group Policy**

Changes in the Protocol will be recommended by the Steering Committee only if they are required to insure subject safety or will significantly enhance the scientific validity of the study. To recommend a Protocol change to the EAC and the NIDDK, three-fourths of the Study Group must approve the change. Each member of the Study Group will have a vote (i.e., each clinic will have 2 votes, the DCC and NIH will have one vote each and the Study Chairman will have the tie-breaking vote).

### 8.12 Procedures

The Study Group will consider proposals for Protocol changes that may originate from the NIDDK, the EEC, the Clinical or Data Coordinating Centers, or one of the working committees. Groups could propose changes based on operational factors or the desirability of performing additional outcome measures. The Study Group will make a recommendation to the Study Group as to whether or not a change of Protocol is warranted and, if so, what form it should take. The recommendations of the group will be reviewed and authorized by the NIDDK before implementation.

### 8.13 Collaborations

The DCCT/EDIC research group welcomes scientific collaboration with investigators in the field of diabetic complications. The Research Group's part in such collaborations is often to provide blood and/or urine specimens, as well as clinical and biochemical data for joint analyses.

The Research Group would like to make clear its policy in providing specimens for joint projects. All the specific measurements that will be made on DCCT/EDIC samples must be designated and agreed on in advance. No additional measurements of any analyte in DCCT/EDIC specimens can subsequently be performed on leftover sample volume without the prior knowledge and concurrence of the DCCT/EDIC research group.

The reason for this policy is not to inhibit scientific advancement or entrepreneurship. Quite the contrary, the Research Group would expect in most instances to agree to additional measurements. The reasons for requiring that a formal request be made before undertaking any new, not previously agreed on measurements, are 3 fold.

1. First, the DCCT/EDIC study group wishes to be an active intellectual partner in any collaboration, rather than simply a passive useful source of samples and phenotypic data.
2. Sample volumes that remain after completing the original planned analyses might be better returned to the DCCT/EDIC repository and stored for other potential future use, than for what a current collaborator wishes to measure ad hoc.
3. Most important, we need to avoid the situation in which 2 different laboratories, unbeknownst to us, are measuring the same analyte on identical specimens. This opens up a Pandora's box of possible conflicting results and interpretations, conflicts of priority and authorship, possible IRB issues with uses for which participants had not given consent or might not if asked after the fact, and a loss of control over the study and its directions.

### 8.14 EDIC Volunteers and Other Research Studies

All subjects are encouraged to maintain the best degree of blood glucose control that is safely possible. To achieve this goal, the use of new therapies in the treatment of T1D and/or its complications will be encouraged.

Participation in research studies that involve the use of experimental agents that can interfere with the objectives of EDIC by affecting EDIC outcomes, or by impairing volunteer participation in EDIC or EDIC data collection must strongly be discouraged whether such studies are conducted by EDIC investigators or not. Participation in other research studies that would not have a negative impact on EDIC should be supported by the EDIC staff.

If the study is being conducted by an EDIC investigator, the EDIC Research Review and/or Executive Committee must review the study protocol to be sure it is compatible with the criteria listed above. If the study is being conducted by an investigator outside the EDIC study, the EDIC Research Review Committee and/or Executive must review the study protocol to be sure it is compatible with the criteria listed above. EDIC volunteers should not be enrolled in such a study prior to central review and approval by EDIC.

As part of the informed consent process for entry into EDIC, all volunteers were asked to review their participation in any other research projects in advance with the EDIC staff. Investigators should discourage participation in any studies that conflict with the EDIC protocol. If an investigator is not sure whether a study poses a conflict, the issues should be reviewed with the EDIC Research Review Committee and/or the Executive Committee.

Expedited review will be provided by the Executive Committee and the Chair and Vice Chair of the Research Review Committee. If substantive issues are involved, the entire Research Review Committee will review the study protocol and decide whether it should be approved or disapproved.

### **8.15 NIDDK Central Repositories**

Specimens and data transferred to the NIDDK Central Repositories will be deidentified (e.g., stripped of dates of birth or death, initials). The Repositories will take measures to protect probands' privacy, although no guarantee of confidentiality can be absolute. However, the Repositories will have some data about the probands, such as age, sex, diagnosis, race, and outcomes from the DCCT/EDIC studies.

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## **9. CLINICAL CENTER PROCEDURES**

### **9.1 Staff and Responsibilities**

Each clinic should have two people, the Principal Investigator and the Study Coordinator, who are both responsible for the conduct of the study.

#### **Participant's Personal Health Care Provider**

At the end of DCCT, each subject's care was transferred from the DCCT clinic and physician to his or her own personal physician. The participant's personal physician or health care provider, not the EDIC physician, is responsible for the participant's overall diabetes care and management. Occasionally, the EDIC physician or Study Coordinator may contact the subject's personal physician in order to obtain more detailed information about certain events (i.e., accidents, hospitalizations, etc.) that occurred between the participant's yearly visits to the EDIC clinic.

#### **9.1.1 Principal Investigator**

The Principal Investigator is responsible for the overall operation of the Protocol within each center. The Principal Investigator is also responsible for failure to adhere to the Protocol by either subjects or staff. He/she is responsible for any local decisions related to deviation from the Protocol, and should personally communicate these to the Data Coordinating Center. He/she is responsible for the hiring and training of new staff, informing the Data Coordinating Center and the NIDDK of any changes in staff, and the appropriate distribution and accounting of funds allocated for this study.

#### **9.1.2 Other Physicians**

The ophthalmologist is responsible for performance of ophthalmologic examinations necessary for analysis, as outlined in appropriate sections of the Manual of Operations and for the completion of the necessary forms related to these procedures.

The sonographer is responsible for performance of the carotid artery ultrasound as outlined in appropriate sections of the Manual of Operations and for the completion of the necessary forms related to these procedures.

The neurologist is responsible for the performance of the neurology exam and nerve conduction studies outlined in appropriate sections of the Manual of Operations, and for the completion of the necessary forms related to these procedures.

Other physicians may be added to the study staff as needed for completion of new specialty procedures.

### **9.2 Study Coordinator**

Each clinical center should have one individual designated as the Study Coordinator. The Study Coordinator will be responsible for the day-to-day operation of the Protocol, as outlined in the following sections, and time/effort should be consistent with the funding allocated.

### **9.2.1 Scheduling Visits**

The Study Coordinator schedules each follow-up visit for all subjects. Visits are scheduled within the allowable window for the designated date of the visit. See Chapter 5 for the description of visits and their windows. The Study Coordinator should find a time suitable for the participant and all necessary personnel from the center, and arrange a specific time and location for the visit to take place.

Confirm scheduled visits with the participant by mail at least 2 weeks in advance and by phone 2 to 3 days before the visit if deemed necessary for that subject. Email reminders may also be appropriate if allowed by local IRB policies.

### **9.2.2 Preparing for a Participant's Visit**

In preparing for a participant's visit, the Study Coordinator should be certain that all center personnel necessary for that visit are aware of the specific time and place for the visit. The Study Coordinator reviews with each team member the procedures necessary during the visit, and should be certain that all the necessary forms and equipment are available. The Study Coordinator prepares an orderly schedule for each visit so that the visit is completed as efficiently as possible and without confusion. Avoid long periods of waiting during the visit. Participants may elect to complete the annual exams and evaluations in two separate visits, if that is deemed easier for their participation.

### **9.2.3 General Visit Procedure**

At each visit, Study Coordinator meets with the subject to review the procedures and schedule for that visit. The Study Coordinator should obtain informed consent from the subject for any new or ongoing protocol and address any questions or concerns about the procedures to be performed before the visit or at the time of scheduling. The Study Coordinator should do everything possible to keep the visit on schedule. Each team member should perform the necessary tasks for that visit, as outlined in the appropriate chapter of the Manual of Operations, and complete the necessary forms. Return forms and other information to the Study Coordinator. Prior to the termination of the visit, the participant should again meet with the Study Coordinator and review the progress of the visit. This will assure that all necessary aspects of the visit were completed prior to the subject leaving, thus avoiding the need for a return visit. The Study Coordinator is responsible for sending necessary forms, laboratory samples and protocol evaluations to the appropriate Central Reading Unit and/or the Data Coordinating Center.

### **9.2.4 Checking Forms**

The Study Coordinator will check all forms for the following:

1. **Completeness**: All items should be appropriately answered. If the information is not available, this should be noted in the margin by writing NA next to the item.
2. **Internal Consistency**: Some items will involve branching, in which case one or more items should or should not be completed based on the response to a preceding item. Check each form to ensure that there is consistency within the branch. For example, a question that includes the phrase "If yes" (to the preceding item) should only be filled out when the preceding item was answered "yes".

3. **Numerical Fields:** Edit numerical responses to identify extreme values that might be due to misplaced decimal points, transposition of digits, or other recording errors. In certain cases, extreme or unusual values may be legitimate, in which case, enter a note into the margin to indicate that the value was verified as correct.
4. **Legibility:** All write-in responses must be printed clearly and legibly.

After reviewing all of the forms, the Study Coordinator sends them to the Data Coordinating Center in the monthly mailing. Copies of all forms should be maintained at the local clinic.

### **9.2.5 EDIC File**

Each subject in the study should have a file containing EDIC records kept for purposes of the study. This record should include notes from each participant's contact, summaries of any defined event, and a checklist indicating completion of the various laboratory work and forms required by this study. The Study Coordinator keeps this record up-to-date and in files separate from the general hospital or clinic records, and sees that they are readily available to necessary team members. The Principal Investigator, Study Coordinator, and any other study staff should have access to this record; however, the record is otherwise confidential, except with permission of the Principal Investigator and the subject.

### **9.2.6 Data Corrections**

Keep the need for corrections of data to a minimum by carefully recording data at the time of collection and reviewing the forms prior to submission. After the forms are received at the Data Coordinating Center, they are entered into a computer and inspected in detail for completeness and errors. The Data Coordinating Center will contact the Study Coordinator if it is determined that a data error occurred and that the error is attributable to the clinic. The Study Coordinator should make any necessary corrections. Data corrections should be submitted to the Data Coordinating Center by mail, fax or secure email.

### **9.2.7 Other Responsibilities**

In addition to the above, the Study Coordinator should perform the following duties:

1. Notify the Data Coordinating Center of all personnel changes within the clinic, including positions of responsibility in affiliated units. Refer to Staff Transitions in Chapter 26.
2. Maintain a file of all general EDIC correspondence from the Data Coordinating Center, central laboratories, and units.
3. Maintain a calendar of forthcoming study related events such as meetings.
4. Obtain death certificates, autopsy reports, and other pertinent information on deceased patients, obtain medical records to verify reported medical events and perform other aspects of patient follow-up as directed by the Principal Investigator.

5. Insure proper mailing of specimens, photographs, and assessments to the Central Biochemistry Laboratory, the Central Ophthalmologic Reading Unit, the Central Carotid Ultrasound Reading Unit, the Central ANS Reading Unit, the Data Coordinating Center and specified central reading units for ancillary studies.
6. Collaborate with the PI in the completion of institutional review board modifications and submissions as they occur in a timely manner. In general, ancillary studies are incorporated into the annual EDIC visits with completion over a two-year period. Thus, waiting to schedule EDIC visits until a particular ancillary study is approved locally is not typically recommended.
7. Collaborate with the PI in the maintenance and submission of fiscal records and/or reports.
8. Contact the participant and the Principal Investigator about any missed visits, and complete the form 141 for a missed clinic visit.
9. Take steps whenever possible to encourage patient adherence. These include the mandatory annual attempt to contact inactive participants that have not withdrawn consent and collect any makeup data collections as specified in the MOO, chapter 10. Refer to Chapter 26 (Adherence) for further details.
10. Assist participants and / or other EDIC clinics with transfers to other EDIC clinics or welcoming a transfer participant into the local EDIC center, using the procedures outlined in Chapter 25 (Transfers) of the MOO.
11. Maintain an inventory of donated EDIC supplies at the EDIC center, and distribute only to EDIC participants.
12. Participate in study wide meetings, and other study wide endeavors as appropriate. (e.g., new project working groups).
13. Ensure certifications for EDIC data collection as outlined in Chapter 24 of the MOO.
14. Obtain and maintain access to the secure EDIC Web access. Contact the DCC for initial password information.
15. Notify DCC of any change in contact information for the local EDIC clinic The SC should insure the DCC has current information for all local EDIC staff.

## **10. SPECIFIC PROCEDURES AND DEFINITIONS FOR ANNUAL FOLLOW-UP VISITS**

### **10.1 Introduction**

The following chapter consists of definitions and procedures to follow when completing the Annual Medical History and Physical Examination Form (EDIC Form 002).

### **10.2 Definitions**

#### **10.2.1 Patient Identification Number**

Each patient was assigned a permanent 5-digit identification number (ID No.) in the DCCT. The first two digits of the patient identification number refer to the clinical center in which the patient was first screened for eligibility and the last three digits are a code to identify the patient. The identification numbers that were assigned to each patient during the DCCT will continue as the patient's identification number in the EDIC.

#### **10.2.2 Patient's Initials**

The patient's initials, comprising the patient's first, middle, and last initials, constitute a second patient identifier. If the patient has no middle name or initial, an "X" is used as the middle initial. The initials that were entered onto the first EDIC Annual Medical History and Physical Form (Form 002) will be the initials used for the duration of the EDIC. After the EDIC first visit, the initials identifier for the EDIC will never change, even if the patient's name changes during the course of the EDIC.

#### **10.2.3 Examination Date**

The examination date is the date when an examination occurs. A number of procedures may be associated with each examination. An examination is not regarded as complete until all procedures are complete.

#### **10.2.4 Follow-up Visit Number**

The follow-up visit number is sequentially numbered starting with 1 for the first annual visit. There is one scheduled follow-up visit per patient per year.

#### **10.2.5 Informed Consent**

The patient must complete the Informed Consent Form before he/she can participate in the EDIC. The Informed Consent Form obtains the patient's permission to participate in the study and explains to the patient the purpose of the study, the procedures to be performed, the risks involved, and the patient's rights. All new or updated consent forms should be filed in the patient's local EDIC files. A patient is not officially enrolled in the EDIC until he/she has signed the Informed Consent.

### **10.2.6 Date of Randomization**

The patient's official date of randomization is the date the treatment assignment was given to the patient in the DCCT by the Data Coordinating Center. This date is the patient's baseline.

### **10.2.7 Patient Visit Schedule**

The Data Coordinating Center provides annual patient schedules to the clinics to identify target dates and visit windows (refer to Chapter 22). A listing of regularly scheduled visits indicates which forms to complete and what the allowable window is for that visit. The Central Biochemistry Laboratory provides pre-printed barcodes for all laboratory samples that can be requested using the CBL Order Form (on the EDIC study website), or refer to Chapter 14 of the MOO.

## **10.3 Annual History and Physical Exam**

### **10.3.1 General Features of Visit**

Each annual visit should include the following:

1. Discussion with the EDIC physician or nurse regarding health status since the last EDIC visit, including the frequency and causes of episodes of hypoglycemia or hyperglycemia
2. A brief physical examination with particular attention to symptoms of hypo- and hyperglycemia, ketonuria, complications of diabetes, blood pressure, maintenance of body weight, condition of feet, and other assessments that are clinically indicated
3. Current diabetes management
4. General standards of care
5. Recommendations for follow-up with local HCP
6. Importance of SMBG
7. Approval to receive pertinent medical records for events or conditions that have been noted since the last EDIC visit

### **10.3.2 Information Regarding Specific Questions on the Annual History and Physical Form**

Complete the Medical History and Physical Examination Form (EDIC Form 002) annually. In general, the information gathered on this form relates to the time frame from the last EDIC visit, or is otherwise specified (e.g., hypoglycemia in the last three months).

Some of the questions on this form call for written specification of certain conditions. For these questions, type or neatly print the answers. Do not use abbreviations.

Some questions ask you to specify the average number of times an event has occurred (e.g., episodes of hypoglycemia) or the amount of a substance that was used (e.g., amount of alcohol consumed). When recording, round the value to the nearest whole number. For example: Two and one-half glasses of wine is reported as three glasses. Put zeros before the number if necessary to fill in extra boxes.

Clarifications of several of the questions on the Medical History and Physical Examination Form follow:

1. Occupation

- a) Professional, technical, and similar workers -- Includes aeronautical, agricultural, chemical, civil, electrical, industrial, mechanical, metallurgical, mining and sales engineers, and agronomists and metallurgists, chiropractors, dentists, dietitians, healers, medical and dental technicians, nutritionists, optometrists, osteopaths, pharmacists, physicians and surgeons, professional nurses, psychologists, therapists, veterinarians, school principals, supervisors, and teachers, accountants and auditors, actors, airplane pilots and navigators, architects, artists and art teachers, athletes, authors, clergymen, college presidents, professors, and instructors, dancers, dancing teachers, designers, draftsmen, editors, technicians, entertainers, farm and home management advisors, foresters and conservationists, funeral directors and embalmers, judges, lawyers, librarians, musicians and music teachers, natural scientists, reporters, sports instructors, and officials and surveyors.
- b) Managers, officials, and proprietors -- Includes buyers, building managers and superintendents, credit men, lodge, society and union officials, postmasters, public administration inspectors and officials, purchasing agents and buyers, railroad conductors, ship officers, pilots, pursers, and engineers.
- c) Craftsmen, foremen, and similar workers -- Includes brick masons, carpenters, cement and concrete finishers, electricians, excavating, grading, and road machinery operators, painters (construction and maintenance), paperhangers, pipe fitters, plasterers, plumbers, roofers and slaters, stone masons, structural metal workers, tile setters, repairers of air conditioning, heating, and refrigeration equipment, airplanes, automobiles, office machines, radios and television, railroad cars, blacksmiths, boilermakers, coppersmiths, die makers and setters, forgemen and hammermen, heat treaters, machinists, metal jobsetters and molders, metal rollers and roll hands, millwrights, pattern and model makers, (except paper), sheet metal workers, tinsmiths, toolmakers, bakers, bookbinders, cabinetmakers, compositors, crane men, derrick men, electrotypers, engravers, furriers, glaziers, goldsmiths, inspectors, jewelers, lens grinders and polishers, lithographers, locomotive engineers, locomotive firemen, log and lumber scalers and graders, loom fixers, millers, motion picture projectionists, opticians, piano and organ tuners and repairmen, plate printers, printing pressmen, shoemakers (except in factories), silversmiths, stereotypers, stationary engineers, stone carvers, stone cutters, tailors, telegraph and telephone linemen and servicemen, typesetters, upholsterers, watchmakers, window dressers.
- d) Clerical and similar workers -- Includes clerk-typists, public stenographers, typing pool supervisors, secretaries, baggage men, bank tellers, bill and account collectors, bookkeepers, cashiers, dispatchers and starters of vehicles, express messengers, file clerks, insurance adjusters, insurance examiners and investigators, library attendants and assistants, mail carriers, messengers and office boys, office machine operators, payroll and time keeping clerks, postal clerks, physicians and dentists office attendants, railway mail clerks, receptionists, shipping and receiving clerks, stock clerks, storekeepers,

telegraph messengers, telegraph operators, telephone operators, ticket, express, and station agents.

- e) Sales workers -- Includes advertising agents and salesmen, auctioneers, demonstrators, hucksters, insurance agents and brokers, insurance underwriters, lottery ticket agents, lottery ticket sellers, newsboys, peddlers, real estate agents and brokers, stock and bond salesmen, salesmen and sales clerks in retail trade.
- f) Operative and similar workers -- Includes bus drivers, chauffeurs, delivery men, routemen, taxicab drivers, truck and tractor drivers, apprentices, asbestos and insulation workers, assemblers, auto service and parking attendants, blasters, boatmen, bus and street railway conductors, canalmen, furnace men, graders and sorters in manufacturing, laundry and dry cleaning operatives, lock keepers, meat cutters, metal heaters, milliners, mine operatives and laborers, motormen, oilers and greasers, packers, painters (except construction and maintenance), photographic process workers, powder men, power station operators, railroad brakemen and switchmen, sailors, sawyers, sewers and stitchers in manufacturing, smelter men, stationary firemen, surveying chainmen, rodmen and axmen, textile knitters, textile spinners, textile weavers, welders and flame cutters, wrappers.
- g) Service workers -- Includes bailiffs, bridge tenders, constables, detectives, firemen (fire protection), guards, marshals, policemen, sheriffs, watchmen, cooks, counter and fountain workers, waiters, attendants and ushers in amusement places, barbers, bartenders, bootblacks, boarding and lodging house keepers, elevator operators, hairdressers, housekeepers and stewards, janitors, kitchen workers, porters, sextons.
- h) Laborers -- Includes carpenters helpers, car washers, fishermen, garage laborers, gardeners, longshoremen, lumber men, oyster men, raftsmen, stevedores, teamsters, truck drivers helpers, warehousemen, wood choppers.
- i) Farmers -- Includes owners, operators, tenant farmers, and sharecroppers.

## 2. Diabetes History

Interpretations of questions G.2.a, G.2.b, G.2.c, and G.2.d on EDIC Form 002:

- a) Question (G.2.a) -- "Hospitalizations" implies overnight admission to the hospital; an emergency ward visit that did not result in hospitalization does not apply.
- b) Question (G.2.b) -- The number of episodes during which the patient lost consciousness with (or without) seizures may be only approximate if the patient was not observed during all episodes. Should the patient not remember an event involving impaired consciousness, but the observations of another person indicate that neither full loss of consciousness nor seizures occurred, then do not include it in this category.

- c) Question (G.2.c) – Interpret the need for "professional medical assistance" as signifying that the person assisting the patient felt that oral glucose administration was either impossible to perform or inadequate to treat the episode effectively. Consider the administration of intravenous glucose or parenteral glucagon as "professional medical assistance" whether or not the person providing the treatments had formal medical training.
- d) Question (G.2.d) -- This category implies that the patient required assistance to obtain oral treatment for hypoglycemia either because he was too symptomatic to help her/himself or because s/he failed to recognize the need for treatment.

### 3. Measuring and recording guidelines

All measurements should be recorded to the nearest unit as allowed on the Annual Medical History and Physical Form (Form 002). After taking each measurement, record its value in the appropriate space.

Do all measurements twice. If the two measures differ by more than the recommended amount, take and record two additional measures as noted on the form.

Allowable limits for difference between measures are:

Weight:	Within 0.2 kg or 200 grams
Stature:	Within 1.0 cm
Waist Circumference:	Within 0.5 cm
Hip Circumference:	Within 0.5 cm
Iliac Crest:	Within 0.5 cm

#### a) Weight

To minimize variability in the weight measurement, request the patient to wear lightweight clothing and to remove shoes and empty bladder before taking the patient's weight.

Check the scale at "0" to be sure it balances before taking measurements. Ask the patient to remove shoes, stand in the center of the scale and not touch or support himself/herself on anything. The patient should stand so that his/her weight is equally distributed on both feet. Take two measures. Have the patient step off the scale between measurements and reset the scale to zero. Repeated measurements should agree within 200 grams. If they do not, take and record two more measures.

#### b) Stature

Ask the patient to stand with his/her back against the stadiometer, with the heels together, and both heels touching a minimal distance from the wall (no greater than the depth of the stadiometer). The back (scapula) and buttocks should also be in contact with the board (See Figure 10.1).

Occasionally it is impossible to position the patient's heels, buttocks, scapula, and the back of the head in one vertical plane against the board and still have him/her stand naturally and comfortably. S/he may arch his/her back due to the large size of the buttocks. If this occurs, move the patient forward and have only the buttocks and heels in contact with the board.

Be sure that in this position the patient maintains erect posture, that is, no slouching. Heels should be together and the medial borders of the feet at an angle of about 45 degrees, with the weight equally distributed and the head in the "Frankfort Horizontal Plane". This requires the subject to look straight ahead. A line running from the opening of the ear to the corner of the eye should be parallel to the floor. Bring down the movable headboard firmly on top of the head. It may be necessary, upon occasion, to remove or alter the hairdress of some of the patients. This may be necessary for the headboard to maintain a right angle and to make contact with the top of the scalp.

Have the patient inhale deeply, again not altering position by, for example, raising the heels off the floor. Measure stature just before the patient exhales. Record the measurement to the nearest millimeter and re-measure. If the measurements differ by more than 1.0 cm, two more measurements should be taken.

#### c) Circumference Measurements

Record the measurements on EDIC Form 002 (Annual Medical History and Physical Form). Use of two different waist references in the EDIC will provide maximum comparability to data published by other trials. Perform all measurements, even for extremely obese individuals, unless the patient refuses.

Insulin can cause both atrophy and hypertrophy of fat. Lipoatrophy related to insulin injections appears as circumscribed depressions from loss of fat in the deep dermal and subcutaneous layers. Hypertrophy related to insulin injections clinically resembles lipomas. It may be important for the analysis of the waist-to-hip ratio to know the extent of the prevalence of these two conditions. A nurse or physician who has some experience with lipohypertrophy or lipoatrophy should assess the presence of these conditions affecting these measurements.

#### i) Natural Waist

Do not take the measurements over clothing. If clothing must be worn, subjects should undress to light underwear and wear only a cloth or paper smock during the measurements. The subject should be in stocking feet and stand erect with abdomen relaxed, the arms at the sides, and the feet together. The measurer faces the subject and places an inelastic tape around the subject, in a horizontal plane, at the level of the natural waist, which is the narrowest part of the torso, as seen from the rear. In some obese subjects, it may be difficult to identify a waist narrowing. In such cases, measure the smallest horizontal circumference in the area between the ribs and iliac crest. Take the measurement at the end of a normal expiration, without the tape compressing the skin. If patients are measured with a gown, pull it tight so that landmarks are obvious. Record the measurement to the nearest 0.1 cm and re-

measure. If there is more than 0.5 cm difference between the two measurements, take measure and record two more times.

#### ii) Iliac Crest Waist

The patient is in a standing position. Ask the patient to hold up his/her gown. The examiner stands behind the patient and palpates the hip area for the right iliac crest. The examiner marks a horizontal line at the high point of the iliac crest and then crosses the line to indicate the midaxillary line of the body. The patient must lower pants and underclothing slightly for the examiner to palpate directly on the hip area for the iliac crest. The examiner then stands on the patient's right side and places the measuring tape around the trunk in a horizontal plane at the level marked on the right side of the trunk. The tape should be parallel to the floor and snug, but not compress the skin. Make the measurement at minimal respiration. Record the measurement to the nearest 0.1 cm and re-measure. If there is more than 0.5 cm difference between the two measurements, take measure and record two more times. If measuring a patient with a gown, pull it tight so that landmarks are obvious.

#### iii) Buttocks (Hip) Circumference

The subject should wear only nonrestrictive briefs or underwear, or light smock over underwear. The subject stands erect with arms at the sides and feet together. The measurer squats at the side of the subject so that the level of maximum extension of the buttocks can be seen. Place an inelastic tape around the buttocks in a horizontal plane at this level without compressing the skin. Make sure the zero end of the tape is below the measurement value. The tape is in contact with the skin but does not indent the soft tissues. Record the measurement to the nearest 0.1 cm and re-measure. If there is more than 0.5 cm difference between the two measurements, take measure and record two more times. If measuring a patient with a gown, pull it tight so that landmarks are obvious.

### **10.4 Study Stop Points**

There are various stop points in the EDIC Study. If a participant reached one of these stop points, his/her data schedule will say "STOP" on the annual schedule, and that particular test is no longer required unless requested by that patient. STOP points are identified by the DCC based on the previous year's information. It is possible a health status could have changed in the intervening year, at which point the clinic would identify that the participant has reached a STOP point. All labs continue despite chemotherapy or pregnancy, unless otherwise contraindicated (e.g., shunt placement in arm, venous accessibility, or water load for renal exam if contraindicated). Also, please note that Ankle/Arm continues on the other side after an amputation. (Table 10.1)

#### **10.4.1 Fundus Photographs**

The stop points for Fundus Photographs are bilateral panretinal photocoagulation, legal blindness in better eye, and/or the inability to visualize retina in both eyes. Please note if the retina in one eye can be visualized, the

exam can proceed with just that eye. Furthermore, it is possible to have photocoagulation in one eye, but the other eye is still photographed. The ophthalmologic exam and Form 030 should be completed regardless.

#### **10.4.2 Visual Acuity**

The stop point for the Visual Acuity Exam is legal blindness (20/200). This exam continues *despite* bilateral panretinal photocoagulation.

#### **10.4.3 4-Hour Renal/Serum Creatinine**

The stop points for 4-Hour Renal/Serum Creatinine are chronic dialysis, or renal or combined renal and pancreas transplant. Please note, that if a patient has a pancreas transplant, but retains the original kidneys, urine collection continues. Advancing Chronic Kidney Disease (CKD) is not a stop point. Rather, the participant should be questioned before the renal exam if CKD has been previously noted. Refer to Chapter 14 (Laboratory) of the MOO for information related to CKD.

#### **10.4.4 Carotid Artery Ultrasound**

The stop point for the Carotid Artery Ultrasound is bilateral carotid endarterectomy.

#### **10.4.5 SF-36/DQOL**

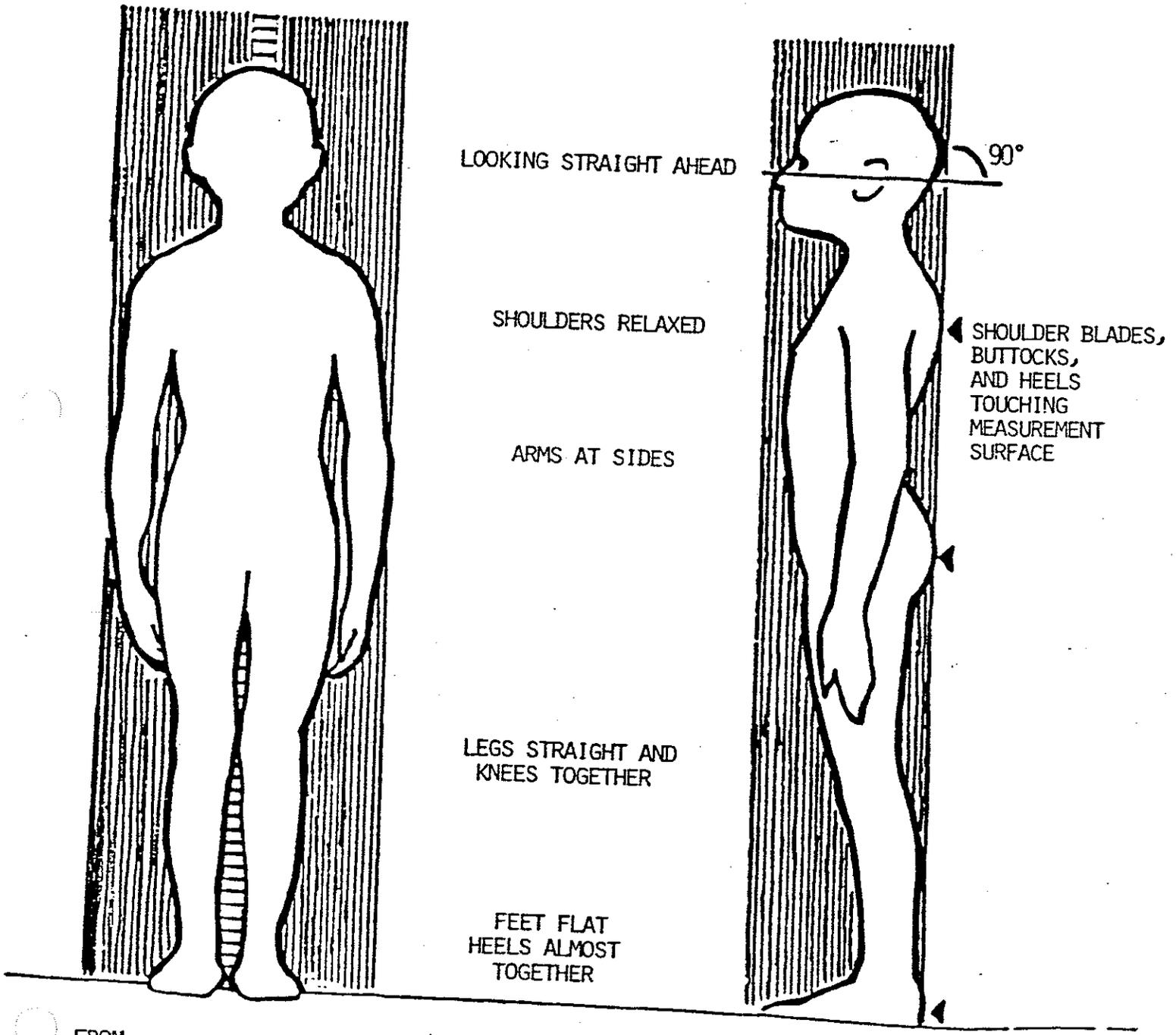
The stop point for the SF-36/DQOL is diagnosis of a fatal disease/life expectancy < 1 year.

#### **10.4.6 Valsalva ANS**

The stop point for the Valsalva ANS test is for participants:

1. with known vitreous hemorrhage;
2. who are undergoing or are scheduled for LASER treatment; or
3. with a history of severe NPDR or worse (EDIC Retinopathy Level of 53 or higher) AND who have not had an eye exam in at least 4 years.

FIGURE 10.1  
POSITION FOR STANDING HEIGHT



FROM: NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY III  
BODY MEASUREMENTS (ANTHROPOMETRY), OCTOBER 1988

**Table 10.1** STOP Points for EDIC Evaluations (19 May 2009)

“Stop points” have been identified for several of the EDIC evaluations. If the patient has reached one of these stop points, completion of that particular evaluation is no longer required for the patient.

EVALUATION	STOP POINT
<b>Fundus Photographs</b>	<ul style="list-style-type: none"> <li>• Bilateral pan-retinal photocoagulation</li> <li>• Legal blindness in better eye</li> <li>• Inability to visualize retina in either eye</li> </ul>
<b>Visual Acuity</b>	Legal blindness (20/200)
<b>4-hour Renal, serum creatinine</b>	<ul style="list-style-type: none"> <li>• Chronic dialysis</li> <li>• Renal transplant</li> <li>• Pancreas transplant</li> </ul>
<b>Carotid Artery Ultrasound</b>	Bilateral carotid endarterectomy
<b>SF-36 / Diabetes Quality of Life</b>	Diagnosis of a fatal disease / life expectancy less than one (1) year
<b>Cardiac MRI</b>	History of metal in the eye in the absence of orbital x-rays
<b>Gadolinium (for CMRI)</b>	History of or current GFR 60 ml/min/1.73m <sup>2</sup> or less

**Additional comments:**

- Renal and retinal stop points will be identified on the patient’s annual EDIC Data Schedule as “STOP” based on the previous year’s information sent to the DCC. It is possible a health status could have changed in the intervening year, at which point the clinic would identify that the participant has reached a STOP point.
- Complete the visual acuity exam despite the presence of pan-retinal photocoagulation
- Obtain usual EDIC blood/urine collections for patients who are pregnant or receiving chemotherapy; indicate these conditions on the specimen mailing lists
- Obtain blood pressure measurements from remaining limbs if a limb is not available for measurements (i.e. amputation, injury, AV fistula)
- Renal and retinal evaluations may be completed despite a “STOP” upon participant request and investigator discretion

## 11. DEFINED EVENTS

### 11.1 Introduction

In this chapter, we provide specific definitions for those events that we are interested in ascertaining.

Document and report these events to the Data Coordinating Center using the EDIC Form 002, Annual Medical History and Physical Examination. In most cases, the documentation of an event on the Form 002 requires the completion of a Verification Form, which asks more specific, detailed questions about the event. For example, if the Annual History and Physical Exam Form documents a case of DKA, then complete EDIC Form 093, Verification of DKA Event.

Events may be reported by the patient or someone reporting for the patient to the clinic staff.

Table 11.6 lists those events that are important to the study, and sections 11.2 through 11.6 present the definitions of those events. The frequency of these events will be tabulated in the statistical analysis of the study results. The clinical centers are required to report each occurrence of some of these events and in other cases the first occurrence of the event to the Data Coordinating Center.

### 11.2 Cardiovascular Events

#### 11.2.1 Myocardial Infarction (MI)

Myocardial infarction (MI) is classified as acute or non-acute and each of these classes is further designated as definite or suspected using criteria presented in Table 11.1. The diagnosis of acute MI depends on the availability of ECGs and/or enzymes measured within 72 hours after (a) arrival in the hospital or (b) the onset of symptoms of a cardiac event occurring in the hospital. The ECG series will be assigned the highest category for which criteria are met, i.e., first, "evolving diagnostic", then "diagnostic", then "equivocal", then "other". The ECGs will be sent to the Central ECG Reading Unit where they will be coded using the Minnesota Code, detailed definitions of which are given in Table 11.2. The various combinations of enzyme results will be classified as "abnormal", "equivocal", "incomplete", or "normal" by criteria, which are given in Table 11.3. A definition of "prolonged cardiac pain" is given in Table 11.4.

1. Acute Myocardial Infarction—A definite or suspected acute myocardial infarction is diagnosed on the basis of the presence or absence of chest pain, ECG findings, and/or enzyme changes as defined in Tables 11.1–11.4.
2. Non-acute Myocardial Infarction—A non-acute or "old" myocardial infarction can, in principle, have occurred either prior to involvement in the EDIC study and not been recognized on the local ECG reading, or during the EDIC study but without appropriate concurrent investigation to yield evidence that meets the criteria for definite or possible acute myocardial infarction.

A definite or suspected non-acute myocardial infarction is diagnosed on the basis of presence or absence of chest pain, ECG findings, and/or enzyme changes as defined in Tables 11.1–11.4

Definite or suspected non-acute MIs diagnosed for the first time on an ECG will be designated as "study" events. Only study events will be counted in comparisons of the incidence of myocardial infarction between the intensive and conventional groups.

The criteria for definite and possible acute and non-acute MIs are summarized in Table 11.1.

### **11.2.2 Coronary Artery Disease**

To have a definite diagnosis of coronary artery disease, a patient must require bypass surgery or angioplasty.

### **11.2.3 Angina Pectoris**

To have a definite diagnosis of clinical angina, a patient must have all three of the following characteristics of chest pain or pressure:

1. The location of the pain includes the sternum at any level.
2. The pain or discomfort usually occurs during a form of exertion or stress.
3. The pain or discomfort on most occasions lasts at least 30 seconds and disappears in 10 minutes or less from the time the subject rests or decreases his intensity of exertion or stress.

The pain or pressure may also be located in the left chest, and may radiate to the arms and/or to the jaw. Meals may be considered a form of cardiovascular stress.

Angina must be confirmed by angiography or by ischemic changes on non-invasive testing.

### **11.2.4 Arrhythmia**

The following types of arrhythmia are to be reported to the Data Coordinating Center documented by an ECG, but only those arrhythmias that include hospitalization will be adjudicated by the MMRC.

1. atrial fibrillation
2. atrial flutter
3. atrial tachycardia
4. junctional tachycardia
5. ventricular tachycardia
6. ventricular fibrillation

7. ventricular premature complexes
  - a) multifocal
  - b) runs of three or more
  - c) six or more per minute
8. second degree AV block
9. complete AV block

The official EDIC classification of the arrhythmia will be made by the Central ECG Reading Unit.

### **11.2.5 Congestive Heart Failure**

Defined as AT LEAST one symptom from EACH of the following two categories:

Category A: Paroxysmal nocturnal dyspnea, dyspnea at rest, or orthopnea

Category B: Marked limitation of physical activity caused by heart disease. Patients are comfortable at rest, but less than ordinary physical activity (for example, walking one or two blocks on level surface or climbing one flight of stairs in normal conditions) causes fatigue, shortness of breath, palpitations, or anginal pain (New York Heart Association Functional Classification III).

Note: CHF might also be associated with the following symptoms: rales, ankle edema, tachycardia, cardiomegaly by chest x-ray, chest x-ray characteristics of CHF, S3 gallop, jugular venous distention, high BNP (brain natriuretic peptide) level, low LV ejection fraction, or echo results showing characteristics of CHF. Although these symptoms may be used by the MMRC to adjudicate a CHF episode, they will not be used by Study Coordinators to define a CHF episode.

### **11.2.6 Hypertension**

The development of hypertension in an EDIC patient is defined as a systolic blood pressure of at least 140 mm Hg, a diastolic blood pressure of at least 90 mm Hg, the presence of documented hypertension, or the use of antihypertensive agents. The most recent definition of hypertension is either a systolic pressure greater than or equal to 130 mm Hg, or a diastolic pressure greater than or equal to 80 mm Hg or the use of antihypertensive agents.

### **11.2.7 Hyperlipidemia**

1. Hypercholesterolemia -- defined as a Central Biochemistry Laboratory (CBL) reported serum LDL cholesterol > 160 mg/dl.
2. Hypertriglyceridemia is defined as CBL reported elevation of serum triglycerides over 500 mg/dl.

Borderline categories for the lipids are given in the table below.

	<b>Acceptable</b>	<b>Borderline</b>	<b>High</b>
Total Cholesterol	< 200	200-239	≥ 240
LDL Cholesterol	< 100	100-130	≥ 130
HDL Cholesterol			≤ 35
Triglycerides	< 200	200-399	≥ 400

### 11.3 Cerebrovascular Events

#### 11.3.1 Stroke (Hemorrhagic or Ischemic)

A stroke (formerly known as a cerebrovascular accident) is defined as rapid onset of a persistent neurologic deficit attributable to an obstruction or rupture of the arterial system (including stroke occurring during a procedure such as angiography or surgery). The neurologic deficit is not known to be secondary to brain trauma, tumor, infection or other non-ischemic cause.

Strokes due to a clot are categorized as ischemic strokes, while those occurring due to a bleed are categorized as hemorrhagic strokes. Although strokes are generally known to affect the cerebral cortex (brain tissue), they can also affect other structures close to the brain, such as: (a) brain stem (including the cerebellum, medulla oblongata, and the cranial nerves), (b) the spinal cord, & (c) the retina. Strokes can also be categorized as fatal or non-fatal.

Strokes are suggested by at least one of the following symptoms:

- a) Carotid arterial system: weakness or numbness in limbs (often one-sided), partial loss of visual field, difficulty producing/understanding speech or writing (dysphasia), or loss of ability to recognize objects (agnosia).
- b) Vertebral-basilar artery system: weakness of single or multiple limbs, numbness of face (especially the mouth), double vision (diplopia), difficulty swallowing (dysphagia), slurring of speech (dysarthria), partial loss of visual field, lack of coordination of muscle movement (ataxia), fast rhythmic eye twitching (nystagmus), altered consciousness, sense of rapid spinning (vertigo), feeling the need to vomit without vomiting (nausea).
- c) Other symptoms: headache, loss of consciousness (more severe than altered consciousness), vomiting, seizures.

Stroke with permanent neurological deficit is diagnosed when there is a persistent abnormality of central nervous system function manifesting itself either on neurological examination or by persistent disability that interferes with normal daily activities. Stroke without permanent neurological deficit is diagnosed when the abnormality is not persistent.

Strokes may be confirmed by radiologic findings, but require description of onset and duration of symptoms to correlate radiologic findings with symptoms.

Thus, Clinic should submit Form 091 and the following types of medical records:

1. Neurology notes (such as a SOAP note from a neurologist or a neurology consultation note)
2. Diagnostic tests (such as MRI, CT, MR or CT Angiography, or Angiogram of the Head)

3. Hospital discharge summary that includes administration of tPA, fibrinogen, clotbuster, or surgery

Neurology notes define the clinical history of present illness, describing the neurologic symptoms and when they started and stopped.

In the past, the rule of thumb was, if symptoms last at least 24 hours, then the lesion is likely a stroke (WHO, 1978). However, many institutions now have “stroke protocols” that dictate treatment (including administration of tPA, fibrinogen, clotbuster, or surgery) within a matter of hours (of the onset of symptoms).

### 11.3.2 Transient Ischemic Attack (TIA)

*Transient Ischemic Attack (TIA)* is a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction (i.e., is not an ischemic stroke) (Easton JD et al., 2009). Clinic should submit Form 091 and the following types of medical records:

1. Neurology notes (such as a SOAP note from a neurologist or a neurology consultation note)
2. Diagnostic tests (such as MRI, CT, MR or CT Angiography, or Angiogram of the Head)
3. Hospital discharge summary

TIA symptoms are like those for strokes (See Section 11.3.1), but the duration is generally shorter. TIAs must be confirmed by angiography or non-invasive testing (such as MRI, CT, MR or CT Angiography, or Angiogram of the Head).

*The use of time to distinguish stroke from TIA.* As TIAs have historically been considered miniature versions of strokes, it has been the neurologist’s challenge to distinguish one from the other. In 1978, the World Health Organization (WHO) published a definition of stroke as a “neurological deficit of cerebrovascular cause that persists beyond 24 hours or is interrupted by death within 24 hours (WHO, 1978). This “24-hour definition” was used around the world for at least two decades. Then in 2002, a group of prominent American neurologists found the “24-hour definition” to be “*misleading in that many patients with transient <24-hour events actually have associated cerebral infarction* (Easton JD et al., 2009).” In addition, this group also determined that the “<1-hour definition” for TIA was also not useful because “*the 1-hour time point, like the 24-hour time point, does not accurately distinguish between patients with or without acute cerebral infarction* (Easton JD et al., 2009).” Thus, this group proposed a new definition for TIA:

“*Transient Ischemic Attack (TIA) is a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction* (Easton JD et al., 2009).”

Since the new definition was adopted, EDIC has updated their stroke and TIA definitions.

In order to distinguish suspected stroke from TIA events in EDIC, Coordinators should determine the duration of the suspected stroke or TIA event. This information can be obtained by asking the patient or someone representing the patient. Event duration should be categorized as lasting “<10 minutes,” “1 hour,” “<24 hours,” or “≥24 hours.”

## 11.4 Peripheral Vascular Events

#### **11.4.1 Peripheral Ischemia (Claudication)**

Peripheral ischemia (Claudication) is diagnosed when dull leg pain (or cramp, tightness) is present, usually brought on by continuous walking, and relieved within 10 minutes by stopping exercise. The site is one or both calves and/or hips and thighs. It does not start at rest. It is possible to confuse these symptoms with symptomatic diabetic neuropathy. In that case, a joint determination of the cause of pain is to be made by the neurologist and diabetologist.

#### **11.4.2 Amputation**

Amputation is diagnosed when a surgical or traumatic resection of the lower extremity or part of the lower extremity has occurred.

#### **11.4.3 Other Arterial Events**

Definite other arterial events are diagnosed when the event requires bypass or angioplasty.

#### **11.4.4 Lower Extremity Ulcer**

Lower extremity ulcer is diagnosed when a traumatic or non-traumatic excavation or loss of subcutaneous tissue in the foot or leg occurs with evidence of inflammation and/or infection that requires medical or surgical treatment by a health professional in an office or hospital setting.

#### **11.4.5 Vascular Disease**

Ischemic will be defined as ankle/brachial index  $< .09$  and calcification will be defined as a ankle/brachial difference of 75 mmHg or greater.

### **11.5 Nephropathic Events**

#### **11.5.1 Renal Insufficiency**

Definite renal insufficiency is diagnosed when the central laboratory reports that serum creatinine is  $\geq 2.0$  mg/dl, and there is an absence of ketonemia, or if GFR is  $\leq 70$  ml/min/1.73m<sup>2</sup>, or if there is a need for dialysis or transplant for chronic renal failure.

#### **11.5.2 Microalbuminuria**

Definite microalbuminuria is diagnosed when the urinary albumin excretion as measured by the annual four-hour timed collection is  $\geq 28$  ug/min.

#### **11.5.3 Albuminuria**

Definite albuminuria is diagnosed when the urinary albumin excretion is  $\geq 208$  ug/min. All efforts should be made to perform a 4-hour renal collection according to the EDIC MOO at the EDIC clinical center. In the rare situation where circumstances do not permit this test to be

performed, the following procedures may be carried out locally in the order of EDIC priority, followed by Principal Investigator/Study Coordinator discretion:

1. 4 hour collection, locally collected, utilizing the EDIC MOO procedure;
2. A carefully-timed overnight collection of  $\geq 6$  hours duration;
3. A carefully timed 24-hour collection.

If a single void sample can only be obtained:

1. Second void morning sample should be collected for measurement of albumin/creatinine ratio.

OR

2. A specimen collected regardless of time should be obtained.

If renal samples must be obtained locally, the responsible EDIC clinic must make the necessary arrangements with the local provider to assure consistency in the collection, preparation, and shipment of samples to the CBL.

#### **11.5.4 Renal Failure (Acute vs. Chronic Renal Failure and End Stage Renal Disease)**

When a patient has a kidney transplant or an initial dialysis event, Renal Failure occurs. However, it is important to distinguish an Acute Renal Failure event with the onset of Chronic Renal Failure. All Renal Failure events must be confirmed through adjudication by the Mortality and Morbidity Review Committee (MMRC). Chronic Renal Failure is also known as End-Stage Renal Disease (ESRD).

Acute Renal Failure (ARF) is the sudden loss of the ability of the kidneys to remove waste and concentrate urine without losing electrolytes. While ARF is potentially life-threatening and may require intensive treatment, it can be resolved after the underlying cause has been treated. This is not the case with Chronic Renal Failure (CRF): CRF requires either dialysis or kidney transplant. Thus, CRF in the EDIC Study will be defined by the need for ongoing dialysis treatment or kidney transplant. While a single kidney transplant can treat CRF, dialysis must be done on a weekly basis to treat CRF. The need of a single dialysis treatment or dialysis during a single hospital stay will define ARF in the EDIC Study.

Diabetes is a major cause of CRF, but it is not known to be a cause of ARF. At the same time, there are many causes of CRF other than diabetes. One other cause of CRF is unresolved ARF. For a list of causes of ARF and CRF, see Recommended Readings on Renal Failure in Chapter 28 of the MOO, Section 28.7.

To distinguish whether Renal Failure is Acute or Chronic, the clinic will: (1) complete Form 096 (Verification of Renal Failure Event) and (2) submit supporting medical records to the DCC. The preferred supporting medical record is Form CMS-2728, but a hospital discharge summary should be used when the Form CMS-2728 is not available. The DCC will provide its own document, the Renal Patient Report, which summarizes renal function throughout EDIC, to help the MMRC adjudicate the renal failure event. The MMRC will review and adjudicate the report of renal failure event by completing Form 151 (Morbidity Review Form: Myocardial Infarction and Other Cardiovascular Outcomes). Based on the adjudication, the renal failure event will be defined by timing (Acute or Chronic), treatment (dialysis or transplant), the need for

continued Chronic Renal Failure treatment (i.e., dialysis), and whether Chronic Renal Failure is newly diagnosed at this event or if it had been a condition that had been present for some time.

The date or year of the beginning of the renal event will be sought, but this might be difficult to obtain, especially in cases of chronic renal failure, which are distinguished by slow onset.

## **11.6 Ocular Events**

Ophthalmic definitions of the events for use in the EDIC are as follows:

### **11.6.1 Loss of Vision or Legal Blindness**

Loss of vision / legal blindness is defined as central visual acuity 20/200 or less in the better eye with best correction of widest diameter of visual field subtending an angle of no greater than 20 degrees.

### **11.6.2 Pan-Retinal (Scatter) Photocoagulation**

Pan-Retinal (Scatter) Photocoagulation is defined as:

1. Full Scatter Treatment -- Full scatter treatment consists of 1200 to 1600 five hundred micron lesions.
2. Mild Scatter Treatment -- Mild scatter treatment consists of 400 to 650 five hundred micron lesions spaced one burn width apart covering a similar area as full scatter.

### **11.6.3 Focal Photocoagulation**

Focal Photocoagulation is defined as focal treatment of discrete leakage; grid treatment of diffuse leakage or nonperfusion.

### **11.6.4 DRS High Risk Characteristics**

DRS High Risk Characteristics are defined as:

1. New vessels on or within one disc diameter of the optic disc (NVD); moderate or severe (equal to or greater in extent than those in standard photograph 10A) with or without vitreous or pre-retinal hemorrhage.
2. New vessels other than NVD (new vessels "elsewhere" - NVE); moderate or severe (equal to or greater than 1/2 disc area in extent in any single standard photographic field) with vitreous or pre-retinal hemorrhage (in any field).
3. NVD; mild (less than standard photo 10A) with vitreous or pre-retinal hemorrhage (in any field).

If vitreous and/or pre-retinal hemorrhage is present and the ophthalmologist believes sufficient new vessels (greater than or equal to 1/2 disc area of NVE or any definite NVD) have been

obscured by this hemorrhage that the preceding definition of high risk characteristics have been fulfilled, then this occurrence is considered a high risk characteristic event.

### **11.6.5 Proliferative Retinopathy Less Than DRS High Risk Characteristics**

The latter stage of diabetic retinopathy in which new, abnormal blood vessels begin to grow on the surface of the retina in response to widespread closure of normal retinal blood vessels due to diabetes. These new, abnormal blood vessels do not restore normal blood flow to the retina and can cause vitreous hemorrhage, detachment of the retina, and permanent vision loss.

### **11.6.6 Clinically Significant Macular Edema**

"Clinically significant macular edema" designates edema that is threatening vision and refers to any of the following characteristics:

1. Thickening of the retina at or within 500 microns of the center of the macula.
2. Hard exudates at or within 500 microns of the center of the macula, if associated with thickening of the adjacent retina.
3. A zone or zones of retinal thickening one disc area or larger in size, any part of which is within one disc diameter of the center of the macula.

Photocoagulation should be carried out in any eye that develops high-risk characteristics and should be considered in any eye detected at the CORU as having significant macular edema as defined in the Early Treatment Diabetic Retinopathy Study findings published in the December 1985 issue of Archives of Ophthalmology. All situations will be considered on a case-by-case basis. Treatment is not rendered by EDIC.

## **11.7 Definitions of Diabetic Events**

### **11.7.1 Ketoacidosis**

The diagnosis of ketoacidosis as an EDIC event requires each of the following four criteria to be satisfied:

1. A symptomatic diabetic state such as polydipsia and polyuria with or without nausea;
2. The presence of
  - a) serum ketones or
  - b) large/moderate ketones in urine;
3. At least one of the following:
  - a) arterial blood pH less than 7.30 or
  - b) venous blood pH less than 7.25 or

- c) serum HCO<sub>3</sub> less than 15 mEq/L.
- 4. Treatment within a health care facility.

### 11.7.2 Hypoglycemia

To document a hypoglycemic event, the clinic staff will complete Form 042 (Notification and Further Details of Severe Hypoglycemia Requiring Assistance).

Two levels of hypoglycemia are distinguished – Hypoglycemia with Sequelae and Severe Hypoglycemia.

#### 1. **Hypoglycemia with Sequelae**

At least one of the following events must have occurred:

- a) death,
- b) neurological insult requiring hospitalization,
- c) myocardial infarction,
- d) stroke
- e) injury to the patient requiring hospitalization,
- f) injury to another person,
- g) property damage, or
- h) traffic violation.

Evidence for a relationship between the event and hypoglycemia may consist of the following, in decreasing order of certainty:

- i) An event in conjunction with a blood glucose less than 50 mg/dl determined in a health care facility.
- ii) An event in conjunction with a finger stick blood glucose less than 50 mg/dl determined by non-medical personnel.
- iii) An event in conjunction with one or more manifestations of severe hypoglycemia, e.g., loss of consciousness, seizure, suspected seizure, unusual difficulty in awakening, irrational or uncontrollable behavior, confusion, or memory loss reversed by intravenous glucose, glucagon, or oral carbohydrates.
- iv) An event in conjunction with prodromal symptoms of hypoglycemia, such as hunger, nervousness or shakiness, sweating, dizziness or lightheadedness, sleepiness, confusion, difficulty speaking, or feeling anxious or weak remembered by the patient as occurring shortly before the event occurred.

## 2. Severe Hypoglycemia

At least one of the following clinical manifestations of severe hypoglycemia, which the patient was unable to treat himself/herself, must have occurred:

- a) memory loss
- b) confusion,
- c) uncontrollable behavior,
- d) irrational behavior,
- e) unusual difficulty in awakening
- f) suspected seizure
- g) seizure
- h) loss of consciousness.

For such an episode to be counted as **Definite Severe Hypoglycemia**, either the blood glucose must have been measured and found to be less than 50 mg/dl or the clinical manifestations must have been reversed by intravenous glucose, glucagon, or oral carbohydrates. When neither of the latter two criteria is fulfilled, such an episode will be considered as **Suspected Severe Hypoglycemia** if the patient recalls typical prodromal symptoms and there is no blood glucose measurement to help explain the clinical manifestations. Hypoglycemia that is less than severe may be too variable in symptomatology to be reliable and therefore will not be documented as an event. However, hypoglycemia of this type will be summarized for the seven days preceding the annual visit.

### Recommended Readings on Hypoglycemia:

*National Diabetes Information Clearinghouse (NDIC) (website) for Hypoglycemia, Viewed 30 September, 2008, <<http://diabetes.niddk.nih.gov/dm/pubs/hypoglycemia/index.htm>>*

## 11.8 Definitions of Other Events

### 11.8.1 Infections

1. Infusion Site Infection: Any infection at the site of the insulin pump infusion catheter that requires oral or parenteral antibiotics or surgical incision or drainage.
2. Urinary Tract Infection: Any infection of the kidney, ureters, bladder, or urethra, that results in symptoms of upper or lower tract infection, such as flank pain, fever, low back pain, dysuria, or frequency of urination and a midstream, clean catch urine culture yielding the following results:

Outpatients:

- Single culture of clean-catch urine with a colony count greater than or equal to 20,000 colonies/ml.

OR

- Two cultures of greater than or equal to 100 colonies/ml Candida species

In the absence of symptoms, two cultures with colony counts of greater than 100,000 of a single organism are required to indicate infection. With gram-positive organisms or fungi lower colony counts may be significant in the absence of symptoms. Pyuria will generally be present in active infection but alone would not indicate infection.

Inpatients: (noncatheterized)

- Same as outpatients.

Inpatients: (catheterized)

- Single culture with one or two organisms, either of which greater than or equal to 10,000 colonies/ml OR

- Single culture of greater than or equal to 100 colonies/ml Candida species.

3. Post-operative Wound or Deep Infections: Pus or serous drainage with local signs of inflammation. Include deep infections where superficial signs may be minimal, e.g., osteomyelitis following orthopedic surgery. A positive culture is one where exudate or tissue yields a pure culture of one species or, when mixed flora is expected, (e.g., bowel surgery) results of cultures should be reported as mixed, e.g., anaerobic/aerobic, and a predominant type of organism described, e.g., mixed gram negative.
4. Gangrene: Dry gangrene is necrosis of tissue of the toes or foot in which darkening or blackness develops and no sensation is present in the affected area. If infection of skin and/or subcutaneous tissues is present, a diagnosis of wet gangrene is made.
5. Cutaneous or Mucocutaneous Infection: Purulent or serous drainage and a pure culture of one organism are needed. If the site normally is rich in normal flora, e.g., mouth, vagina, then the Gram stain or KOH prep and the culture both must be used to confirm the diagnosis. Furunculosis, impetigo, and cellulitis are included under this heading.

### **11.8.2 Major Accident**

A major accident is defined as an event that produces serious injury to the patient or to other persons whether or not hospitalization is required.

### **11.8.3 Psychiatric Disease Requiring Treatment**

1. A definite event should be recorded only if the psychiatric illness involves an episode of treatment by a mental health professional (psychiatric social worker, psychologist, or psychiatrist) and a primary diagnosis of psychiatric illness is made.

Psychiatric illness is defined and reported using diagnostic criteria in the Diagnostic and Statistical Manual of Mental Disorders III published by the American Psychiatric Association.

- a) Outpatient treatment includes evaluations and/or treatment in an emergency room, office or while on a medical/surgical inpatient service for a primary medical problem.
- b) Inpatient treatment means hospital admission to a psychiatric service for a primary psychiatric diagnosis and treatment by a mental health professional.

Specify diagnosis and treatment provided.

2. A probable event may be specified when criteria for treatment and/or diagnosis are unclear or not verifiable, e.g., treatment by a mental health professional when records about specific diagnoses are not obtainable and the patient's report is insufficient to document the nature or severity of the problem. Specify diagnosis and treatment provided.
3. Available records should be used to document the occurrence of an event. In either case, the decision is to be made by the behavioral scientist on the EDIC site.

#### **11.8.4 Pregnancy**

Capture pregnancy information in the FEMALE/REPRODUCTIVE section of Form 002.

Table 11.1

## Summary of Diagnostic Criteria for Nonfatal MI

<u>Prolonged Cardiac Pain</u>	<u>ECG Findings</u>	<u>Enzymes</u>	<u>Diagnosis</u>
Present	Evolving Diagnostic	Abnormal	Definite Acute MI
		Equivocal	Definite Acute MI
		Incomplete	Definite Acute MI
		Normal	Definite Acute MI
Diagnostic	Diagnostic	Abnormal	Definite Acute MI
		Equivocal	Suspected Acute MI
		Incomplete	Suspected Acute MI
		Normal	Definite Nonacute MI
Equivocal	Equivocal	Abnormal	Definite Acute MI
		Equivocal	Suspected Acute MI
		Incomplete	Suspected Acute MI
		Normal	Suspected Nonacute MI
Absent, Uncodable, or Other	Absent, Uncodable, or Other	Abnormal	Definite Acute MI
		Equivocal	Suspected Acute MI
		Incomplete	Suspected Acute MI
		Normal	No MI
Not Present	Evolving Diagnostic	Abnormal	Definite Acute MI
		Equivocal	Definite Acute MI
		Incomplete	Definite Acute MI
		Normal	Definite Acute MI
Diagnostic	Diagnostic	Abnormal	Definite Acute MI
		Equivocal	Suspected Acute MI
		Incomplete	Definite Nonacute MI
		Normal	Definite Nonacute MI
Equivocal	Equivocal	Abnormal	Suspected Acute MI
		Equivocal	Suspected Acute MI
		Incomplete	Suspected Nonacute MI
		Normal	Suspected Nonacute MI
Absent, Uncodable, or Other	Absent, Uncodable, or Other	Abnormal	Suspected Acute MI
		Equivocal	No MI
		Incomplete	No MI
		Normal	No MI

Table 11.2  
Definitions of ECG Types

1. Evolving Diagnostic ECG

An evolving pattern on serial ECGs of ECG changes within lead groups (i.e., anterior (V1-V5); lateral (I, avL, V6); inferior (II, III, avF)). Two or more ECG recordings during the hospitalization are needed for this classification. New Q waves must persist on all subsequent tracings. One or more of the following criteria must be met:

- a) No Q code in one ECG record followed by a record with a diagnostic Q code (Minnesota Code 1-1-1 through 1-2-5 plus 1-2-7). or
- b) An equivocal Q code (Minnesota Code 1-2-8 or any 1-3 code) and no major ST segment depression in one ECG record followed by a record with a diagnostic Q code plus a major ST segment depression (Minnesota Code 4-1 or 4-2). or
- c) An equivocal Q code and no ST segment elevation in one ECG record followed by a record with a diagnostic Q code plus an ST segment elevation (Minnesota Code 9-2). or
- d) An equivocal Q code and no major T wave inversion in one ECG record followed by a record with a diagnostic Q code plus a major T wave inversion (Minnesota Code 5-1 or 5-2). or
- e) No Q code and neither 4-1 nor 4-2 followed by a record with an equivocal Q code plus a 4-1 or a 4-2. or
- f) No Q code and no 9-2 followed by a record with an equivocal Q code plus a 9-2. or
- g) No Q code and neither 5-1 nor 5-2 followed by a record with an equivocal Q code plus a 5-1 or a 5-2.

2. Diagnostic ECG

- a) Minnesota Code 1-1-1 through 1-2-5 plus 1-2-7 for Q and QS patterns. or
- b) Minnesota Code 9-2 for ST segment elevation plus a major T wave inversion (Minnesota Code 5-1 or 5-2).

3. Equivocal ECG

- a) Q and QS patterns 1-2-8 through 1-3-6. or
- b) ST junction and segment depression 4-1 through 4-3. or
- c) T-wave items 5-1 through 5-3. or
- d) ST segment elevation item 9-2.

4. Other ECG

All other findings, including normal.

5. Uncodable ECG

a) Missing lead.

b) Baseline drift greater than 1 in 20, if it obscures ST-T wave.

c) Muscle tremor artifact giving more than 2 mm peak-to-peak oscillation.

d) Other technical errors making Q-wave measurements impossible, such as extreme lack of centering, or marked clipping.

6. Absent ECG

No ECG available for coding.

Table 11.3

## Definitions of Enzyme Criteria

Enzymes will be considered for the categories of "abnormal" or "equivocal" only if (a) the upper limit of normal for the laboratory making the determination is recorded and (b) the enzyme has been measured within 72 hours after arrival at the hospital or after an in-hospital CHD event (whichever is later).

1. Abnormal Cardiac Enzymes

Enzymes will be classed as "abnormal" if all the following criteria are met:

- a) Total CPK is at least twice the upper limit of normal (ULN). and
- b) Either CPK-MB is "present" (if laboratory uses criteria of "present" and "absent"), or CPK-MB (heart fraction) or total LDH or SGOT are at least twice the ULN. and
- c) There is no known non-ischemic cause (defibrillation, surgery, liver disease, injections, etc.) for the elevated enzymes.

2. Equivocal Cardiac Enzymes

Enzymes will be classed as "equivocal" if the following criteria are met:

- a) The criteria for "abnormal" enzymes are not met

AND

At least one of total CPK, CPK-MB (heart fraction), total LDH, or SGOT is above the ULN, or CPK-MB is "present" (if laboratory uses criteria of "present" or "absent"). or

- b) The first two criteria for "abnormal" enzymes are met but there is a non-ischemic cause for elevated enzymes.

3. Normal Cardiac Enzymes

Enzymes will be classed as "normal" if they meet the criteria for consideration as "abnormal" or "equivocal" but do not meet any of the criteria for these categories.

4. Incomplete Cardiac Enzymes

Enzymes will be classed as "incomplete" if they do not meet the criteria for consideration as "abnormal" or "equivocal".

Table 11.4

## Definition of Prolonged Cardiac Pain

Pain having the following characteristics:

1. It occurs anywhere in the anterior chest, left arm, or jaw, and may also involve the back, shoulder, right arm, or abdomen on one or both sides.
2. It has a duration of more than 20 minutes. (See item 4 below for an exception.)
3. There is no definite non-cardiac cause of chest pain (all cases of non-cardiac chest pain to be reviewed by physician panel).
4. If additional doses of nitrates or calcium blockers were self-administered before medical care was sought without obtaining relief of the pain, this is considered sufficient evidence of prolonged cardiac pain without documentation of duration.

Table 11.5

Plasma Total Cholesterol (mg/dl)\*

<u>AGE</u>	<u>MEAN</u>	<u>MALES (white)</u>	
		<u>S.D.</u>	<u>MEAN + 2 S.D.</u>
10-14	157.6	23.86	205.3
15-19	149.9	26.70	203.3
20-24	166.5	29.70	225.9
25-29	182.2	36.15	254.5
30-34	192.2	34.61	261.4
35-39	201.3	38.53	278.4
40-44	206.5	39.42	285.3
45-49	212.2	38.33	288.9
<u>AGE</u>	<u>MEAN</u>	<u>MALES (black)</u>	
		<u>S.D.</u>	<u>MEAN + 2 S.D.</u>
10-19	160.4	25.30	211.0
20-29	178.5	36.44	251.4
30-39	191.6	37.36	266.3
<u>AGE</u>	<u>MEAN</u>	<u>FEMALES (white)</u>	
		<u>S.D.</u>	<u>MEAN + 2 S.D.</u>
10-14	157.6	22.84	205.3
15-19	157.6	27.36	212.3
20-24	171.7	31.66	235.0
25-29	175.8	28.07	231.9
30-34	179.0	32.47	243.9
35-39	186.4	31.40	249.2
40-44	195.0	36.22	267.4
45-49	204.5	37.09	278.7
<u>AGE</u>	<u>MEAN</u>	<u>FEMALES (black)</u>	
		<u>S.D.</u>	<u>MEAN + 2 S.D.</u>
10-19	160.4	28.33	221.7
20-29	178.5	33.58	244.5
30-39	191.6	35.13	255.3

\*From the Lipid Research Clinic Population Studies Data Book, Volume 1, The Prevalence Study - Visit 2, U.S. Department of Health and Human Services, Public Health Service, NIH Publication No. 80-1527, July 1980.

Table 11.6  
Events

Cardiovascular Events

Myocardial infarction  
Coronary artery disease  
Angina pectoris  
Arrhythmia  
Congestive heart failure  
Hypertension  
Hyperlipidemia

Cerebrovascular Events

Ischemic stroke with permanent neurological deficit  
Ischemic stroke without permanent neurological deficit  
Hemorrhagic stroke with permanent neurological deficit  
Hemorrhagic stroke without permanent neurological deficit  
Transient ischemic attack

Peripheral Vascular Events

Peripheral ischemia (claudication)  
Amputation (traumatic or surgical)  
Other Arterial Events  
Lower Extremity Ulcer  
Vascular Disease

Renal Events

Renal insufficiency  
Microalbuminuria  
Albuminuria  
Acute Renal Failure  
Chronic Renal Failure / End-Stage Renal Disease (ESRD)

Ocular Events

Loss of vision or Legal Blindness  
Pan-retinal (scatter) photocoagulation  
Focal photocoagulation  
DRS High-risk characteristics (HRC)  
Proliferative retinopathy less than DRS HRC  
Clinically significant macular edema

Diabetic Events

Ketoacidosis  
Hypoglycemia with Sequelae  
Definite Severe Hypoglycemia  
Suspected Severe Hypoglycemia

Other Events

Infusion site infection  
Urinary tract infection  
Post-operative wound or deep infection  
Gangrene  
Cutaneous or mucocutaneous infection  
Major accident  
Overnight hospitalization  
Psychiatric disease requiring treatment

Pregnancy

## 12. PROCEDURES TO BE FOLLOWED IN THE EVENT OF A DEATH OF AN EDIC VOLUNTEER

Given the number of volunteers enrolled, the expected duration of the EDIC, and the mortality associated with insulin-dependent diabetes mellitus, volunteers will die during the course of the study. In order to assign appropriately a cause of death, carefully collect and document timely and accurate information regarding the clinical course and events occurring immediately before and after each death. The requested information is in addition to the information mandated for the various events described in Chapter 11, and may become causes of death. The circumstances surrounding each death will be unique and it is impossible to anticipate all of them. What follows is a description of basic procedures that should be followed.

### 12.1 General Procedures

Immediately upon learning of the death of an EDIC volunteer, the Principal Investigator or Study Coordinator notifies the Data Coordinating Center by telephone. The staff of the Data Coordinating Center attempts to obtain information about the specifics of each death. See Figure 12.1 for a list of questions that the Data Coordinating Center will ask when they receive a call regarding the death of a patient. The Data Coordinating Center notifies each member of the EDIC Executive Committee when a death occurs.

Complete EDIC Form 140, Notification of Death, within 24 hours of the volunteer's death or discovery of death, and sent it to the Data Coordinating Center. Send copies of the autopsy report, laboratory reports, and death certificate to the Data Coordinating Center as soon as they become available.

As soon as possible after the death, interview family members, friends, hospital staff, or others who may have attended the death or precipitating events, as well as those who had last contact with the deceased. These interviews may take place over the phone. Transmit the information in written narrative form to the Data Coordinating Center. The interview should obtain any information on medical problems, psychosocial problems, and diabetes management in the past 24 hours, 72 hours, and previous ten days. A checklist of possible problems follows:

	Problems occurred within the previous		
	<24 hours	<72 hours	<10 days

#### Medical

- Hypoglycemia
- Symptoms of ketosis/ketoacidosis
- Other illness or symptom
- No illness or symptom

#### Psychosocial

- Clinical symptoms of depression
- Marital discord
- Job disruption
- Substance involvement
- Other

If an autopsy is to be performed, the information gathered from these interviews should be shared with the medical examiner or pathologist with the object of making the determination of the death as accurate as possible. It is important to determine if the victim received

intravenous fluids (especially glucose solutions) or glucagon injections during resuscitative measures as these can affect post-mortem body fluid glucose concentrations measured subsequently.

## 12.2 Special Procedures

In many cases, determining the immediate, underlying, and contributory causes of death is straightforward; in other cases, particularly in unattended, sudden, or accident-related deaths, the cause(s) may be obscure. There are several causes of death that could be related to insulin therapy for IDDM. The following is a list of causes of death that are associated with insulin therapy and should be in the differential diagnosis of the medical examiner or pathologist:

1. Hypoglycemia
2. Diabetic ketoacidosis
3. Hyperosmolar coma (without acidosis)
4. Hypokalemia
5. Toxic shock syndrome
6. Bacterial endocarditis
7. Myocardial infarction
8. Accidents (automobile, drowning, falls, etc.)
9. Renal failure
10. Cerebrovascular accidents
11. Suicides

Other causes of death related to diabetes and insulin therapy may come to light and should be considered when determining the cause of death of an EDIC volunteer. These causes may require other special procedures to be performed to substantiate their presence. Professional judgment will need to be exercised to determine when such procedures are indicated.

Figure 12.1

**INFORMATION TO BE COLLECTED DURING CALLS  
TO REPORT THE DEATH OF AN EDIC PATIENT**

Clinic \_\_\_\_\_ Name of Person Calling \_\_\_\_\_

Date of Call \_\_\_\_\_ Patient ID # \_\_\_\_\_

Patient Gender \_\_\_\_\_ Patient Age \_\_\_\_\_ Treatment Group \_\_\_\_\_

Data Coordinating Person Receiving Call \_\_\_\_\_

I DETAILS OF DEATH

Date of Death \_\_\_\_\_ Date Clinic Learned of Death \_\_\_\_\_

Brief Description \_\_\_\_\_

Suspected Cause of Death \_\_\_\_\_

Are copies of death certificate available/obtained? \_\_\_\_\_

Was the patient hospitalized overnight? \_\_\_\_\_

Did the patient require ER/Paramedic assistance? \_\_\_\_\_

If so, what treatment? \_\_\_\_\_

Who was with the patient? \_\_\_\_\_

Any injuries to other persons? \_\_\_\_\_

Hospitalization to other persons? \_\_\_\_\_

Were authorities involved/notified? (police, paramedics, fire, etc.) \_\_\_\_\_

If an accident, are copies of accident reports/certificate available/obtained? \_\_\_\_\_

If an MVA, was the patient driving? \_\_\_\_\_

If not, who was driving? \_\_\_\_\_

If an MVA, was patient restrained or unrestrained (seat belts)? \_\_\_\_\_

If motorcycle or ATV vehicle, was patient wearing helmet? \_\_\_\_\_

If an accident, who appears to be responsible for the accident? (patient or other vehicle involved) \_\_\_\_\_

If an accident, what appears to be the cause of accident? (weather, speeding, ETOH or drugs, hypoglycemia, etc.) \_\_\_\_\_

\_\_\_\_\_

Were there witnesses? \_\_\_\_\_

## II. RELATIONSHIP TO HYPOGLYCEMIA

Is glucose information available? \_\_\_\_\_

If an accident, blood glucose value at time of accident \_\_\_\_\_

Who measured it, with what (meter, lab) and was reading before or after treatment with glucose? \_\_\_\_\_

Were there symptoms of hypoglycemia? \_\_\_\_\_

Does this patient normally have symptoms associated with hypoglycemia?

\_\_\_\_\_

If anyone was with the patient, were they capable of recognizing hypoglycemia?

\_\_\_\_\_

If so, did they take appropriate action? \_\_\_\_\_

## 13. CHANGES IN FOLLOW-UP SCHEDULE

### 13.1 Introduction

While the success of the EDIC study depends heavily on the extent to which participants adhere to the directions of the Protocol, the study group recognizes that circumstances will arise in which participants become unwilling or unable to maintain the request for follow-up. The term "change in follow-up schedule" is used in a broad sense to include several types of events, such as a modification in the annual evaluations, a change in assigned follow-up schedule, transfer to inactive status, or a loss to follow-up.

This chapter presents definitions of these several types of changes and establishes a terminology by which to refer to them. Inability to obtain measurements of outcome variables may result in loss to follow-up.

The Adherence Monitoring Committee (AMC) is charged with reviewing the overall performance at each clinic on a quarterly basis. Study performance is reviewed as it relates to visit completion and measurements of the major outcome assessments for participants at their assigned clinic. Clinics document their inability to obtain data or evaluations to the DCC by completion of either the EDIC form 141, or acknowledging a participant may have become temporarily inactive (form 144) or have had annual attempted contact by the clinic (form 145). A participant's lack of follow-up may occur despite efforts to prevent it.

Any alteration in a subject's follow-up schedule from that outlined in the Protocol or Manual of Operations represents a modification of outcome visit schedule, or a transfer to inactive status, as discussed below.

### 13.2 Modification of Outcome Visit Schedule

The failure of a participant to undergo an annual follow-up visit does not require a transfer to inactive status. Report each missed measure on EDIC Form 141, Notification of Missed Clinic Visit. Continue to complete Form 141 for all annual visits missed until the subject is transferred to inactive status or resumes the Protocol-specified visit schedule. Avoid transfer to inactive status whenever possible as it applies only when a subject will not return for ANY participation in the study, Avoid pushing a participant as this may result in the withdrawal of informed consent. Reasons for inability or unwillingness to participate in clinic visits may include life constraints from health, family or employment issues. However, clinic staff should remain welcoming to any participant who desires to return to active status at any time throughout the study.

The over-arching principle embraced to maintain participation, is recognizing that an extended 1-day visit to the EDIC center may not be feasible for all participants every year, and that flexibility in maintaining participation is necessary. Therefore, a participant may continue in EDIC by modifying their participation in number of ways. Inability to travel to the EDIC center for a regular, in person annual visit does not mean data cannot be collected. The clinics may consider modifying a visit to encourage continued participation from participants.

Modified visits may include:

- a) Phone visits
- b) Remote lab collections
- c) Splitting the annual evaluations into two shorter duration visits to the clinic

- d) Combined biennial visits
- e) Outreach visits to the participant by the EDIC staff

### **13.2.1 Phone Visits**

The history information required annually can be collected via a phone call interview at a time convenient for the participant. Form 002, Annual History and Physical form, allows for notating that the visit is a phone interview. Additionally, the clinic can mail the participant questionnaires to complete and return in addressed, stamped envelopes. The labs associated with a visit might be collected by remote labs (see section 13.2.2.). It is preferable to complete a phone visit with questionnaires completed via mail vs. declaring the participant inactive because of an inability to return to the clinic annually.

Complete the following forms during a phone visit interview:

- Form 002, Annual Medical History and Physical Examination
- Form 004, Current Medications
- Form 033, National Eye Institute Visual Functioning Questionnaire. This form is completed in conjunction with scheduled eye exam and fundus photography once every four years. Even if photographs are not obtained, the participant can complete this form.
- Form 050 (pg 1), Michigan Neuropathy Screening Instrument
- Form 143, Notification of Update to Personal Locator Form (for clinic use only).
- Other forms may be required for Ancillary Study protocols

The ordering of the clinic specific forms may change dependent upon the year of the phone visit. The following forms can be sent to the patient for completion or by interviewing the participant over the phone:

- Form 060, Quality of Life Questionnaire (per biannual or ancillary study schedule)
- Form 061, Health Status Questionnaire 2.0 (per biannual or ancillary study schedule)
- Form 070, Health Care Delivery Questionnaire
- Other self-completed forms may be required for Ancillary Study protocols.

Document missed information on EDIC Form 141.

### **13.2.2 Remote Lab Collections**

The clinic should consider obtaining lab specimens (HbA1c, lipids, serum creatinine, or cystatin C) with a “remote” collection for those individuals who are unable /unwilling to return to the clinic. Saved specimens need not be collected. Remote lab collections are a collaborative effort between the participant, the EDIC clinic, local health care provider/lab, and the EDIC CBL. This entails having the participant identify their local MD or lab that would be willing to draw the specimens and ship to the EDIC CBL on a day convenient for the participant. The same guidelines for fasting labs, quantities, and shipping procedures that are mandated by the EDIC protocol are used to ensure the quality of the data. The EDIC Study Coordinator is responsible for contacting the lab and ensuring their comfort level with obtaining the specimens, processing, and shipping per the Protocol. The Study Coordinator will then send the labeled aliquot tubes, patient-specific sample shipping forms, instructions, and supplies to either the participant or local lab, based on individual circumstances. The EDIC CBL will be notified when specimens are being obtained via a remote collection, the date they are being drawn, and shipped

(preferably Monday–Thursdays), and given the tracking number of the shipping form. The clinic may notify the CBL via email of the remote collection. The EDIC mailing lists, completed in advance except for date by the Study Coordinator, should indicate to the CBL that it is a remote collection. The EDIC clinic should arrange for reimbursement to the lab so that the participant has no out-of-pocket expenses.

For reference, see EDIC MOO chapters 14 (Labs) and chapter 26 (Adherence).

### **13.2.3 Splitting the annual evaluations & exams in two visits vs. one visit**

Annual evaluations may also be modified to allow participants to complete the evaluations in more than one visit to provide flexibility in meeting the demands of a given visit (such as fasting labs, availability of staff, personal demands, and scheduling realities). The clinic can determine at the time the participant is contacted for scheduling the annual exam what may be most beneficial for the demands of a given year, the availability of various staff (such as the ophthalmology department, neurologist, etc.), and suggest separating the visit into two. It is preferred that the two visits occur within the scheduling window and as close together as possible.

### **13.2.4 Combined biennial visits**

There may be infrequent times that a participant cannot make it to the clinic in a given calendar year. When this happens, combining two annual visits may be conducted in the next calendar year if feasible for the participant. For example, the visit could start with the collection of fasting lipids, and then proceed to the 4-hour renal collection and other evaluations in one day, thus combining 2 years worth of collections. Because the scheduling windows remain open until the next scheduled exam, clinics are encouraged to combine visits when convenient for the participant, rather than missing all of the data associated with a given year. Combined visit barcodes for the labs may be obtained from the CBL. This ensures that all samples collected on a given day are labeled with the same barcode number.

### **13.2.5 Outreach Visits to the Participant by the EDIC Staff**

Because of the extensive geographic distribution and movement of the EDIC cohort across the United States and Canada, traveling to the participant(s) may offer another alternative to completion of the annual EDIC visit. An outreach visit may be arranged, if the Study Coordinator or staff can travel to an area conducive to conducting visits for one or more EDIC participants. Prior to arranging for an outreach visit, the center should arrange for CCC approval of expenditures, and staff should review and follow all local and institutional guidelines. Please see the “Modifications to Allow EDIC Home Visits” section on the Study Coordinators page of the EDIC web site for examples of IRB approved language used at select EDIC centers. Outreach visits could be conducted at the home of a participant, in a local health care office if identified and arranged for, or in some other facility. These visits may provide the flexibility to obtain some of the EDIC exams, evaluations, and labs by the certified EDIC personnel as mandated by the Protocol. The EDIC Adherence Monitoring Committee should be consulted for guidance if needed. Any evaluations not obtained at an outreach visit should be documented on Form 141, Missed Clinic Visit.

### **13.2.6 Protocol Sanctioned Failure to Obtain Annual Determinations**

There are some events or circumstances, such as hypoglycemia, which may result in a protocol-mandated cancellation or postponement of a test procedure or evaluation. Additionally, reaching a previously-defined study endpoint may result in a MOO mandated cancellation or postponement of annual determinations, such as renal studies or eye photographs. These are defined as protocol sanctioned failures to obtain annual determinations. (Reference Chapter 10 of the MOO for a listing of Stop points.)

### **13.2.7 Unsanctioned Failure to Obtain Annual Determinations**

This category embraces participant non-adherence to requested attendance at regularly scheduled annual examinations or participant refusal to undergo certain procedures at such visits. Since participants were transferred to the care of other physicians at the close of the DCCT, some subjects may be reluctant to continue attending the EDIC center for procedures that they do not perceive as essential for the overall care of their diabetes. Each and every reasonable approach to the facilitation of such visits should be taken. This may frequently need to include reimbursement (or in some cases pre-reimbursement) for the cost of transportation either to the original EDIC center or, in the case of participants who have relocated, to the nearest EDIC center. (See Chapter 25 for specifics regarding reimbursement for participant travel.)

## **13.3 Transfer to Temporary Inactive Status**

Transfer to inactive status is defined as a temporary or permanent moratorium on subject participation in the study. Transfer to inactive status occurs in the following situations:

1. When in the judgment of the Principal Investigator and Study Coordinator, any manner of participation in the study would be directly injurious to the participants well-being or could no longer be considered informed, e.g., catastrophic injury or illness resulting in coma, dementia.
2. When there is complete inaccessibility to obtain annual determinations. Examples of this are, long-term imprisonment or repeated inability to have the participant respond to phone, mail or email messages.
3. Participant withdraws consent for continued participation in the study or communication with the staff at the staff's initiative. (This is the only permanent moratorium on participation, reversible if the participant changes his/her mind and contacts the clinic in the future).

EDIC participants who are in the temporary inactive status category should be given every opportunity to return to the study as active participants at any time. The Principal Investigator and/or Study Coordinator are required to attempt contact with the participant at least annually. Form 145, Tracking of Inactive Participants needs to be completed annually and sent to the DCC. Resources that may be used to find a current phone number or address for a hard-to-find participant include, but are not limited to:

- Historic Personal Locator Form 143, (for clinic use only) which includes next of kin contact and employer contact information

- See Appendix 13-2 & 3, “EDIC Suggestions for Looking for Lost Participants” and “Internet Resources for Incarcerated Participants” which offers suggestions or methods of internet searches. Any use of internet searches should be deemed appropriate by local, IRB guidelines.
- Check the EDIC Web for resources that may be utilized if sanctioned locally.

Clinics should continue to include these participants in the mailings of study updates, EDIC Gazettes and study gifts.

Should a previously recalcitrant / inactive participant be reached, and wish to engage in completion of Form 002, Annual Medical History and Physical or schedule an in-person visit, this would “re-activate” his/her status. The participant then becomes active (see Section 13.2).

### **13.3.1 Procedure for Transfer to Inactive Status**

At the earliest knowledge of a participant requiring or anticipating transfer to inactive status, EDIC Form 144, Notification of Transfer to Inactive Status, should be filed with the Data Coordinating Center. The Adherence Monitoring Committee (AMC) will review all cases of transfer to inactive status at their regular meetings.

## **13.4 Lost to Follow-up**

The criteria for assignment to the category of Lost to Follow-up can only be fulfilled retroactively at the end of the study. The DCCT experience indicates that by maintaining close contact with the participant, the number of participants lost to follow-up is minimized. .

## **13.5 Summary**

1. Modification of outcome visit schedule:
  - a) Report missing data on EDIC Form 141
  - b) Phone visit: Complete Form 002, Annual History & Physical, check A.5, Phone visit. Complete the other forms listed in section 13.2.1
  - c) Splitting the annual exam into two visits: complete Form 141 after the first visit; indicate when the second half of the visit will be completed
  - d) Combined biennial visit: Complete the Form 002, Annual History & Physical, write in “combined” visit on top of form
  - e) Remote lab visit: Complete Form 141 for any missed data
  - f) Outreach visit: Complete the Form 141 for any missed data
2. Transfer to inactive status:
  - a) Report on EDIC Form 144.
3. Annual tracking of inactive status
  - a) Report annual contact on Form 145 for all participants who have NOT withdrawn consent.
  - b) Utilize resources (Appendices 13 – 1, 2, 3: EDIC Suggestions for Looking for Lost Participants, and other resources) as deemed appropriate by local IRB’s to search for inactive participants. This includes web sites to ascertain vital statistics.

### **13.6 Cross-Sectional contact in January, 2012 to ascertain vital status**

In January 2012, a request to contact all participants was made to ascertain the vital status of each participant, to be used for the mortality manuscript(s). A letter was sent to all participants for which last contact occurred PRIOR to November 1, 2011. (See Appendix 13-1: Letter to EDIC Participants.) Participants were requested to contact the clinics to ensure that their contact information on file was accurate. This provides a surrogate to determine if the person was alive. If no response to the letter was forthcoming, the Study Coordinators were instructed to search through previous contact information on file, as well as utilize institutionally approved methods of searching for the participants. (See Appendix 13-1: EDIC Suggestions for Looking for Lost Participants, and other resources.)

If the clinic had contact with the participant AFTER November 1, 2011, the Study Coordinators were instructed to complete the Form 146 using that date of contact. .

All completed Form 146s (one for each participant) are to be returned to the Data Coordinating Center by April 30, 2012. This is a point-in-time ascertainment of vital status.

For instructions for completing Form 146, see Appendix 13-3: Letter to Clinics from DCC Regarding Form 146: Checklist for Tracking Vital Status of All DCCT/EDIC Patients.

## Appendix 13-1:

### “EDIC Suggestions for Looking for Lost Participants”

Date: 10/06/2010 (Revised 05/09/2012)

Based on information from M. Bayless, K. Gunyou, S. Strowig & S. Villavicencio

#### Contents

- I. Rationale for searching for EDIC participants
- II. Suggested IRB submission template language
- III. Instructions to search for inactive patients using Ancestry.com
- IV. Other Internet resources for searching for lost participants
  - I. Rationale for IRB submission

Annually, EDIC is responsible for tracking all participants that are living and were part of the original DCCT cohort. Accounting for all participants is attempted to ascertain their geographic location, see if they might be re-engaged to participate, and to determine if they are still living. The first source of information should be the historic form 143's that are kept in the clinic locally: looking at next of kin, employers, etc. Clinics may need to search beyond clinic information for the geographic location of inactive participants, or access vital statistics to determine if they are living,. This may be attempted by using search engines on the internet. Search engines require the use of sensitive patient information such as first, middle, and last name, dates of birth, location of birth, current location, time at the current location, marriage and divorce information.

Every clinic should know what their institutional IRB requires for approval to (a ) use Social Security Number, or (b ) search for the patient's living status on the internet. This may require a change in your consent or IRB application.

General premises: Since HIPAA, some institutions have allowed for the search for participants who have given permission to search for them on the internet. Some institutions may require telling participants you intend to use their social security number to look for them in the future or search for them on the internet. Depending on your institutional IRB regulations, you may or may not be able to search for vital status of inactive patients. Please ask your local IRB if you have questions on whether or not you can search for the living status of inactive patients. In 2010, the DCC indicated they no longer keep names and addresses on file so there is the expectation that the searches will be done at the local clinic level.

If you are allowed to search for the living status of inactive patients, then please review the attached examples (searching using Ancestry.com, or using one of the other resources in the attached documents). The AMC and DCC want to know the results of your searches.

If you have completed a search on a lost participant, please complete Form 140. If you learn the participant is no longer living, note the date you learned of the death in Question B.2. There is not a field on Form 140 to mention how you learned of the death, so please write on Form 140, underneath your answer the search engine used. If you learn of a death, please contact the DCC (Paddy) and send Form 140 to the DCC. (Further information, such as clinical diagnosis of probable cause of death and whether an autopsy and/or death certificate, might be pending until obtained.) Fax Form 140 to the DCC at 301-881-4471.

## II. EXAMPLE IRB submission template (based on EDIC Clinic 10, 2010):

The DCC no longer keeps personal information on participants. The individual clinics will be responsible for searching for those hard to find participants.

The language dissected and approved at Iowa refers to two points:

- Language to include in consent
  - Requests permission to use Social Security #
  - Requests permission to search on the internet

Below , are two check-off's that have been added to the EDIC Core Follow up Consent. Please feel free to use, not use, edit or amend as needed. Having an articulated plan approved that allows local searches for lost participants is critical as EDIC moves forward.

### **SOCIAL SECURITY NUMBER (SSN) USAGE**

You have previously given your social security number on the EDIC Form 143, Personal Locator Form that was sent to the EDIC Data Coordinating Center and retained by the UI research team. The collection of your social security number is to assist the EDIC study group in locating you in the future should we lose contact with you. We would use your social security number to ask state and/or federal agencies to check to see if you are still alive, or to ask Internet services (peoplesearch.com, etc.) that assist in locating individuals for your address and contact information. The collection of your social security number, **for research purposes other than payment**, is strictly optional and is not required for participation in the study. We will only use these services as a last resort if we are unable to locate you.

\_\_\_\_ I allow you to collect and use my social security number for the purposes outlined above.

\_\_\_\_ I do NOT allow you to collect or use my social security number for the purposes outlined above.

(Initial your choice above)

**Do you give us permission to search on the internet for you?** (Please place your initials in the space in front of your response): \_\_\_\_\_ Yes \_\_\_\_\_ No

### III. Example of searching for inactive patients using Ancestry.com

- 1) Identify the inactive patient(s). Make sure your IRB allows you to search for these participants.
- 2) When you do your search, you will use the first, middle, and last name of the inactive participant. It is helpful to know if/how the participant's name has changed based on marriage(s).

It also helps to know other information on the inactive participant. This information includes: date of birth, place of birth (may be able to work with only state, but city and state are preferred), current location, approximate time at that location, marriage year, name of spouse, divorce year (if applicable), and the number of marriages the patient has had (if applicable).

- 3) Note: You can try different combinations (first name, middle initial, and last name; first and middle initials and last name) if one does not work. Your results may differ if there are multiple people with the same first and last name. Thus, it helps to know if the participant has a parent or a child with the same first and last name (and to be able to distinguish birth year of participant versus the parent or the child of the participant).
- 4) Note 2: Even if you don't enter the participant's social security number (SSN), if the participant has died and the record is in the social security death index (SSDI), you might see the SSN. You may then go to <http://www.cdc.gov/nchs/w2w.htm> (a free CDC database) to ascertain how to get a copy of the death certificate for your state if you are in the US).
- 5) Option: You can test the system by looking up patients from your clinic who you know have passed away.
- 6) Option 2: You may want to pay for a membership, based on the results of accessing ancestry without a membership. (It will ask for a credit card # for even the trial 14 day membership). However, there may be less accurate results if there are multiple people with the same first and last name. In case we choose to pay for membership, the cost schedules (as of July 21, 2010) are:

U.S. Cost Schedule		Cost at initiation	Frequency of billing	Number of bills per year	Annual Cost
1	Annual	12.95	billed 1 per yr	12	155.40
2	Every 3 Months	16.95	billed every 3 mo	3	50.85
3	Monthly	19.95	billed every mo	1	19.95
World Cost Schedule (may be needed for Canada)		Cost at initiation	Frequency of billing	Number of bills per year	Annual Cost
1	Annual	24.95	billed 1 per yr	12	299.40
2	Every 3 Months	27.95	billed every 3 mo	3	83.85
3	Monthly	29.95	billed every mo	1	29.95

**NOTE: There are other search engines if Ancestry.com does not provide you the information.**

**APPENDIX 13-2:****INTERNET RESOURCES FOR FINDING LOST PARTICIPANTS**

Compiled at the International Diabetes Center, February, 2010 for the  
Epidemiology of Diabetes Interventions & Complications (EDIC) Trial  
Modified October, 2010

Almost anyone can be located using the Internet. The process is not difficult but can be time-consuming.

In searching for someone, there are four important pieces of information that are needed, which are the person's **name, SSN, DOB, and last known address**. You should have all of this on your contact sheet.

Information about a person, which is found on the Internet, is contained in databases. These databases contain either consumer records (e.g. credit card companies) or public records (government). If someone has not recently participated in a consumer activity (e.g. homeless individual or nursing home resident) then finding information about him or her will be more difficult. Companies who require a fee usually control accesses to databases on the Internet. However, there are many that are free.

**WHITE PAGES:** Phone numbers and addresses of participants, family member, or neighbors

<http://www.555-1212.com>

<http://www.whitepages.com>

<http://www.yellowpages.com>

<http://www.whowhere.com>

**VITAL RECORDS:** Checking for possible deaths and requesting death certificates

<http://www.cdc.gov/nchs/w2w.htm> (This is the CDC data base accessed by Ancestry.com), but you can use for free. Click on your identified state and it walks you through state specific info for obtaining records. In the US, this is the national Death Index through the Centers for Disease Control:

<http://www.cdc.gov/nchs/deaths.htm>

<http://ancestry.com/search/rectype/vital/ssdi/main.htm>

<http://www.vitalchek.com>

<http://collectionsCanada.gc.ca/about-us/index-e.html>

**NEWSPAPERS:** Obituaries

<http://www.cyndislist.com/obits.html>

<http://www.obitlinkspage.com/obit/canada.htm>

**PUBLIC RECORDS:** Resources (May be Fees and Membership required)

<http://www.vericheckinfo.com>

<http://www.publicdata.com>

<http://www.brbpub.com/>

**SEARCH SERVICES:** (Fee Based)

<http://www.canadafind.com>

<http://www.ustrace.com>

<http://www.peoplesearching.com>

<http://intelius.com>

<http://ussearch.com>

<http://beenverified.com>

**GENEALOGY SERVICES:** (Fee Based)

<http://ancestry.com> **(Paid membership is required, but a trial 2 week membership is possible.)**

<http://genealogy.com>

<http://www.usgenweb.com>

<http://www.rootsweb.com>

Hrc\_shr/research resources/recruitment and retention/internet resources for finding lost participants

**APPENDIX 13 – 3:****SUGGESTIONS IN SEARCHING FOR INCARCERATED PARTICIPANTS**

January 20, 2012

Prepared by K. Koepsell, Esq.

The search for incarcerated participants is going to vary, state by state. Generally, criminal files and names of offenders are a matter of public record (unless sealed for some reason, e.g. juveniles or mental health commitments), so I don't anticipate you'll run into any privacy issues.

Always start by googling "[state] online court records," or "[state] department of corrections" and make sure that you're using an actual government site, not a clearinghouse (which may not be current, or may charge you.)

Hunting someone down may be more difficult in states that don't keep their records online (you may end up having to submit a written request, wait for the answer, etc.) However, most Midwestern states, at least, tend to have court and offender records online.

For instance, the Indiana DOC website: <http://www.in.gov/apps/indcorrection/ofs/ofs>

For example, in Wisconsin, we have the CCAP (Circuit Court Access Program) system for court records: <http://wcca.wicourts.gov/index.xsl>

WI's Department of Corrections website to find individual offender information:  
<http://offender.doc.state.wi.us/lop/home.do>

In Iowa, the court records program is here:  
<https://www.iowacourts.state.ia.us/ESAWebApp/>

A wider search of court records can be accessed: <http://mycase.in.gov/default.aspx>

There are two ways to go about searching for someone (which will help in the event you need to "go digging" for someone with a common name):

1) Department of Corrections [DOC] records (which will probably be limited to inmate names, numbers, and potentially institution addresses).

2) Court records (which will list names, case numbers, sentences, etc.) Depending on state, offender level, etc., court records may give you a more thorough picture of where someone is (e.g. "He went into Prison A on B date, sentenced until C, released on D, most recent address of E.")

If confused, it never hurts to call the DOC and ask; they are usually very helpful if you tell them why you're hunting someone down

**Appendix 13-4:****LETTER TO CLINICS FROM DCC REGARDING FORM 146:  
Checklist for Tracking Vital Status of All DCCT/EDIC Patients**

Please find attached a new EDIC form: Form 146, “Checklist for Tracking Vital Status of All DCCT/EDIC Patients”. The purpose of this form is to ascertain the vital status of all EDIC participants as of November 1, 2011. The study group wishes to ensure we know if participants are alive or deceased as of this date for the DCCT/EDIC Mortality Manuscript that is underway.

This is a first time cross-sectional census of the cohort to ascertain the status of the cohort on a given date. We may use this form again in the future for another census.

Form 146 will document four pieces of information:

**1) Study identifying information****2) Your contact with the participant**

If you have **had** contact with the participant since November 1, 2011, you need not contact the participant, but fill in the form. If your contact preceded the November 1, 2011 date, please attempt to contact the participant with the attached letter requesting he/she contact the clinic. The letter requests that each participant contacts the study coordinator by phone, mail or email to verify their contact information. If you do not hear back from a participant, please call or email him/her. If you are unable to contact the individual, do a web search for information about death. (Refer to MOO Chapter 13, Appendix 13-2: EDIC Suggestions for Looking for Lost Participants). Ensure all search activities have been approved by your IRB.

**3) Web Search data on those that do not respond to the letter and those who have withdrawn consent****4) Additional information**

For instance, the participant may not have been reached, but a relative confirms that the participant is living or deceased, etc.

A revised Chapter 13 of the EDIC Manual of Operations, “Changes in Follow-Up Schedule” that outlines the use of Form 146 will be available on the EDIC web site. This can be submitted to your IRB requesting a modification for this contact.

The time line to complete this cross-sectional contact is the month of January 2012. Please complete a Form 146 for each of your current DCCT/EDIC participants and fax all Form 146s to Stephan V. at the DCC (301-881-4471) by April 30, 2012. The contact at the DCC for questions is Stephan V. ([stephanv@bsc.gwu.edu](mailto:stephanv@bsc.gwu.edu) or 301-881-9260 x6832).

TO: "LETTER TO EDIC PARTICIPANTS" to accompany Form 146, January, 2012  
FROM: Personalized from each EDIC clinic

Dear EDIC participants,

Happy New Years to you. Due to your long and dedicated commitment, the DCCT/EDIC study continues to provide the diabetes community with information to increase the understanding of the natural history of type 1 diabetes.

We are being asked by the DCCT/EDIC leadership to make contact with each participant by the end of January. No specific information is needed from you at this time, beyond knowing that we have the correct contact information for you.

Please call XXX or email XXX to confirm your contact information by January 30, 2012. This request is being made to ensure that information about the entire group is current as of this date.

We appreciate your continued involvement in DCCT/EDIC and thank you in advance for your response to this request.

SIGNED: EDIC SC & PI

## 14. LABORATORY SPECIMENS AND THE CENTRAL BIOCHEMISTRY LABORATORY

### 14.1 Introduction

The Central Biochemistry Laboratory (CBL), located at the University of Minnesota Medical Center, in Minneapolis, Minnesota will participate actively in EDIC. The determinations made by the CBL will be used in the analysis of EDIC outcomes and may be used to make decisions about routine patient care. The continuity of high quality laboratory performance is critical. It is important to emphasize that the quality of the laboratory and its work depends upon the quality of the specimens obtained in each clinical center. Thus, prompt processing and preservation of specimens under ideal conditions with secure and speedy delivery to the CBL will help to maintain the quality of laboratory work. Directly address any questions regarding procurement, preservation, and delivery of the specimens to the CBL.

#### 14.1.1 Overview

This chapter describes the standardized procedures used in this study for collecting specimens for outcomes analyses. These specimens include serum and urine for renal studies (Section 14.2); serum for lipids and creatinine (Section 14.3); and hemoglobin A1c (Section 14.4). Section 14.6 of this chapter presents details of specimen collection, processing, labeling, and mailing. Appendix A is the form for ordering supplies from the CBL.

### 14.2 Renal Collections (Creatinine in Serum and Random Urine for Calculated Albumin Creatinine Ratio (ACR) ) (See Figure 14.2)

The measurements of creatinine in serum and creatinine and albumin in urine are used in determining **both renal function and damage**. Renal **damage** will be assessed from a random urine, preferably collected in the morning. Calculation of Albumin Creatinine Ratio (ACR) will be **calculated** from a random urine, and serum creatinine. **Starting August 1, 2012, cystatin C measurement will be discontinued**. The guidelines outlined below should be implemented and followed as closely as possible to decrease intra-person variability.

#### 14.2.1 Preparing for the Procedure

1. The **random** urine should be collected under the same circumstances previously identified for the 4-hour renal collection.
2. The **random** urine collection should not occur if the patient is acutely ill, has a urinary tract infection, is menstruating, or has vaginitis. If the patient is unable to return to the clinic on another day to complete the renal collection, collect the urine per protocol and record all comments on the **ACR, Creatinine and Saved Specimens Mailing List** (Form 115).
3. Non-steroidal anti-inflammatory medications (aspirin, Motrin, Advil, ibuprofen, etc.) should be discontinued 48 hours prior to the random urine collection. Acetaminophen (Tylenol) can be substituted as needed.
4. All routine, daily medications should be continued (i.e., antihypertensives, diuretics, thyroid medication, birth control pills, etc.) per usual. Antibiotics may be taken if the person is not acutely ill or does not have a fever.

5. Exercise can alter albumin excretion. The patient should be instructed to refrain from exercise 24 hours prior to the random urine collection. Normal daily heavy job activity may be continued. For the person who does planned exercises daily, they should refrain from exercise 24 hours prior to the random urine collection. Exercise/activity deviations should be recorded on the **ACR, Creatinine and Saved Specimens Mailing List**.
5. Smoking should be avoided for 1 hour prior to the **random** urine collection. Use of nicotine patch or gum should also be avoided. Any variance should be recorded on the Renal Studies Specimen Mailing List.
6. Preferably, the **random** urine collection is done in the morning after the patient has had breakfast and the first injection of insulin. However, the collection can be obtained anytime during the day or night, if necessary.
7. Caffeine should be avoided for 1 hour prior to the random urine collection. There are no other dietary restrictions or requirements. Blood glucose levels should be above 80 mg/dL at the time of the collection.
8. If the patient is pregnant, record this information on the **ACR, Creatinine and Saved Specimens Mailing List** and proceed with the collection.
9. If the patient is hyperglycemic and ketotic (in the absence of illness), clinical judgment should dictate whether or not to proceed with the collection.
10. If the patient is on dialysis, no urine is collected. However, blood for creatinine should be obtained and a comment recorded on the appropriate mailing list. Patients who have had a kidney transplant have met the criteria for a stop point in EDIC. The stop point for the renal exam is referenced in section 10.4.3 of the MOO.
11. The **random** urine collection will be performed on all EDIC participants every 2 years, according to the patient's Schedule of Patient Evaluations for Outcome Analysis.
12. Questions regarding individual circumstances or issues should be referred to the CBL.

#### **14.2.2 Collection Procedures**

1. The **random** urine should be collected in the EDIC clinic, preferably in the morning.
2. Ask the patient to void and retain the sample. Record the time. **This sample will be mixed and aliquoted into seven 1.8 mL cryotubes per Section 14.6.8 and frozen pending shipment to the CBL.**
3. The blood for HbA1c, serum creatinine and serum for saved samples is drawn the AM of the urine collection. Whenever possible, to minimize multiple venipunctures, obtain all EDIC blood samples at one time. Check the blood glucose level prior to the blood draw to ascertain there is a serum glucose level greater than 80 mg/dL.

- a) Collect two 10 mL red-top tubes and allow to clot **for at least 30 minutes**.
- b) Spin and separate the serum and cells, ideally within 30 minutes.
- c) Draw a 5 mL EDTA tube for the HbA1c at the time the red tops are drawn.

### 14.2.3 Specimen Processing (See Figure 14.2)

#### 1. Urine Processing, RANDOM

- a) Thoroughly mix the single void urine specimen and aliquot with a transfer pipette into **seven 1.8 mL cryotubes labeled URCrA (2 tubes) and URSav (5 tubes)**. **If the urine output is less than the 13 ml required to fill seven urine cryotubes, fill completely a minimum of one cryotube for URCrA and one to four cryotubes for URSav .** (See Figure 14.2) Discard any remainder of the first void sample.
- b) Freeze all specimens after transfer to labeled tubes and store frozen until shipment to the CBL. The samples should be stored in a freezer that does not pass through a frost-free cycle. A -70°C freezer is preferred, but a -20°C freezer can be utilized if that is all that is available. Store samples at the back of the freezer to ensure the most constant storage temperature. It is important that the specimens, once frozen, are not thawed.

**1) One URCrA tube will be retained in the clinic as a backup sample. The remaining urine tubes will be sent to the CBL in the monthly shipment. If the samples are stored at -20°C, samples should be sent to the CBL within 2 weeks of collection.**

**2) All URSav tubes will be stored in the CBL at -70°C (-94° F).**

#### 2. Serum Processing

- a) Separate the serum and cells ideally within 30 minutes after spinning the blood in a centrifuge for 10 minutes at 3000 rpm.
- b) With a transfer pipette, separate the serum from one 10 mL blood collection tube into **two 1.8 mL cryotubes labeled for serum creatinine (Cr)**. **Separate the serum from the second red top tube into three 1.8 mL cryotubes labeled Serum Saved (SSav)**. Once aliquoted, the samples should be stored frozen until shipment to the CBL. The samples should be stored in a freezer that does not pass through a frost-free cycle. It is important that the specimens, once frozen, are not thawed. **One Cr tube will be retained in the clinic as a backup sample. The remaining tubes will be sent to the CBL in the monthly shipment. If the samples are stored at -20°C, samples should be sent to the CBL within 2 weeks of collection.**
- c) All SSav tubes will be stored in the CBL at -70°C (-94° F).

3. **Record the number of URSav and SSav tubes, weight in kg, height in cm, time and date of collection, the EDIC follow-up year and any deviations in patient circumstance on the ACR, Creatinine and Saved Specimens Specimen Mailing List (Form 115).**
5. If you have any questions regarding a collection and are unable to obtain assistance from the CBL staff, always collect the urine and blood and note the issue on the **ACR, Creatinine and Saved Specimens Mailing List (Form 115).**

#### **14.2.4 Collection of Renal Outside of the EDIC Clinical Center**

1. All efforts should be made to collect the random urine according to the EDIC protocol at the EDIC clinical centers. In the rare situation where circumstances do not permit this collection to occur at the EDIC clinical center, the following procedure may be carried out locally at the discretion of the Principal Investigator / Study Coordinator.
  - a) Random urine collection utilizing the EDIC Manual of Operations procedure.
  - b) Collect a blood sample of 10 mL in a red-top tube, centrifuge, and aliquot into **two labeled 1.8 mL cryotubes for serum creatinine (Cr)**. Whenever possible, to minimize multiple venipunctures, obtain all EDIC blood samples at one time. Send both tubes to the CBL. Do not collect blood for saved serum (SSav).
2. All urine and centrifuged/separated serum must be refrigerated after collection **until able to be frozen.**
3. Within 3 days of an off-site collection, the specimens **must be shipped on a cold pack** to the CBL for storage at -70°C as described in Section 14.2.3.8.
4. The blood for serum creatinine may be drawn anytime during the morning of the random urine collection.
5. **When the sample random collection is received or obtained at the clinical center, record the time of voiding. Aliquot the urine equally into seven 1.8 mL cryotubes; labeled URCrA (2 tubes) and URSav (5 tubes). Send all tubes to the CBL as described in the Random Section 14.2.3.8). Do not collect Saved Urine samples.**
6. **Record the number of URSav tubes, time of the random urine collection, weight, height, date of collection, and the EDIC year of follow-up on the ACR, Creatinine and Saved Specimens Mailing List (EDIC Form 115).** Indicate any special circumstances or differences in collection from the in-clinic Renal procedure on the **ACR, Creatinine, and Saved Specimens Mailing List Comment Section.**
7. Once aliquotted, the samples should be frozen in a freezer that does not pass through a frost-free cycle until shipment to the CBL. Store samples at the back of freezers to insure the most constant storage temperature. It is important that the specimens, once frozen, are not thawed. All backup samples are sent to **the CBL for retention and are not stored at the local clinic. Samples will be sent frozen using the small box used for A1C sample shipment. The gel pack should be**

**frozen, the samples wrapped and bagged per usual procedure, the samples placed into the Styrofoam box under the frozen gel pack. Please note that frozen samples and HbA1c cannot be enclosed and shipped in the same container. Two small shipment boxes will be needed.**

8. If renal samples must be obtained by someone other than EDIC staff, the responsible EDIC clinic must make the necessary arrangements with the local provider to assure consistency in the collection, preparation, and shipment of samples to the CBL according to the EDIC Manual of Operations Laboratory chapter.

### **14.3 Lipids (Cholesterol, Triglycerides, HDL Cholesterol) and Creatinine (See Figure 14.3)**

1. For this collection, instruct the patient to refrain from eating or drinking (except water) after midnight on the night prior to testing in order to be fasting for at least eight hours. If the fast has been broken and the patient cannot be rescheduled, draw the blood and make a note on the Lipid, Serum Creatinine and Saved Specimen Mailing List Form 105.
2. Draw blood into a 10 mL red-top serum tube, allow to clot for at least 30 minutes and spin in a centrifuge for 10 minutes at 3000 rpm. Separate the serum with a transfer pipette and freeze the separated serum as follows: transfer the serum in equal volumes into **two 1.8 mL cryotubes labeled CrLip. One CrLip tube will be sent to the CBL. The second CrLip tube will be retained at the clinic as a backup sample.**
3. Backup samples are frozen and maintained for 1 year following collection. Once aliquotted, the samples should be frozen in a freezer that does not pass through a frost-free cycle until shipment to the CBL. -70°C freezers are preferred, but -20°C can be utilized if that is all available. Store samples at the back of the freezer to insure the most constant storage temperature. It is important that the specimens, once frozen, are not thawed.

#### **14.3.1 Collection of Lipid Saved Specimens**

1. Obtain specimens for both serum and plasma, in the fasting state from all patients at all visits when a blood specimen is drawn for the assay of lipids. The purpose of this collection is to have a central storage of extra fasting serum and plasma so that assays, currently unspecified, may be performed in the future. In the following section, specific instructions are given for the collection, processing, and storage of these specimens.
2. Draw blood into a 10 mL red-top serum tube, allow **to clot at room temperature** for at least 30 minutes and spin in a centrifuge for 10 minutes at 3000 rpm. **Separate the serum into three 1.8 mL cryotubes labeled "NTra" and promptly freeze.**
3. Draw the selected size and number of (see chart below in 3.d.) pre-chilled EDTA (lavender stopper) tubes, allowing each tube to fill completely. Mix eight times by inversion and place the tube(s) on ice:

- a) **Add selected mLs of Trasylo/aptopinin to the EDTA tube(s): 0.50 mL Trasylo per mL of whole blood collected.** This can be done with a pipette or an insulin syringe. The syringe needle can be inserted through the lavender rubber stopper or the stopper can be removed when adding the selected amount of Trasylo / aprotinin to the tube. Keep a supply of EDTA tubes and one or more vials of Trasylo/aprotinin refrigerated. (Do not use EDTA tubes past the expiration date of the tube.) **Trasylo/aprotinin has no expiration date; an opened vial should be stored in the refrigerator and used until the contents are gone.**
- c) After addition of Trasylo/aprotinin, mix thoroughly and place the tube on ice immediately. Chilling helps maintain the stability of analytes in the blood, permitting centrifugation of this tube together with the serum tube once the latter has clotted. The blood is then spun as soon as possible in a centrifuge at 3000 rpm for 10 minutes. The plasma is transferred to three 1.8 mL cryotubes (labeled "Tras") and immediately placed on dry ice where it will freeze in 5 to 10 minutes.

d) If Using:

	Add Trasylo/aprotinin	# Tubes to draw/pt
3 mL tube	0.15 mL	3 tubes
7 mL tube	0.35 mL	1 tube
10 mL tube	0.50 mL	1 tube

4. All 1.8 mL vials are labeled with the barcode number utilized for the lipid profile specimens. Barcodes for saved specimens are provided (Tras, NTra).
5. Send the three vials of serum (NTra) and the three vials of plasma (Tras) to the CBL with the lipid specimen. Indicate in the comment column of the mailing list (EDIC Form 105) that these serum and/or plasma saved specimens are included.
6. If the patient is pregnant or on dialysis, draw the samples and record patient status on the Lipid, Serum Creatinine and Saved Specimen Mailing List (Form 105).

#### **14.3.2 Collection of Lipids Outside of the EDIC Clinical Center by non-EDIC Staff**

1. All efforts should be made to perform the Lipid (Cholesterol, Triglycerides, HDL cholesterol) and Creatinine collection according to the EDIC protocol at the EDIC clinical centers. In the rare situation where circumstances do not permit this collection to occur at the EDIC clinical center, the following procedures may be carried out locally at the discretion of the Principal Investigator / Study Coordinator, using the following priority ranking:
  - a) Fasting specimens utilizing the EDIC Manual of Operations procedure; OR
  - b) Non fasting specimens and make a note on the mailing list
  - c) An attempt must be made to centrifuge the above samples within 30 minutes of draw but if this is not possible, keep the samples cool and process within 3 hours.

2. Collect one 10 mL red top tube; clot for 30 minutes and centrifuge at 3000 rpm for 10 minutes. Aliquot into 2 1.8 mL cryotubes labeled (**CrLip**) and freeze. All centrifuged/separated serum must be frozen after collection.
3. Within 3 days of an off-site collection, the frozen specimens must be shipped to the CBL **using the small box used for A1C sample shipment. The gel pack should be frozen, the samples wrapped and bagged per usual procedure, the samples placed into the Styrofoam box under the frozen gel pack. Please note that frozen samples and HbA1c cannot be enclosed and shipped in the same container. Two small shipment boxes will be needed.**
4. **No saved specimens are drawn for remote Lipid collections. Send the backup tube to the CBL; do not store locally.**
5. **If lipid samples must be obtained locally, the responsible EDIC clinic must make the necessary arrangements with the local provider to assure consistency in the collection, preparation, and shipment of samples to the CBL according to the EDIC Manual of Operations Laboratory chapter**

#### 14.4 Hemoglobin A1c<sup>1</sup> (See Figure 14.2 and Figure 14.3)

1. Hemoglobin A1c (glycated hemoglobin) tubes will remain as whole blood and should be refrigerated or placed on ice immediately. Whenever possible, to minimize multiple venipunctures, obtain all EDIC blood samples at one time.
2. Pipette a minimum of 1 mL sample of the 5 mL whole blood taken in EDTA into **two 4.5 mL cryotubes** labeled HA1c. One tube will be shipped to the CBL; the other will be stored refrigerated as a backup sample for 2 weeks and then discarded.
3. Ship to the CBL using frozen gel pack and packing from the CBL within 6 days of collection.

##### 14.4.1 Collection of Hemoglobin A1c Outside of the EDIC Clinical Center by non-EDIC Staff

1. All efforts should be made to perform the Hemoglobin A1c test according to the EDIC protocol at the EDIC clinical centers. In the rare situation where circumstances do not permit this collection to occur at the EDIC clinical center, the following procedures may be carried out locally at the discretion of the Principal Investigator / Study Coordinator.
  - a) Collect a sufficient sample in a EDTA tube to transfer into one 4.5 mL cryotube labeled HA1c. Keep sample cool until shipping can take place.
  - b) Ship both tubes to the CBL using frozen gel pack and packing from the CBL within 6 days of collection.

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<sup>1</sup> Steffes M, Cleary P, Goldstein D, Little R, Wiedmeyer H, Rohlfing C, England J, Bucksa J, Nowicki M, and DCCT/EDIC Research Group. Hemoglobin A1c Measurements over Nearly Two Decades: Sustaining Comparable Values throughout the Diabetes Control and Complications Trial and the Epidemiology of Diabetes Interventions and Complications Study. Clin Chem 2005;51:753-758.

2. If this sample must be obtained outside of the EDIC clinical center, the responsible EDIC clinic must make the necessary arrangements with the local provider to assure consistency in the collection, preparation, and shipment of samples to the CBL according to the EDIC Manual of Operations Laboratory chapter.

#### **14.5 Prioritizing Specimen Collection**

1. In those situations where the desired amount of blood cannot be collected (dialysis anemia, venous access, etc) collect one EDTA tube and process for HbA1c as described in section 14.4. Also collect one red-topped serum tube for lipids and creatinine and process as directed in section 14.3 paragraph 2.
2. If capillary samples must be submitted in place of the usual sample amounts, collect capillary samples according to the directions in section 14.6.12.1 of this chapter. (A capillary collection kit must be ordered from the central laboratory prior to the patient visit. Capillary tubes should not be used if expired.)
3. For a combined visit (Renal and Lipid) use the cryotube labels for a combined visit. The labels will contain Hemoglobin A1C, Renal and Lipid labels with the same accession number.

If the visit samples are completed per the standard visit protocol (i.e., **random renal** collection, usual amounts of blood) draw one EDTA tube for the Hemoglobin A1c and one to 3 EDTA tubes (depending on the tube size) for the Tras specimens, and two red topped serum tubes for the **CrLip** and NTras specimens. **Do not collect duplicate saved serum samples.**

For a combined visit (Renal and Lipid) that will not be completed per the standard visit protocol, collect as many specimens as you can and mark the mailing lists with the appropriate comments for the change in collection amount or directions. Primary samples should be collected before any saved specimen samples.

#### **14.6 Specimen Collection, Processing, Labeling, and Mailing**

##### **14.6.1 The Facility**

Under optimal circumstances, utilize a facility oriented for examination of patients and procurement of specimens; e.g., Clinical Research Unit or Outpatient Clinic. Equipment, including a centrifuge to spin the blood specimens, is ideally located adjacent to the patient facility. Storage of back-up specimens should be ideally maintained in a -70°C freezer (preferred) or -20°C freezer. See section 14.6.6.

##### **14.6.2 Supplies for Blood and Urine Specimens**

Supplies for drawing blood and obtaining urine include venipuncture tubes, needles, containers, alcohol swabs, tourniquet, and racks to hold the tubes and containers. The **CBL** and the Data Coordinating Center have collaborated to produce barcodes, attempting to minimize labeling errors (See Section 14.6.7). The set of barcode labels generated by the **CBL** contains sufficient copies for the blood and urine aliquots. Prior to obtaining these specimens, organize and make available appropriately labeled venipuncture containers and urine receptacles and labeled

cryotubes. The procedures outlined in subsequent sections identify the containers needed for each protocol in the study.

A supply reorder form is provided in Appendix A of this chapter and on the website to enable the clinics to replenish their supply of the items listed. These include bar-coded accession number labels for the specimen tubes for the Lipid, Renal and Combination visits, aliquot cryotubes in sizes 1.8 mL and 4.5 mL, absorbent pads, Trayslol/aprotinin, Exempt Human Specimen labels and specimen shipment boxes. **All other collection and processing supplies must be furnished by the EDIC sites.**

### **14.6.3 Drawing Blood**

Prior to drawing blood, it is imperative to recheck the appropriate barcodes and forms for the patient. Blood is drawn from an antecubital vein or another convenient vein in the arm. Swab the venipuncture site with an alcohol wipe and allow to dry before venipuncture. Apply the tourniquet prior to venipuncture and remove after successful venipuncture. The person drawing the blood should be sufficiently well organized so the tourniquet will be in place no longer than 1 minute during the actual collection, due to the possible occurrence of hemoconcentration and infiltration of blood into tissue. Avoid vigorous motion of the arm in an attempt to improve the ability to locate the vein. Care should be taken to minimize the formation of hematomas. The needle is introduced into a vein, and the tourniquet is released as soon as the blood enters the first tube, within one minute. Fill the required number of vacutainer tubes as completely as possible. Gently invert all vacutainer tubes containing additives at least four times to mix the blood and the additive. Use a dry pad to apply pressure when removing the needle from the skin.

Exception: For patients with fragile veins that might collapse or other situations where release of the tourniquet might result in stoppage of blood flow, the tourniquet is sometimes left on until the last tube is filled.

#### **14.6.3.1 No Venous Access**

Because of medical circumstances in which venous access for blood collection is difficult or impossible, a fingerstick or use of central lines or intravenous ports may be utilized. While blood collected from finger capillaries can yield quality analytical results, the blood collection technique becomes critical in the ascertainment of the sample. A comprehensive procedure for proper blood collection from fingerstick and the required blood volumes and collection devices required is located in the Appendices, and section 14.6.1 of this chapter, on the EDIC Study website, or you may contact the CBL. The use of central lines or intravenous ports to obtain blood samples should be guided by local institution policies.

### **14.6.4 Processing Specimens**

Once the appropriate amount of blood is drawn into the correct vacutainer tube as listed for each test (Table 14.1), processing must be done according to the guidelines outlined in the above sections.

#### **14.6.5 Recommended Precautions for Preventing Transmission of Bloodborne Infectious Diseases**

The processing of human biological specimens presents significant biohazard safety concerns. The individuals involved should work under the assumption that all biological specimens may be infectious and require scrupulous aseptic handling.

##### Routes of Infection:

Infectious microorganisms may be contracted by several primary routes. They are:

1. Droplet aerosols. These may be formed when liquids are agitated, causing microscopic droplets to leave the surface of the liquid and become airborne. Aerosols may be created by pouring or pipetting liquids, removing tightly fitting caps from test tubes and during centrifuging.
2. Ingestion. This occurs when infectious microorganisms are taken into the mouth and swallowed. Avoid hand to mouth contact, poor hand washing practices, mouth pipetting of biological specimens, and placing objects in the mouth such as pencils, etc.
3. Direct Inoculation. Parenteral exposure occurring as a result of a break in the skin or contact with mucous membranes (conjunctiva). Examples are nicks, cuts, scratches, needle sticks, or splashes to the eyes.

##### Several Ways to Assure Infection Control Protection During Venipuncture are:

1. Glove use should follow local institutional guidelines. The safest method involves use of gloves whenever handling body fluids, substances, etc. from another person.
2. Consider all needles as potentially infective, and handle them with extraordinary care to prevent accidental injuries.
3. Place disposable syringes and needles into puncture-resistant containers located as close as practical to the area in which they were used. To prevent needle stick injuries, needles should not be recapped, purposefully bent, broken, removed from disposable syringes, or otherwise manipulated by hand.
4. Promptly clean blood spills with a disinfectant solution such as sodium hypochlorite or follow institutional guidelines.

##### Several Ways to Assure Infection Control Protection During Specimen Handling and Processing are:

1. Treat all specimens as if they are contaminated; that is, a source of hepatitis B virus, AIDS agent, slow virus such as Creutzfeldt-Jacob, or other disease producing agents.
2. Wear protective rubber gloves when processing all specimens.
3. Tightly cap all specimens before centrifuged.

4. Separate/aliquot all specimens with transfer pipettes, not by pouring.
5. No mouth pipetting.
6. Frequent hand washing with an approved antiseptic soap is essential.
7. Clean work areas with 1% sodium hypochlorite solution or follow institutional guidelines.
8. Dispose of all potentially contaminated materials following institutional guidelines.

#### **14.6.6 Storage of Frozen Serum and Urine Specimens Prior to Shipment to the Central Biochemistry Laboratory**

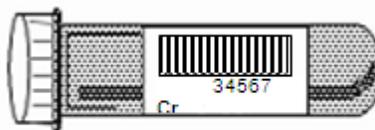
Identify a freezer, either a  $-70^{\circ}\text{C}$  (preferred) or a  $-20^{\circ}\text{C}$  freezer, that can serve for safe storage of serum, plasma and urine specimens. The freezer must not have an automatic defrost mode; it is very important that the specimens not thaw once frozen. Check the temperature of the freezer frequently to ensure a constant temperature range of  $-70^{\circ}\text{C} \pm 5^{\circ}\text{C}$  degrees or  $-20^{\circ}\text{C} \pm 5^{\circ}\text{C}$ . Maintain all frozen backup samples and discard after 1 year. If samples are stored at  $-20^{\circ}\text{C}$ , ship to the central laboratory within 2 weeks of storage. Samples stored at  $-70^{\circ}\text{C}$  may be shipped monthly.

#### **14.6.7 Specimen Identification**

Specimens are identified by barcodes generated by the CBL and sent to each clinic. The barcodes are not patient specific; however, once a barcode has been designated for a patient, all of that patient's CBL assessments will be labeled with the same barcode series for that annual visit.

Before aliquotting samples, barcode labels are to be placed on the cryotubes. Apply the white portion of the label first, aligning it so that the leading digit of the barcode ID number is closest to the top of the cryotube. Then wrap the rest of the label around the cryotube.

The barcodes are provided in sheaves; one sheaf consists of a series of labels that all share the same unique barcode ID. Three label sequences have been generated according to the testing protocol: a Hemoglobin A1c/Lipid sequence, a Hemoglobin A1c/Renal sequence, and a Combined Visit Lipid/Renal sequence. The label sheaf used for a Lipid Visit consists of 18 barcode ID labels. (See Figure 14.4.) The sheaf of labels used for a Renal Visit consists of 21 labels. (See Figure 14.5.) If a patient is to have a lipid and renal collection done on the same day, the same barcode number should be used for the entire visit. Request the combined visit barcode sheets from the CBL. A sheaf of Combination Lipid/Renal Visit barcode ID labels consists of a total of 30 labels that share the same barcode ID: 15 Lipid Visit labels followed by 15 Renal Visit labels. (See Figure 14.6.)



Each sequence of barcodes also has unique identifiers for specific test tubes. Instructions for the use of these labels follows:

#### Hemoglobin A1c-Lipid Sequence (Labels 1-18)

Affix labels to:

- |                 |          |  |
|-----------------|----------|--|
| Labels          | (ML):    | Mailing Lists (N=3)  |
| Labels          | (HA1c):  | Hemoglobin A1c cryotubes (N=2)   |
| Labels          | (CrLip): | Serum cryotubes for creatinine and lipid assay (N=2)   |
| Labels<br>(N=3) | (Tras):  | Storage cryotubes for saved plasma treated with Trasylol/aprotinin   |
| Labels          | (NTra):  | Storage cryotubes for "No trasylol"/Aprotinin saved serum (N=3)  |
| Labels          | (x):     | These extra labels may be used to label the blood collection tubes used in drawing the samples for this sequence. They may also be used for any additional paperwork involving the participant. If one of these labels is used to replace a damaged label having an assigned identifier (e.g., HA1c), write the identifier onto the replacement label. |

#### Hemoglobin A1c-Renal Sequence (Labels 1-21)

Affix labels to:

- |        |          |   |
|--------|----------|---|
| Labels | (ML):    | Mailing Lists (N=3)   |
| Labels | (HA1c):  | Hemoglobin A1c cryotubes (N=2)  |
| Labels | (Cr):    | Serum cryotubes for creatinine assay (N=2)  |
| Labels | (SSav):  | Storage cryotubes for saved serum (N=3)   |
| Labels | (URCrA): | Urine cryotubes for creatinine and albumin assays (N=2)   |
| Labels | (URSav): | Urine cryotubes for saved random urine (N=5)  |
| Labels | (x):     | These extra labels may be used to label the blood collection tubes used in drawing the samples for this sequence. They may also be used for |

any additional paperwork involving the participant. If one of these labels is used to replace a damaged label having an assigned identifier (e.g., HA1c), write the identifier onto the replacement label.

If the same mailing list is used for more than one patient, affix the Barcode labels so that they overlap, aligning each barcode number within its respective line on the Mailing List. The original Mailing List must be enclosed with the specimens when shipped overnight to the CBL so that the CBL can scan the original barcodes (there is no need to separately mail a copy of the Mailing List to the CBL). Always retain a copy of the Mailing List in the clinic's files and send a copy of the mailing list to the DCC in the monthly mailing.

#### **14.6.7.1 Quality Control Barcodes**

Several extra specimen ID number sets are provided to each clinic to accommodate the collection of HA1c, lipid, and renal duplicate samples. If the duplicate sample collected is for HA1c or lipids, use a new set of 18 labels for identifying the samples. Extra labels may be discarded. Do not use the remaining labels to identify a future quality control sample. If a renal duplicate set is collected, use a new set of 21 labels for identifying those samples. Again, discard the extra labels. Notify the Data Coordinating Center that the quality control specimens were shipped by completing the appropriate EDIC Quality Control Mailing List (Form 110, Form 111, Form 112, or Form 113). Please do not contact the CBL for questions regarding collection of Quality Control samples. Questions should be directed to the EDIC Data Coordinating Center.

#### **14.6.7.2 Repeat Collections**

If specimens need to be recollected, use a new complete set of barcodes.

If a complete set of specimens is not sent to the CBL (e.g., the participant was not fasting for lipids) and only a partial set is collected (e.g., hemoglobin A1c) retain the remaining original set of labels for that visit and use them if or when the participant returns to complete the visit. Make a note on the respective specimen mailing list to explain incomplete or delayed collection.

#### **14.6.8 Shipment to the Central Biochemistry Laboratory**

Serum and urine specimens will be sent frozen on dry ice to the CBL every two weeks (if stored at -20°C) or once a month (if stored at -70°C). Whole blood samples for Hemoglobin A1c measurements will be sent in specific mailing containers with frozen gel packs (provided by the CBL) to the CBL within 6 days of the collection. The Federal Express account number for the shipment to the CBL is 1085-9444-6.

The mailing address and phone number for the CBL are:

Maren Nowicki  
EDIC Central Biochemistry Laboratory  
Advanced Research and Diagnostic Laboratory  
University of Minnesota  
Room L275 Mayo  
420 Delaware St. S.E.  
Minneapolis, MN 55455-0341

Phone 612-273-3645

Use the following protocol when shipping to the laboratory. If there are any questions regarding specimen status or shipment, please contact the CBL.

#### **14.6.8.1 For Frozen Specimens**

Specimens should be sent Monday through Thursday (being careful to avoid any weeks in which a holiday may occur). Shipping on Monday or Tuesday avoids problems in transporting the specimens over weekends. Any shipment deviations or questions should be discussed directly with the CBL.

The frozen specimens need to be shipped within two weeks of collection if stored in a -20°C freezer. They can be stored in the EDIC clinic for four weeks if stored in a -70°C freezer.

These shipping directions meet the requirements of the International Aviation Transportation Association (IATA) guidelines.

Each clinical center should utilize the following protocol:

1. Using the insulated shipping containers provided by the CBL for frozen specimens, pack the specimens with at least 2½ to 3 pounds of dry ice. This amount should be increased during the warmer months. Specimens should be wrapped in absorbent material, placed in a plastic bags with an absorbent pad enclosed, grouped by specimen type (i.e., lipids, renal) or by patient ID number. Enclose the completed specimen mailing list on top of the insulated shipping container prior to sealing the cardboard box.
2. Affix a UN3373-Biological Substance Category B label and a Dry Ice label with all requested information filled in to the outside of the transport box. This information includes the sender and recipient addresses and the weight of the shipment. These labels are provided by the CBL upon request.
3. Complete the appropriate Federal Express shipping forms. In answer to the query, 'Does this shipment contain dangerous goods?', check 'Yes – Shippers' Declaration Not Required'. The Dry Ice section of the shipping form must be completed with the weight of the dry ice and the weight of the shipment. Samples must be shipped Priority Overnight. The Federal Express account number for the shipment to the CBL is 1085-9444-6.
4. Contact Federal Express (800-GO-FEDEX) for pick up. The package can be tracked by going to fedex.com and entering in the number from the Fed Ex shipping receipt.
5. Shipping containers and other supplies will be returned to each of the clinical centers by Federal Express. If you are running short of any supplies, please contact the CBL.

#### **14.6.8.2 For Whole Blood Hemoglobin A1c**

Specimens should be sent Monday through Thursday of each week to ensure the integrity of the samples. Shipping on Monday or Tuesday avoids problems in transporting the specimens over weekends. Any shipment deviations or questions should be discussed directly with the CBL.

These shipping directions meet the requirements of the International Aviation Transportation Association guidelines

Each clinical center should utilize the following protocol:

1. Tubes of whole blood should be stored at 4°C (39°F) in the refrigerator until shipped. Shipping must be accomplished within six days of collection.
2. Assure that the appropriate barcode is on the tube. Small styrofoam shipping boxes have been provided with an 8 oz. gel pack by the CBL.
3. Once the shipping box is received from the CBL, place the gel pack (fold one end to reduce the size of the pack once frozen to accommodate the shipping box) into a freezer until the box is to be sent.
4. Wrap the 4.5 mL cryotube(s) to be sent in absorbent paper.
5. Place in a ziplock bag along with an absorbent pad. More than one tube can be placed into the bag.
6. Place the ziplock bag in the styrofoam box.
7. Place the frozen gel pack on top of specimens.
8. Place the lid on the styrofoam box and slide it into its cardboard sleeve (box).
9. Complete the "Hemoglobin A1c Specimen Mailing List" (Form 105). Make a copy for local records and a copy for the DCC. Fold the original mailing list so that it can be inserted between the styrofoam box and its outer cardboard sleeve.
10. Close the tab on the sleeve.
11. Place the box assembly into a FedEx UN3373 Pak.
12. Complete Federal Express air bill and attach the air bill to the outside of the UN3373 Pak. Samples must be shipped Priority Overnight.
13. Contact Federal Express (800-GO-FEDEX) for pick up.

#### **14.6.9 Specimen Mailing List**

Complete the appropriate mailing list (EDIC Forms 105, 108, and 115) for each shipment of specimens to the CBL in order to identify all specimens included in the shipment. Overlap Barcode labels so that the barcode number of each label is aligned within its respective line on

the mailing list. Note any abnormalities or issues related to the collection in the "Comments" section on the appropriate mailing list.

#### **14.6.10 Reporting Results to the EDIC Data Coordinating Center**

The CBL sends results electronically to the Data Coordinating Center on a weekly basis via FTP. The following table summarizes the reference ranges for the EDIC analytes assayed at the CBL:

<b>Calculated ACR</b>	<30 mg/g creatinine
Hemoglobin A1c	4.3–6.0%
Cholesterol	<200 mg/dL
Triglyceride	<150 mg/dL
HDLC	>40 mg/dL
LDL	<100 mg/dL
Creatinine	0.5–1.2 mg/dL.
<b>Estimated GFR</b>	>70 mL/min/1.73m <sup>2</sup>

#### **Tests Performed By Central Biochemistry Laboratory**

<b><u>PROCEDURE</u></b>	<b><u>TESTS</u></b>	<b><u>STATUS AND FREQUENCY</u></b>	<b><u>SPECIMEN PROCESSING &amp; TRANSPORT</u></b>
<b>Renal Studies:</b>			
<b>Estimated GFR and Calculated Albumin-Creatinine Ratio</b>			
Serum* (10 mL red-topped tube with or without serum separator)	Creatinine	13th, 15th, 17th, 19th, etc. DCCT randomization anniversary	Serum frozen in 2 equal aliquots (Cr) CBL: <b>Cr x 1</b> Store: <b>Cr x 1</b>
Urine, random collection	Albumin Creatinine	13th, 15th, 17th, 19th, etc. DCCT randomization anniversary	Urine frozen in 2 x 1.8 mL aliquots ( <b>URCrA x 2</b> ) CBL: <b>URCrA x 1</b> Store: <b>URCrA x 1</b>
<b>Saved Specimen</b> Serum (10 ml red-topped tube with or without serum separator)	Unspecified	Biennial on same schedule as renal	Serum frozen in three 1.8 mL aliquots (SSav x 3) CBL: <b>SSav x 3</b> Store: none

<b>Saved Specimen</b> Urine	Unspecified	Biennial on same schedule as renal	Urine frozen in <b>5x1.8mL</b> aliquots <b>(URSav x5)</b> CBL: <b>URSav x 5</b> Store: none
<b>Lipid Profile/Creatinine</b> Serum* (10 mL red-topped tube with or without serum separator)	Cholesterol Triglycerides HDL-C LDL-C (calc) Creatinine	Biennial 14th, 16th, 18th 20th, etc. DCCT randomization anniversary	Serum frozen in 2 aliquots <b>(CrLip x 2)</b> CBL: <b>CrLip x 1</b> , Store: <b>CrLip x 1</b>
<b>Saved Specimen</b> Serum (10 mL red-topped tube) Plasma (7 mL EDTA tube)	Unspecified	Biennial on same schedule as lipids	Serum and plasma frozen separately in 6 equal (1.8 mL) vials: 3 plasma with Trasylol (Tras), 3 serum without Trasylol (NTra)  CBL; Tras x 3, NTra x 3 Store: None
<b>HbA1c (Glycated Hemoglobin)</b> Blood* (5 mL EDTA tube)	HbA1c (Glycated hemoglobin)	Annually	Whole blood divided into two 4.5 mL transport tubes (HA1c) CBL: HA1c x1 Store: HA1c x 1

#### **14.6.11 Discarding Locally Saved Specimen for Backup**

Discard all back-up frozen specimens (urine, serum, plasma) according to local institution guidelines and regulations 1 year after the date of collection. A year will be sufficient time for the Data Coordinating Center to detect the loss of data from specimens lost in transit.

Discard all back-up whole blood samples 2 weeks after the collection, according to local institution guidelines and regulations.

#### **14.6.12 Supplies and Documents For Blood Collection From Patients With Poor Venous Access**

Because of medical circumstances in which venous access for blood collection is difficult or impossible, a finger stick or use of central lines or intravenous ports may be utilized. A comprehensive list of supplies provided by the CBL and procedures for proper blood collection from finger stick and the required blood volumes and collection devices are described below. The items listed will enable you to perform one capillary collection for either a renal, lipid or combined visit for one of your patients who may have poor venous access. You need to have a set of capillary collection tubes readily accessible to you in the event that one of your patients presents for their annual visit and it is impossible for you to perform an adequate venipuncture.

6 gold-top Microtainers™  
1 purple-top Microtainer™  
1 HbA1c Sample Prep Vial with a 5uL capillary tube and a green capillary tube holder  
Instruction sheet for capillary collections of Lipids and Renals  
Instruction sheet for the alternative collection of HbA1c

Refer to the Instructions in the following sections for proper collection, volumes, processing, and storage of these samples.

Since the Microtainer tubes and the HbA1c Sample Prep Vial are subject to expiration, it is no longer recommended that capillary collection kits be routinely kept on hand since long intervals may elapse prior to use. Please order a kit from the CBL via email at [sconawa1@fairview.org](mailto:sconawa1@fairview.org) and a copy to [mnowick1@fairview.org](mailto:mnowick1@fairview.org) or phone to order a capillary kit.

NOTE: Clearly note on the Mailing List that these collections are Capillary.

You may call the CBL at 612-273-3645 at any time during the workday with questions and concerns on this procedure.

#### **14.6.12.1 Blood Collection by Skin Puncture**

Skin puncture collection is useful for collection of minimum amounts of blood from patients. It is applicable for patients with bleeding tendencies, geriatric patients, or other patients in whom venous access is limited or minimum blood loss is required.

Ensure consistent technique to prevent patient infection or injury.

1. Identify the Patient  
All patients must be positively identified before specimen collection is performed.
  - a. Patient's EDIC identification number/initials and laboratory accession number must be recorded on the appropriate mailing lists. The specimen labels must be affixed to the collection tubes.
2. Considerations
  - a. The skin-puncture site must be warm, and should not be edematous (swollen) because accumulated fluid in the tissues will contaminate the blood specimen.
  - b. Avoid puncturing patient more than two times.
  - c. Identify allergies to latex, band aids, iodine, alcohol or tape.
3. Selection of Site
  - a. The palmar surface of the distal phalanx of a finger
4. Assemble Supplies
  - a. Gloves (non-sterile)
  - b. Alcohol prep or povidone iodine pads
  - c. Gauze
  - d. Micro-collection containers and caps
  - e. Lancet or calibrated puncture device
  - f. Bandage
5. Put on Gloves  
Always wear gloves and observe Standard Precautions when collecting biological specimens.
6. Warm the Site

Skin-puncture blood is a mixture of blood from arterioles, venules, and capillaries and contains interstitial and intracellular fluids. The proportion of arterial blood is greater than that of venous blood due to the greater pressure in arterioles than venules. Since skin has a low energy requirement, venous blood in the skin is more like arterial blood, especially when the puncture site is warmed.

Warming can increase blood flow up to seven-fold. Because warming primarily increases arterial blood flow, specimens from warmed sites are called “arterialized skin-puncture blood”.

- a) Wrap the site for a minimum of three minutes with warm, moist cloth at a temperature no higher than 42°C. This temperature can be achieved by placing cloth under hot tap water until it is hot to the touch, but does not cause discomfort.

#### 7. Cleanse the Site

- a) Cleanse skin-puncture site with alcohol prep pad (70% isopropyl alcohol).
- b) Thoroughly air dry site before puncture; residual alcohol will cause specimen hemolysis.
- c) If povidone-iodine is used to prepare site, cleanse with alcohol prep pad.

#### 8. Puncture the Site

To avoid contaminating patient’s clothing with blood, place cloth or disposable diaper under the site.

- a) Grasp patient’s finger firmly between thumb and index finger.
- b) Use appropriate device to puncture:

For finger sticks, use lancing device / lancet according to manufacturer’s guidelines on depth.

#### 9. Inducing Blood Flow

- a) Wipe away first drop of blood (which may contain excess tissue fluid) with gauze.
- b) A drop of blood will form over puncture site; when tip of micro-collection tube (or 5uL capillary tube used with HbA1c Sample Prep Vial) touches this drop, blood flows into tube by capillary action.
- c) Blood flow is increased by holding puncture site downward, and gently applying intermittent pressure to surrounding tissue (or proximal to puncture site when blood is obtained from a finger). Periodically relieve pressure so blood flow returns to area.
- d) If an adequate puncture has been performed, 0.8 – 1.5 mL of blood can be collected from a single puncture site.

#### 10. Blood Collection

MICROTAINER:

- a) Hold Microtainer™ in upward position. Touch collector end of reservoir to drop of blood. Blood will freely flow to the bottom of the tube. **See Figure 14.1**
- b) Fill purple-top EDTA Microtainer™ plasma tube first, followed by gold-top Microtainer™ serum tubes. Mix EDTA Microtainer™ plasma tube frequently during collection to minimize chance of clotting.
- c) When collection is complete, replace cap and mix tube containing additive (EDTA Microtainer tube) by inverting 8-10 times. Refrigerate the Microcontainer™ tube labeled HA1c until ready to ship.
- d) Allow serum Microtainer tubes to clot for at least 30 minutes, then centrifuge at room temperature for 10 minutes at 3000 rpm. Separate the serum with a transfer pipette into one 1.8 mL cryotube labeled CrLip. Fasten screw caps and place in freezer until ready to ship.

<b>Order of Collection</b>	
1 <sup>st</sup> : Hemoglobin A1c	<p>One purple-top EDTA Microtainer™ tube containing 250uL - 500uL whole blood. Mix frequently during collection to minimize chance of clotting. Collect for both <b>Lipid</b> and <b>Renal</b> annual visits.</p> <p><b>Alternative collection:</b> HbA1c sample preparation vial with 5uL capillary whole blood gently mixed in hemolysis reagent in tube. (See following section for instructions.)</p>
2 <sup>nd</sup> : Lipids	Three gold-top Microtainer™ tube with gel containing 600uL each of whole blood.
<i>AND/OR:</i>	
3 <sup>rd</sup> : Renal	Two gold-top Microtainer™ tube with gel containing 600uL each of whole blood.

HbA1C SAMPLE PREP VIAL (See Figure 14.1 HbA1c Capillary Collection):

- a) Attach the 5uL glass capillary tube in the hook of the green capillary holder.
- b) Fill the capillary tube completely with blood. It must be filled end-to-end.
- c) Do NOT wipe the capillary tube however be sure that there are no residual blood drops on the outside of it. Transfer the filled capillary tube into the HbA1c Sample Prep Vial.
- d) Cap the Vial and shake it to rinse the blood completely from the capillary tube. Be sure that no blood remains in the capillary tube.
- e) Refrigerate the HbA1c Sample Prep Vial labeled HA1c until ready to ship.

## 11. Aftercare

- a) Keep site elevated.
- b) Apply pressure to site with gauze until bleeding stops, usually 1-2 minutes.

**Figure 14.1 HbA1c Capillary Collection**

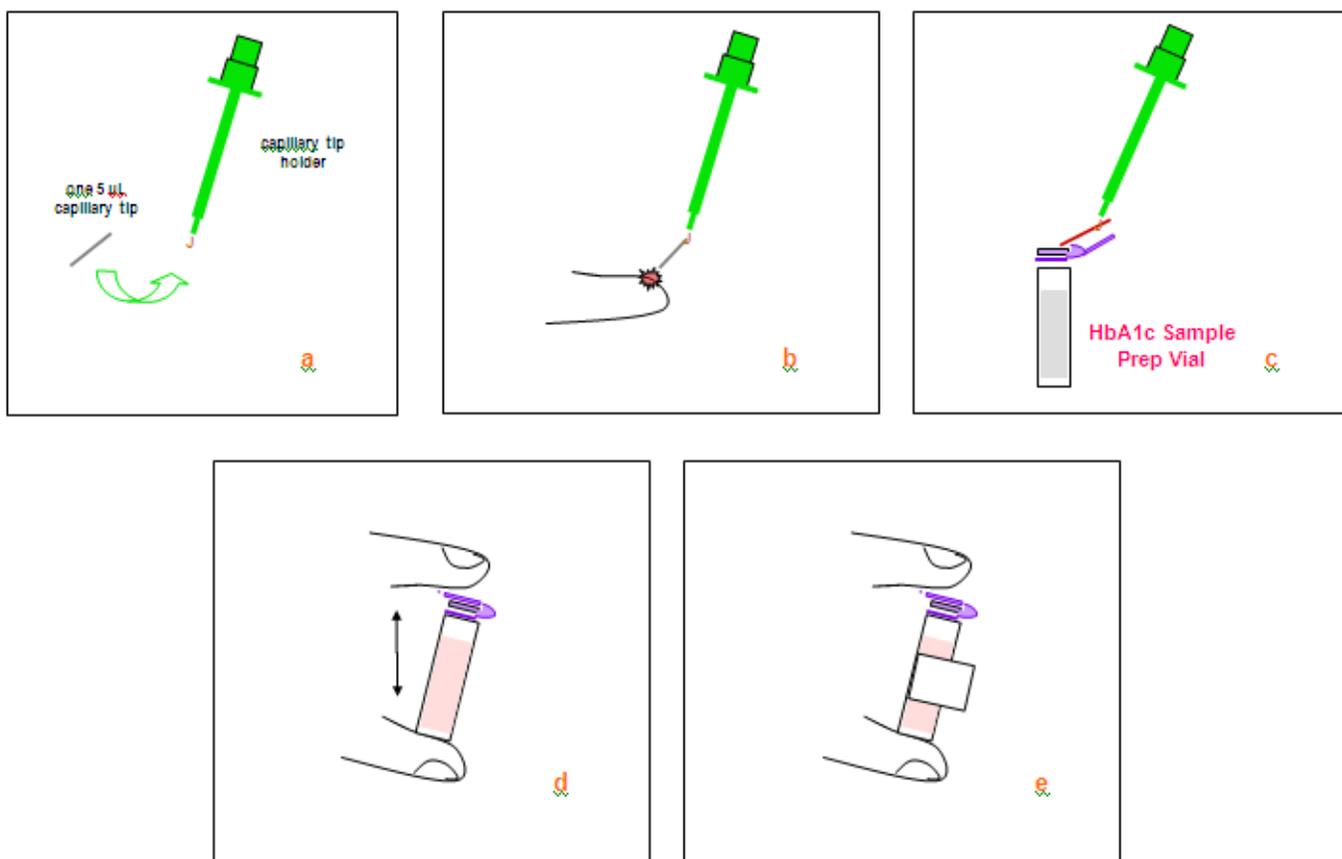
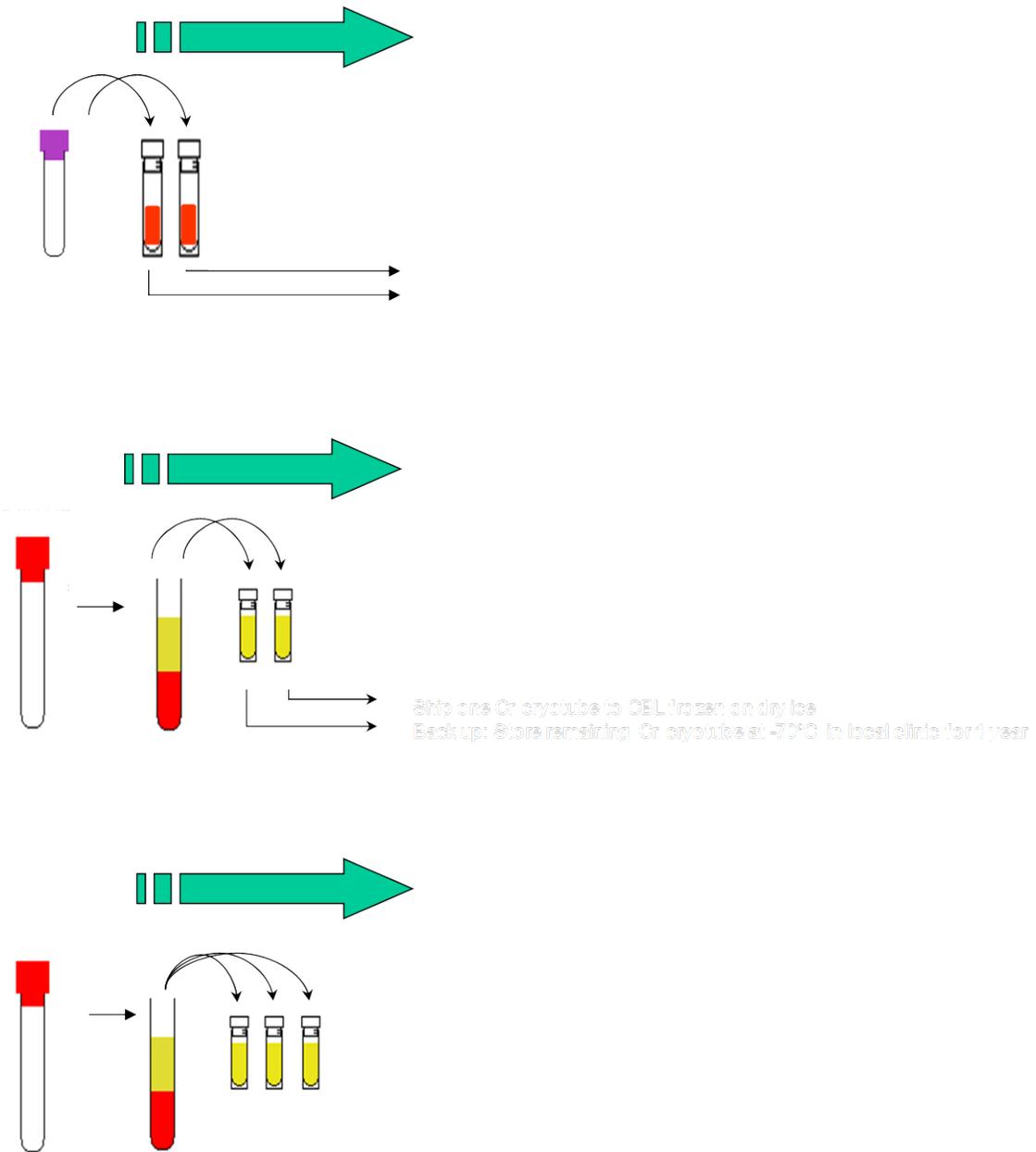


Figure 14.2



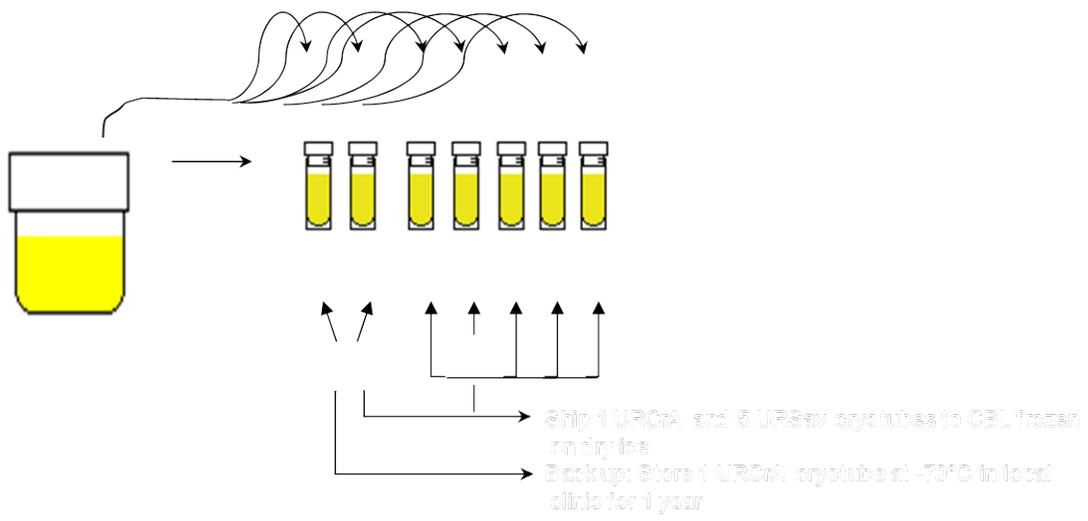
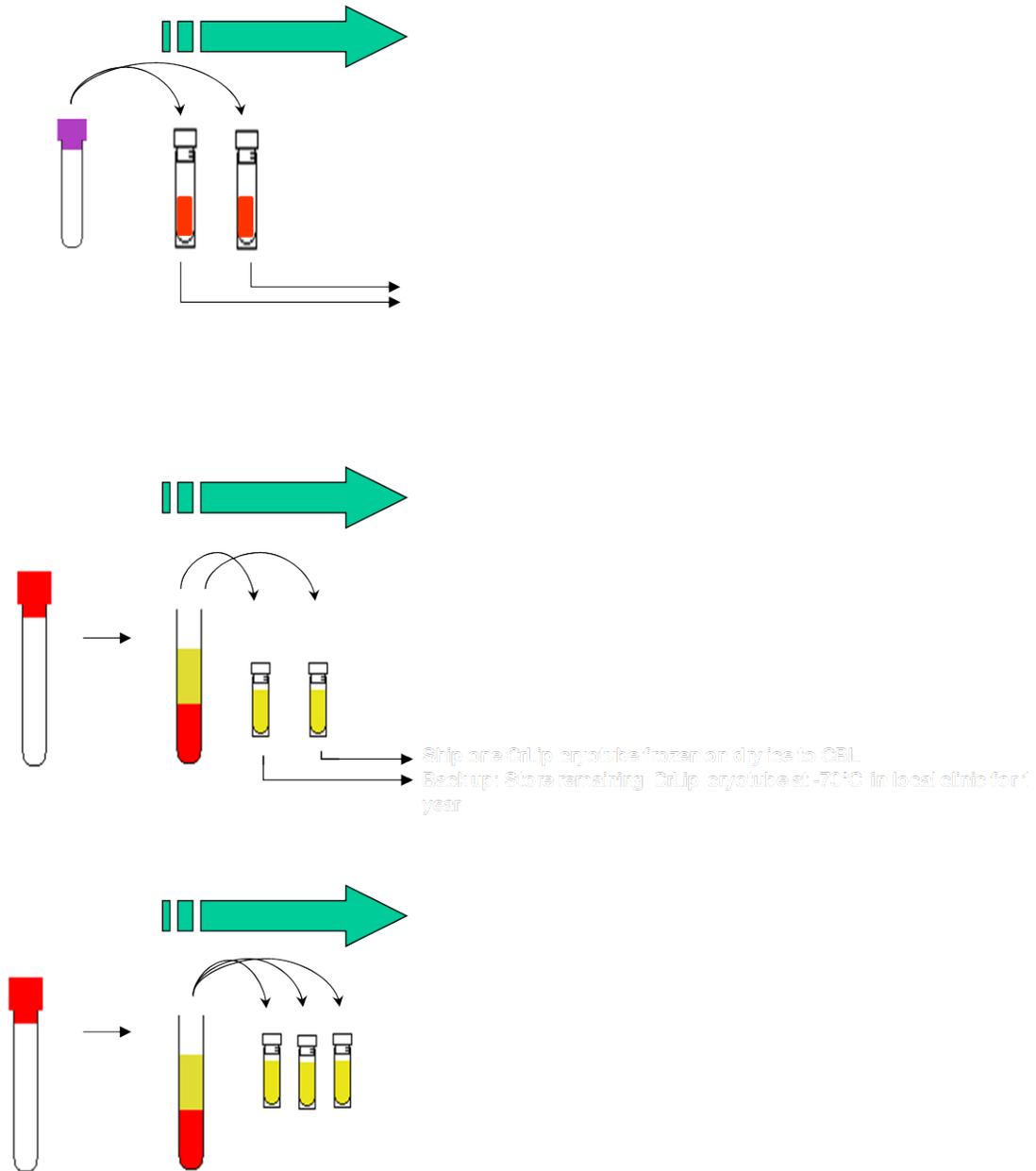
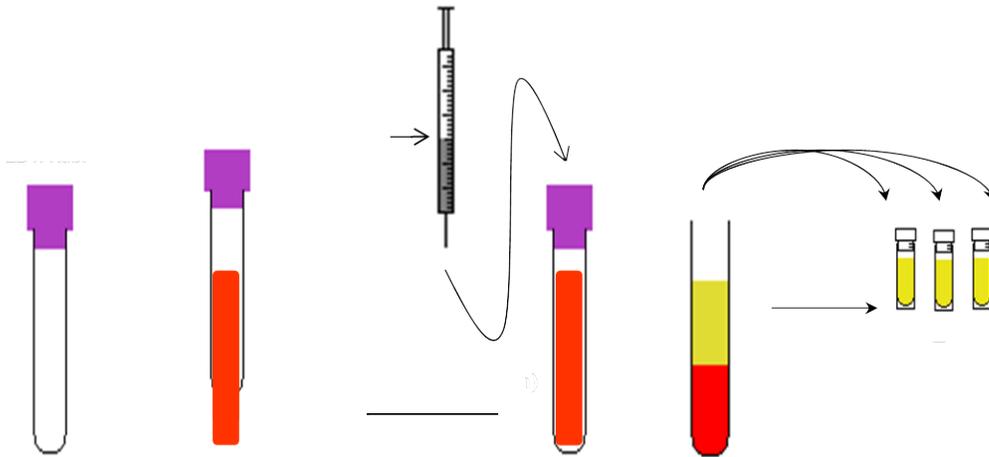


Figure 14.3





**Figure 14.4**  
Lipid Visit



**Figure 14.5**  
Renal Visit



**Figure 14.6****Combined Visit (Lipid)****Combined Visit (Renal)**

**Appendix A**

**EDIC CBL Supply Reorder Form**

8/22/12

Clinic Number: \_\_\_\_\_ Clinic Name: \_\_\_\_\_

Study Coordinator: \_\_\_\_\_ Phone Number: \_\_\_\_\_

Date: \_\_\_\_\_

Dear Study Coordinator:

Please use this form to reorder supplies from the CBL for the EDIC Study. Please email this form to Sherry Conaway ([sconawal@fairview.org](mailto:sconawal@fairview.org)) and copy to Maren Nowicki ([mnowick1@fairview.org](mailto:mnowick1@fairview.org)).

You should allow 1-2 weeks for us to process and ship your request, so please plan ahead.

<b>ITEM</b>	<b>QUANTITY</b>
LIPID LABELS (1 Participant per sheaf of 18 labels)	_____
RENAL LABELS (1 Participant per sheaf of 21 labels)	_____
COMBINATION VISIT LABELS (Same accession number) (1 Participant per sheaf of 30 labels)	_____
ALIUOT TUBES (1.8 mL, serum, plasma and urine) (50/bag)	_____
ALIUOT TUBES (4.5 mL, whole blood for HbA1c only) (50/bag)	_____
ABSORBENT PADS	_____
TRASYLOL / APROTININ VIAL	_____
UN3373-BIOLOGICAL SUBSTANCE CATEGORY B LABELS for outer box (15/page)	_____

*Note: Once unpacked at the CBL, the large shipping boxes are automatically returned to the site. Receipt of small shipping boxes is tallied at the CBL and once 5 have been received, the site is automatically re-supplied so that at least 10 small boxes per site are in rotation. Additional shipping boxes may be ordered at any time using this form.*

LARGE SHIPPING BOXES (for frozen specimens) \_\_\_\_\_

SMALL SHIPPING BOXES / GEL PACK (for whole blood HbA1c) \_\_\_\_\_

CAPILLARY COLLECTION KIT \_\_\_\_\_

*Note: It is no longer recommended that capillary collection kits be routinely kept on hand since long intervals may elapse prior to use.*

## 15. ECG AND SITTING BLOOD PRESSURE PROCEDURES

### 15.1 Electrocardiogram Procedures

### 15.2 Introduction

Obtain resting electrocardiograms (ECGs) during the annual follow-up visits. Participants who have a pacemaker in place will continue to have ECGs collected annually. In addition, collect ECGs to document any myocardial infarction (MI) or other cardiovascular events. Study policy, operational guidelines, and procedures for obtaining and processing ECGs required for this study are discussed in the following sections.

#### 15.2.1 Study Policy

During the DCCT, our policy was to do a local reading of each ECG, even though it was obtained for research purposes and was eventually interpreted at a reading center. Despite the fact that in many clinics and/or for many participants, we may not have provided primary care beyond responsibility for diabetes management, we felt it was our obligation at least to screen each ECG tracing for any obvious change or abnormality of major clinical significance. It was the responsibility of the Principal Investigator to either review the ECG himself/herself, or get a friendly cardiologist to do it routinely or to do it if the P.I. had looked at it and was unsure of the significance of some findings.

That same general policy must hold for EDIC just to protect against the unlikely, but still real, possibility that a new ECG abnormality has developed to which clinical attention should be paid promptly. Take proper measures to promptly diagnose coincident silent or virtually silent myocardial infarction that might have happened just before a routine EDIC visit and any life threatening arrhythmia that could happen during an EDIC visit. To guard against such possibilities, a physician must review all ECGs before the participant leaves in the following conditions:

- 1) If a participant complains of chest pain, palpitations, or shortness of breath during the EDIC visit. If necessary, an emergency room physician should review the ECG if no one else is available and the participant could even get medical attention there if needed.
- 2) If the participant has no symptoms during the EDIC visit but complains of or admits to chest pain of any degree or variety just before the visit.
- 3) If the participant has no symptoms during the EDIC visit, but the nurse notices a grossly irregular rhythm as she records the ECG. This does not mean all nurses must have special skills to do this. It simply means scanning lead II to see if the intervals between each electrical complex are reasonably similar in length or are very dissimilar.
- 4) If the participant has had no recent symptoms but gives a history of intermittent chest pain with exertion during the preceding year for which the participant has not sought medical attention.

In the absence of any of the above situations, a physician should routinely look at the ECG within 7 days of recording. Promptly inform the participant and his/her physician should any change be noted.

This policy is necessary, first to protect the participant in case of a cardiac event occurring coincidentally in proximity to an EDIC visit, and second to protect the EDIC from the claim that we did not even examine an ECG obtained in such a circumstance because it was only recorded for research purposes.

### **15.2.2 Follow-up ECGs**

The ECG machines and ECG recording procedure should meet the ACC/AHA recommendations [Guidelines for Electrocardiography (JACC Vol. 19, No. 3, March 1, 1992:473-81)] and [ACC/AHA Clinical Competence Statement on Electrocardiography and ambulatory Electrocardiography (*Circulation* December 18/25, 2001)]. Any modern ECG machine is acceptable for use during the EDIC. The ECG machine may be either a single channel lead machine or a multichannel lead machine. However, it is desirable that only one machine be used for all evaluations on EDIC participants.

Obtain at least 1 full minute of ECG tracing consisting of at least 5 seconds of each of the leads (I, II, III, aVR, aVL, aVF, V1-V6). You may use a stopwatch to assure that you obtain a full minute of tracing. Unless automatically recorded, record a series of one mV calibration pulses at the beginning of the ECG recording. Record tracings at a paper speed of 25 mm per second. Leads that must be recorded at one-half standard should be preceded by a half standard calibration pulse and should be marked with the words "1/2 STD". If electrocardiographs providing simultaneous 12-lead recordings are used, then only 10 seconds recording is required.

Comparability of baseline ECG records with subsequent follow-up records requires that uniform procedures for electrode placement and skin preparation are followed. The procedure for standardizing electrode locations is described in Section 15.3.2.

Check the ECG strips for the following details:

1. Each lead is clearly identified.
2. A standardization strip should be included.
3. There should be no overlap of tracings.
4. The paper speed is indicated on the ECG if it is other than 25 mm/second.
5. If the sensitivity is other than 1 mV = 1 cm, the grade should be indicated on the ECG.

For the labeling and mailing of ECGs, follow the directions in either A or B below, depending on what type of ECG machine you are using.

#### **A. 12 Channel Lead Machine**

- 1) Place 1 completed ECG label directly on the ECG paper ensuring that none of the beats or complexes are covered by the label.

2) Batch the ECGs by participant and include with the mailing list (Form 103) when sending to the DCC in the monthly mailing (there is no need to fold the ECGs or to put each ECG in a separate envelope).

#### B. Single Channel Lead Machine

- 1) Complete 2 ECG labels.
- 2) Record the participant ID, initials, and date on the strip.
- 3) Fold the strip accordion style (see Figure 15.1). Beginning with V<sub>6</sub>, make a 6-inch fold towards V<sub>5</sub>. Fold back 6 inches away from V<sub>4</sub>. The folds do not have to correspond to lead changes. The strip should measure 6 inches in length once the entire ECG is folded.
- 4) Place one label on the outside of the envelope and insert the folded ECG and the second label inside the envelope.
- 5) Batch the ECGs by participant and include with the mailing list (Form 103) when sending to the DCC in the monthly mailing.

All ECGs received at the Central ECG Reading Centre (EPICARE) are coded according to the Minnesota Code. The Minnesota code is summarized in Table 15.1.

### **15.3 Procedure for Obtaining the 12-Lead Electrocardiogram**

The procedures for recording the 12-lead resting electrocardiogram are discussed below.

#### **15.3.1 Preparation of the Participant**

- Ensure that there are clean sheets or examination paper on the examination table or clinic bed, and that the bed is wide enough for the participant to lie comfortably. If the patient is unable to lie flat on the examination table or clinic bed for the ECG recording, the ECG recording can be completed in the sitting position.
- Introduce yourself; ask the participant to relax.
- Give a brief explanation of the study or at least explain the ECG procedure briefly
- Be responsive to participants' needs; help participant on and off of the examining table.

#### **15.3.2 Skin Preparation**

- Briskly rub each electrode location with an alcohol swab in a circular motion. This removes all the dead, dry skin and oil. Re-mark the electrode positions and apply the electrodes

- In case of excessive hair in the chest with a possibility to affect recording, If possible and with the participant's consent, remove any excess hair from each electrode site on the chest using an electric shaver or safety razor.

### **15.3.3 Electrode Position Measuring and Marking**

Use a non-toxic washable marker to mark the 12 electrode positions as detailed below. It is important that care be taken to locate and mark the chest electrode positions accurately. Chest electrodes should be attached in the following order: V1, V2, V4, V3, V5, then V6. If old model electrode connectors that need gel application are used, it is important not to smear the electrode jelly over a wider area than necessary to avoid low impedance pathways between electrodes and production of marked distortion of the ECG waveforms.

#### **15.3.3.1 LIMB LEADS (Figure 15.2)**

##### **1. Right Leg (RL):**

- a. The right leg electrode serves as a ground connection, and problems here will influence all other leads.
- b. On the inner side of the right leg (above the ankle), prepare an area about 1-2 inches in diameter. With an alcohol swab, rub briskly using firm, circular motions
- c. Mark the position and place the electrode.
- d. In amputees, the limb lead electrode may be placed higher up on the torso.

##### **2. Left Leg (LL):**

- a. Repeat this procedure for the Left Leg (LL).

##### **3. Right Arm (RA).**

- a. On the inner side of the right arm (above the wrist), prepare an area about 1-2 inches in diameter. With an alcohol swab, rub briskly using firm, circular motions
- b. Mark the position and place the electrode.
- c. In amputees, the arm electrode may be placed on the Shoulder, below the clavicle.

##### **4. Left Arm (LA)**

- a. Repeat the process for the Left Arm (LA).

#### **15.3.3.2 CHEST LEADS (Figure 15.3)**

##### **1. V1 Electrode**

- a) Using your right hand, locate the sternal notch (figure 15.2 and 15.3.B) with your right index and middle fingers. Move your fingers down the sternum about 1 ½ to 2 inches to feel the sternal angle. This is a slightly raised, bony area on the sternum.
- b) From the sternal angle, move your right index and middle fingers left to palpate the union of the 2<sup>nd</sup> rib and the sternum.
- c) Count down to the fourth rib and identify the fourth intercostal space below it.

d) Locate V1 in the fourth intercostal space at the right of the sternal border.

## 2. V2 Electrode

Locate electrode V2 in the fourth intercostal space at the left sternal border. This should be at the same level as V1 and immediately to the right of the sternum.

## 3. V4 Electrode

Apply V4 electrode at the left midclavicular line in the 5th intercostal space. The midclavicular line is an imaginary vertical line passing through the mid-shaft of the clavicle or collarbone (Figure 15.3.B)

## 4. V3 Electrode:

Apply V3 electrode midway between V2 and V4.

## ■ 5. V5 Electrode:

Apply V5 electrode at the left anterior axillary line in the 5th intercostal space at the same horizontal level of V4. The anterior axillary line is an imaginary vertical line along the anterior axillary fold or crease of armpit (Figure 15.3.B)

## 6. V6 Electrode

Apply V6 electrode at the left mid-axillary line in the 5th intercostal space at the same horizontal level of V4 and V5. Mid-axillary line is an imaginary vertical line passing through the middle of the axilla or armpit (Figure 15.3.B)

### 15.3.4 Fault Detection Procedures

If you encounter problems with noise or drift, replace the electrodes. The following is a guide for determining which electrodes may be faulty. The underlined electrodes are the predominant determinants of the appropriate lead and, therefore, are most likely to be the faulty electrodes for a given lead. After adjustment and/or replacement of suspect electrodes, record all leads again.

<u>Lead Affected</u>	<u>Possible Faulty Electrode</u>
I	RL, RA, LA
II	RL, RA, LL
III	RL, LA, LL
aVR	RL, RA, LL, LA
aVL	RL, LL, RA, LA
aVF	RL, LL, RA, LA
V1	RL, LL, RA, LA, V1
V2	RL, LL, RA, LA, V2
V3	RL, LL, RA, LA, V3

V4  
V5  
V6

RL, LL, RA, LA, V4  
RL, LL, RA, LA, V5  
RL, LL, RA, LA, V6

### 15.3.5 Self-Evaluation of Technical Performance

Obtain a reasonable estimate of the noise level and amount of baseline drift by examining the ECG recording; an indication of technical performance level can thereby be obtained. Based on the requirements of the Minnesota Code, acceptable levels of noise and baseline drift were established as indicated by grades 1, 3, and 5 as follows:

- **Grade 1:** Considered good, nothing you can do about it
- **Grades 3:** ECGs have some artifacts and are indicators of a clinic's attention to details during ECG recording. ECGs data are still readable
- **Grade 5:** ECGs have a big problem and data can not be retrieved for the study analysis e.g. missing leads, lead reversal, major baseline drift or noise

Grade levels take into account measurement accuracy requirements, the ability of the readers to achieve the required accuracy in the presence of noise and drift, and the level of technical quality expected from the conditions, equipment, and the procedures specified for this study.

Baseline drift problems, which are essentially caused by poor electrode-skin interface, should be particularly easy to remedy, as should 60 Hz noise. Examine the ECG recordings for obvious errors such as waveform clipping, missing tracing, or excessive noise and drift. Then, check the tracings for right arm - left arm and other common lead misplacements. Once satisfied that the waveforms are basically correct and no obvious errors are present, check the baselines (PR, ST, and TP segments) for the level of noise. No 60-Hz noise should be present, and the baseline should be steady and free of transients.

Converting the noise level to peak-to-peak values, and noting that recording sensitivity is 1 mV per centimeter, the allowable noise level in terms of number of small paper deviations (one small paper deviation = 1 mm or 0.1 mV) is obtained as indicated for each grade level. These "eyeball" measurements serve as indications of the noise level performance grade. For instance, baseline fluctuations approaching five small paper deviations (0.5 mV or 5 mm peak to peak) are indicative of unacceptable noise levels. The overall drift criteria may be checked and an indication of the overall drift grade level obtained by searching the record for the maximum and minimum baseline levels (as determined by the PR and TP segments) and measuring the vertical distance between them. This distance must be less than ten small paper deviations (1 mV) to satisfy the minimum drift criteria. Determine the beat-to-beat drift level by searching for the pair of successive QRS complexes and having the largest amplitude differences (vertical distance) between successive PR segments. These figures are approximate and serve only to give a general indication of beat-to-beat drift grade level. Certainly, however, a difference of four small paper divisions (0.4 mV) or more indicates an unacceptable record.

Examples of technical problems encountered in the ECG recording and possible solutions are as follows:

#### 1. Muscle Tremor

Muscle tremor causes irregular oscillations (deflections) of low amplitude and varying rapidity, superimposed upon the ECG waveform (Figure 15.4). Muscle tremor is the involuntary muscle activity of a participant whose state is tense, apprehensive, or uncomfortable. Therefore, a clear explanation of the electrocardiogram test and reassurance are necessary for the participant. Also, always seek a wide examination table and a warm room. If the temperature of the room is too low for the participant, use a blanket.

## 2. Participant Movement.

Sudden participant movement leads to drift of the baseline in the part of the ECG recorded during the movement (Figure 15.5). Instruct the participant to relax, lie still, and breathe normally. Also, avoid talking during the recording and do not alert the participant that you are pressing the start button

## 3. Improper Skin Preparation or Electrode Application

Improper skin preparation or electrode application produces baseline drift, wandering baseline, or irregular or bizarre deflections (Figure 15.6). Faulty skin-electrode interface is the usual cause of baseline wandering, drift or irregular and bizarre deflection on an ECG tracing. Avoid these problems by carefully following the prescribed procedure for skin preparation and electrode placement.

## 4. Tension on lead wires:

Tension on one or more lead wires due to tight or tangled wires gives the same effect as improper lead connection and/or participant movement because it causes interference with proper electrode contact (Figure 15.7). Always make sure the lead wires are hanging loosely. Baseline wandering or drift only in the precordial leads (V1 to V6) might be due to the participant's respiratory movements. Also, suspect a faulty connection between an electrode and a lead wire.

## 5. Sixty- Hz Interference

Sixty-Hz interference is characterized by perfectly regular fine oscillations occurring at the rate of 60 cycles per second (Figure 15.8). Electrical equipment of any kind may be the source of AC interference in all or some of the leads. AC interference that appears only in two standard limb leads (i.e., in two of leads I, II, and III), brings suspicion to the extremity that is common to them.

Lead I is the potential difference between LA and RA.

Lead II is the potential difference between LL and RA.

Lead III is the potential difference between LL and LA.

Therefore, if only leads II and III show 60-Hz interference, the left leg, being the common member, must be at fault. It must, therefore, be checked with regard to:

- a) Quality of skin preparation and electrode contact;

- b) Secure attachment of the LL cable tip to the electrode;
- c) Possible contact to left leg with any metal part of bed or other equipment (or proximity to a wall with hidden wiring);
- d) A partially broken cable.

#### **15.4 Clinic Options for ECG Recording**

The clinical centers may obtain qualifying visit electrocardiograms for the EDIC by any of three procedures:

Option 1: A properly trained technician may record ECGs in the clinical center. This is the preferred procedure and it is expected that most clinics will follow this option.

Option 2: In some instances, the clinic may find it expedient to have the electrocardiogram recorded in the cardiology laboratory of the local institution. ECGs recorded in this manner should be retrieved by clinical center staff and processed in the usual way. Although it is specified to send ECGs to the Data Coordinating Center unmounted, it is recognized that this may be contrary to the established and unchanging practice of the cardiology laboratory. If it is not possible to obtain an unmounted ECG from the cardiology laboratory, a mounted electrocardiogram will be accepted by the Data Coordinating Center along with the mounted or unmounted rhythm strip. Retain a copy of the ECG for the clinic files.

Option 3: An internist assigned to the EDIC clinic may record the ECG according to the protocol outlined in this chapter.

#### **15.5 Certification Procedures for ECG Technicians and Laboratories**

Certification procedures will differ for the three options described in Section 15.4.

Option 1: Technicians charged with responsibility for ECG recording in the clinics should obtain three electrocardiograms according to the specific instructions given in this chapter. Mail the electrocardiograms with the appropriate forms to the Data Coordinating Center in order to obtain certification. If the technician has not had previous experience as an ECG technician, the internist assigned to the clinic should review the technique and tracing for lead placement, elimination of artifact, and appropriate calibration.

Upon receipt of the three electrocardiograms and a Request for Certification for ECG Technician (EDIC Form 120) at the Data Coordinating Center, the ECGs will be sent to the EPICARE. Recommendations regarding certification will be returned to the Data Coordinating Center. If certification is recommended, the ECG technician will be issued a certification number by the Data Coordinating Center.

Option 2: Tracings recorded by staff of the cardiology laboratory should be obtained under the same circumstances as will be operative for participants in the EDIC. One such tracing should be sent to the Data Coordinating Center with a letter of explanation of any alterations that have been necessary by virtue of local policy.

Upon receipt at the Data Coordinating Center, the tracing will be sent to the EPICARE for review for acceptability for EDIC purposes. If quality and technique are acceptable,

certification of the clinic for this task will be recommended to the Data Coordinating Center and a certification number will be issued for the cardiology laboratory.

Option 3: Principal Investigators who elect to use private internists to obtain ECGs should assure themselves that the internists are interested and available for appropriate periods of time. Both the primary internist and a backup internist should be certified for EDIC procedures for ECGs. Each internist to be certified for obtaining ECGs in the EDIC should record tracings for one participant. The ECG will be reviewed by the EPICARE upon receipt of a Request for Certification for ECG Technician (EDIC Form 120). Certification will be granted or withheld on the basis of this review. If certification is recommended, a certification number will be issued to the internist.

If any problems are observed during review of the ECGs submitted to obtain certification under any of the above options, the EPICARE will contact the Principal Investigator of the clinical center to resolve the problem.

## **15.6 Procedures for Measuring Blood Pressure**

### **15.6.1 Equipment for Measuring Blood Pressure**

#### Sphygmomanometer

1. Bladder and Cuff. The bladder must be the correct width for the participant's arm. If it is too narrow, blood pressure will be falsely high; if too wide, falsely low.

The recommended dimensions for blood pressure cuffs are related to arm circumference (cm) at the midpoint of the arm. This is 50% of the distance from the acromion to the olecranon. Recommended dimensions are as follows:

<u>Arm Circ (cm)</u>	<u>Cuff Name</u>	<u>Width</u>	<u>Length (cm)</u>
17-26	Small Adult	11	17
24-32	Adult	13	24
32-42	Large Adult	17	32

The cuff should be of the contact closure (Velcro or hook) type.

2. Manometers. A mercury manometer should be used. Care must be taken to avoid loss of mercury. The edge of the mercury meniscus must be kept at zero, with no pressure applied to the cuff, by adding mercury as needed. The column should be vertical for correct reading. Annual servicing is required to check for clogging in air vent or filter and to calibrate.
3. Inflating System, Exhaust Valve, Tubing. These must be checked monthly for significant leaks in pressure (greater than one mm Hg/second) and for smooth functioning of the input system and exhaust valves.
4. Stethoscope. Standard variety, in good condition. Sounds generated over the vessels are of low frequency, so the bell head of the stethoscope should be used.

### **15.6.2 Determination of Blood Pressure**

1. The Observer. Prior experience in determining blood pressure is essential. One must be able to hear well and to see well enough to read the manometer. Eyes should be level with the meniscus of the vertically placed mercury column. Inattention, carelessness, or bias may cause errors. An example of bias is "digit preference", a well-documented phenomenon that results in recording blood pressures ending in zero more often than expected by chance. Knowledge of earlier readings and preconceived notions of "normal" blood pressure are other sources of bias to be avoided.
2. The Participant. The participant should be comfortably seated, with the arm slightly flexed, and with the forearm supported at heart level on a smooth surface. Readings representative of ordinary circumstances are sought. Standard conditions are that the participant be in a quiet room at a comfortable temperature, with the arm unstricted by clothing or other material. The subject is to avoid exertion, exposure to cold, eating, and smoking for at least ½ hour before and should be seated for at least 5 minutes before the measurement of blood pressure.

### Technique

On the baseline and all follow-up physical examinations, blood pressure is to be taken using the right arm, or the left arm if for some reason the right arm cannot be used.

The deflated cuff is applied with its lower margin 2½ cm above the antecubital space. The bladder is applied directly over the compressible artery, over the medial surface of the arm. The cuff pressure is raised and lowered so as to give a preliminary palpatory determination of systolic pressure in the radial pulse.

The bell stethoscope is applied to the antecubital space, directly over the previously palpated brachial artery. The stethoscope bell is applied firmly but gently, with no space between the skin and the stethoscope, and with the stethoscope not touching clothing or the blood pressure cuff.

The pressure is raised approximately 30 mm Hg above the point at which the radial pulse disappears. It is then released at a rate of 2 to 3 mm Hg/second. As the pressure falls, the Korotkoff sounds become audible. These are:

Phase I: That period marked by the first appearance of faint, clear tapping sounds that gradually increase in intensity.

Phase II: The period during which a murmur or swishing quality is heard.

Phase III: The period during which sounds are crisper and increase in intensity.

Phase IV: The period marked by the distinct, abrupt muffling of sound so that a soft, blowing quality is heard.

Phase V: The point at which sounds disappear.

In some participants, there may be an auscultatory gap in the latter part of Phase I and Phase II. This can lead to underestimation of systolic pressure or overestimation of diastolic

pressure. It can be excluded by palpating for disappearance of radial pulse as the cuff pressure is raised.

#### Systolic Pressure

This is the point at which the initial tapping sound is heard. One should hear at least two consecutive beats as the pressure falls. If the palpatory pressure is higher, it should be recorded as systolic pressure. Pressures should be read to the nearest 2 mm Hg mark on the manometer scale. Visual oscillations are not to be used.

#### Diastolic Pressure

The fifth phase, the point at which sounds disappear, is to be used as the diastolic pressure.

### **15.6.3 Special Conditions Affecting Blood Pressure Measurement**

#### Arrhythmias

An occasional ventricular contraction will have no effect on blood pressure. However, if they are frequent, or if atrial fibrillation is present, approximate readings must be made. The systolic blood pressure is the average of a series of three readings of the appearance of the first sound. The diastolic pressure is an average of three readings of the fourth and fifth phases. The presence of an irregular rhythm should be recorded on the appropriate item on the form.

#### Obesity

Falsely high pressures are obtained if standard size bladders are used. Bladders may be narrow and short, and there is excessive loss of cuff pressure through the thick compressible tissues of the obese arm. A proper size cuff is necessary (see above).

TABLE 15.1

ECG Reading Codes

All electrocardiograms collected in the study will be read centrally using Minnesota Code for resting electrocardiograms except that Q/QS patterns, T wave items, S-T junction and segment depression, and S-T segment elevation will be coded separately for three different anatomical sites. These sites are: (1) anterolateral if the findings are in leads I, aVL, or V6; (2) posterior (inferior) for leads II, III, or aVF; and (3) anteroseptal for leads V1 through V5. This modification of the Minnesota Code will make it easier to detect new electrocardiographic changes in the presence of existing findings, particularly when a new pathological event, such as infarction or ischemia, occurs in an area of the myocardium different from that of previous events.

The Minnesota Code for resting electrocardiograms is reproduced below. With regard to the modification described above, note that it is possible for an ECG to have 1-1-1 code for each of the three anatomical sites. Thus, if the Q/R amplitude ratios is 1/3 or more and the Q duration is 0.03 sec or more in either of leads I or V6, a code 1-1-1 is recorded for the anterolateral site; if these criteria are met in leads II, a code 1-1-1 is recorded for the posterior site; and if these criteria are met in any of leads V2, V3, V4, V5, a code 1-1-1 is recorded for the anteroseptal site.

1. Q and QS Patterns

(Not to be coded in the presence of codes 6-4-1, 6-8, or 7-1-1.)

a) Anterolateral site (leads I, aVL, V6)

- 1-1-1 Q/R amplitude ratio 1/3 or more plus Q duration 0.03 sec or more in either of leads I or V6.
- 1-1-2 Q duration 0.04 seconds or more in any of leads I, V6.
- 1-1-3 Q duration 0.04 seconds or more, plus R amplitude of 3.0mm<sup>1</sup>
- 1-2-1 Q/R amplitude ratio 1/3 or more plus Q duration at least 0.02 seconds and less than 0.03 seconds in any of leads I, V6.
- 1-2-2 Q duration at least 0.03 seconds and less than 0.04 seconds in any of leads I, V6.
- 1-2-3 QS in lead I.
- 1-3-1 Q/R amplitude ratio at least 1/5 and less than 1/3 plus Q duration of at least 0.02 seconds and less than 0.03 seconds in any of leads I, V6.
- 1-3-3 Q duration at least 0.03 seconds and less than 0.04 seconds, plus R amplitude of 3.0 mm or more in lead aVL.

1-3-8 Initial R amplitude decreasing to 2 mm. or less in every beat, absence of codes 3-2, 7-1-1, 7-2-1, or 7-3 between V5 and V6.

b) Posterior (inferior) site (leads II, III, aVF)

1-1-1 Q/R amplitude ratio 1/3 or more plus Q duration 0.03 seconds or more in lead II.

1-1-2 Q duration 0.04 seconds or more in lead II.

1-1-4 Q duration 0.05 seconds or more in lead III plus Q wave of at least 1.0 mm amplitude in a majority of beats in aVF.

1-1-5 Q duration 0.05 seconds or more in lead aVF.

1-2-1 Q/R amplitude ratio 1/3 or more plus Q duration at least 0.02 seconds and less than 0.03 in lead II.

1-2-2 Q duration at least 0.03 seconds and less than 0.04 seconds in lead II.

1-2-3 QS pattern in lead II. Not coded in the presence of 7-1-1.

1-2-4 Q duration of at least 0.04 seconds and less than 0.05 seconds in lead III, plus a Q wave of at least 1.0 mm amplitude in the majority of beats in aVF.

1-2-5 Q duration at least 0.04 seconds and less than 0.05 seconds in lead aVF.

1-3-1 Q/R amplitude ratio at least 1/5 and less than 1/3 plus Q duration of at least 0.02 seconds and less than 0.03 seconds in lead II.

1-3-4 Q duration of at least 0.03 seconds and less than 0.04 seconds in lead III, plus any Q wave of at least 1.0 mm amplitude in a majority of beats in lead aVF.

1-3-5 Q duration of at least 0.03 seconds and less than 0.04 seconds in lead aVF.

1-3-6 QS pattern in each of leads III and aVF. Not coded in the presence of 7-1-1.

c) Anteroseptal site (leads V1, V2, V3, V4, V5)

1-1-1 Q/R amplitude ratio 1/3 or more plus Q duration 0.03 seconds or more in any of leads V2, 3, 4, 5.

1-1-2 Q duration 0.04 seconds or more in any of leads V1, 2, 3, 4, 5.

- 1-1-6 QS pattern when initial R wave is present in adjacent lead to the right on the chest in any of leads V2, 3, 4, 5, 6. For lead V1, an initial R is considered present when the majority of beats have an initial positive deflection in the QRS of greater than or equal to 0.25 mm. For leads V2-V5, if any beat has an initial R greater than or equal to 0.25 mm it is considered present for all beats in the lead.
- 1-1-7 QS pattern in all of leads V1-V4 or V1-V5.
- 1-2-1 Q/R amplitude ratio 1/3 or more, plus Q duration at least 0.02 seconds and less than 0.03 seconds in any of leads V2, 3, 4, 5.
- 1-2-2 Q duration at least 0.03 seconds and less than 0.04 seconds in any of leads V2, 3, 4, 5.
- 1-2-7 QS pattern in all of leads V1 through V3. Not coded in the presence of 7-1-1.
- 1-3-1 Q/R amplitude ratio at least 1/5 and less than 1/3 plus Q duration of at least 0.02 seconds and less than 0.03 seconds in any of leads V2, 3, 4, 5.
- 1-3-2 QS pattern in absence of code 3-1 or 7-1-1 in each of leads V1 and V2.
- 1-3-8 Initial R amplitude decreasing to 2.0 mm or less and absence of codes 3-2, 7-2-1, or 7-3 in every beat between any of leads V2 and V3, V3 and V4, and V4 and V5. All beats in the lead immediately to the right must have an initial R greater than 2 mm.

## 2. High Amplitude R Waves

(Not to be coded in the presence of codes 6-4-1, 7-1-1, 7-2-1, or 7-4.)

- 3-1 Left: R amplitude greater than 26 mm in either of leads V5 or 6; or R amplitude greater than 20 mm in any of leads I, II, III, aVF; or R amplitude greater than 12 mm in lead aVL.
- 3-2 Right: R amplitude equal to or greater than 5 mm and R amplitude equal to or greater than S amplitude in the majority of beats in lead V1, when S waves greater than R waves somewhere to the left of V1 on the chest. (Includes code 7-3 which meets the above criteria.)
- 3-3 Left: (optional code when 3-1 is not present): R amplitude greater than 15 mm but less than or equal to 20 mm in lead I, or R amplitude in V5 or 6, plus S amplitude in V1 greater than 35 mm.
- 3-4 Criteria for 3-1 and 3-2 both present.

3. S-T Junction (J) and Segment Depression

(Not to be coded in the presence of codes 6-4-1, 7-1-1, 7-2-1, or 7-4; codes 4-1, 4-2, and 4-3 require a concomitant T wave code in 5-1, 5-2, 5-3.)

a) Anterolateral site (leads I, aVL, V6)

4-1-1 S-T-J depression 2 mm or more and S-T segment horizontal or downward sloping in any of leads I, aVL, V6.

4-1-2 S-T-J depression at least 1 mm but less than 2 mm, and S-T segment horizontal or downward sloping in any of leads I, aVL, V6.

4-2 S-T-J depression at least 0.5 mm and less than 1 mm and S-T segment horizontal or downward sloping in any of leads I, aVL, V6.

4-3 No S-T-J depression as much as 0.5 mm but S-T segment downward sloping and segment or T wave nadir at least 0.5 mm below P-R baseline in any of leads I, aVL, V6. (4-3 may have an elevated J point.)

4-4 S-T-J depression of 1 mm or more and S-T segment upward sloping or U-shaped in any of leads I, aVL, V6.

b) Posterior (inferior) site (leads II, III, aVF)

4-1-1 S-T-J depression 2 mm or more and S-T segment horizontal or downward sloping in any of leads II or aVF.

4-1-2 S-T-J depression at least 1 mm but less than 2 mm, and S-T segment horizontal or downward sloping in any of leads II or aVF.

4-2 S-T-J depression at least 0.5 mm and less than 1 mm and S-T segment horizontal or downward sloping in any of leads II or aVF.

4-3 S-T-J depression as much as 0.5 mm, but S-T segment downward sloping and segment or T wave nadir at least 0.5 mm below P-R baseline in any of lead II. (4-3 may have an elevated J point.)

4-4 S-T-J depression of 1 mm or more and S-T segment upward sloping or U-shaped in lead II.

c) Anteroseptal site (leads V1, 2, 3, 4, 5)

4-4 S-T-J depression of 1 mm or more and S-T segment upward sloping or U-shaped in lead II.

4-1-1 S-T-J depression 2 mm or more and S-T segment horizontal or downward sloping in any of leads V1, 2, 3, 4, 5.

4-1-2 S-T-J depression at least 1 mm but less than 2 mm, and S-T segment horizontal or downward sloping in any of leads V1, 2, 3, 4, 5.

- 4-2 S-T-J depression at least 0.5 mm, and less than 1 mm and S-T segment horizontal or downward sloping in any of leads V1, 2, 3, 4, 5.
- 4-3 No S-T-J depression as much as 0.5 mm but S-T segment downward sloping and segment or T wave nadir at least 0.5 mm below P-R baseline in any of leads V1, 2, 3, 4, 5. (4-3 may have an elevated J point.)
- 4-4 S-T-J depression of 1 mm or more and S-T segment upward sloping or U-shaped in any of leads V1, 2, 3, 4, 5.

#### 4. T Wave Items

(Not to be coded in the presence of codes 6-4-1, 7-1-1, 7-2-1, or 7-4.)

##### a) Anterolateral site (leads I, aVL, V6)

- 5-1 T amplitude negative, minus 5 mm or more negative in any of leads I, 6, or in lead aVL when R amplitude is 5 mm or more.
- 5-2 T amplitude negative or diphasic (positive-negative or negative-positive type) with negative phase at least minus 1 mm but not as deep as minus 5 mm in any of leads I, V6, or lead aVL when R amplitude is 5 mm or more.
- 5-3 T amplitude zero (flat), or negative, or diphasic (negative-positive type only) with less than 1 mm negative phase in any of leads I, V6, or in lead aVL when R amplitude is 5 mm or more.
- 5-4 Optional code: T amplitude positive and T/R amplitude ratio less than 1/20 in any of leads I, aVL, V6; R wave amplitude must be 10 mm or more.

##### b) Posterior (inferior) site (leads II, III, aVF)

- 5-1 T amplitude negative, minus 5 mm or more negative in lead II, or in lead aVF when QRS is mainly upright.
- 5-2 T amplitude negative or diphasic (positive-negative or negative-positive type) with negative phase at least minus 1 mm but not as deep as minus 5 mm in lead II, or in lead aVF when QRS is mainly upright.
- 5-3 T amplitude zero (flat), or negative, or diphasic (negative-positive type only) with less than 1 mm negative phase in lead II; not coded in lead aVF.
- 5-4 Optional code: T amplitude positive and T/R amplitude ratio less than 1/20 in lead II; R wave amplitude must be 10 mm or more.

- c) Anteroseptal site (leads V2, V3, V4, V5)
  - 5-1 T amplitude negative, minus 5 mm or more negative in any of leads V2, 3, 4, 5.
  - 5-2 T amplitude negative or diphasic (positive-negative or negative-positive type) with negative phase at least minus 1 mm but not as deep as minus 5 mm in any of leads V2, 3, 4, 5.
  - 5-3 T amplitude zero (flat), or negative, or diphasic (negative-positive type only) with less than 1 mm negative phase in any of leads V3, 4, 5.
  - 5-4 Optional code: T amplitude positive and T/R amplitude ratio less than 1/20 in any of leads V3, 4, 5; R wave amplitude must be 10 mm or more.

5. A-V Conduction Defect

- 6-1 Complete (third degree) A-V block (permanent or intermittent) in any lead. Atrial and ventricular complexes firing independently and atrial rate faster than ventricular rate, with ventricular rate less than 60.
- 6-2-1 Mobitz Type II.
- 6-2-2 Partial (second degree) A-V block in any lead. (2:1 or 3:1 block)
- 6-2-3 Wenckebach.
- 6-3 P-R (P-Q) interval 0.22 seconds or more in the majority of beats in any of leads I, II, III, aVL, aVF.
- 6-4-1 Wolff-Parkinson-White syndrome: Persistent, normal P wave. P-R (P-Q) interval less than or equal to 0.12 seconds, plus QRS duration 0.12 seconds or more, plus R peak duration 0.06 seconds or more, coexisting in the same beat and persistent in the majority of beats in any of leads I, II, aVL, V4, 5, or 6.
- 6-4-2 WPW-Intermittent, WPW pattern in less than or equal to 50% of beats in appropriate leads.
- 6-5 Short P-R (P-Q) interval: P-R (P-Q) interval less than 0.12 seconds in all beats in any two leads I, II, III, aVL, aVF.
- 6-6 Intermittent aberrant ventricular conduction: P-R greater than 0.12 seconds (except in presence of 6-5 or heart beat greater than 100). Bizarre QRS complex greater than 0.12 seconds wide. Normal P wave when most beats are normal sinus rhythm. (Suppressed by 6-4-2.)
- 6-8 Artificial pacemaker.

## 6. Ventricular Conduction Defects

- 7-1-1 Complete left bundle branch block (LBBB) -- suppressed by 6-1, 6-4-1, 6-8, 8-2-1 or 8-2-2 QRS duration greater than or equal to 0.12 seconds in a majority of beats (of the same QRS pattern) in any of leads I, II, III, aVL, aVF, PLUS R peak duration greater than or equal to 0.06 seconds in a majority of beats (of the same QRS pattern) in any of leads I, II, aVL, V5, V6. 7-1-1 suppresses 1-2-3, 1-2-7, 1-3-2, 1-3-6, 1-3-8, all 3, 4, 5, 9-2, 9-4, 9-5 codes. If any other Q wave coexists with the LBBB pattern, code the Q and drop the 7-1-1 code to a 7-4 code.
- 7-1-2 Intermittent left bundle branch block -- same as 7-1-1 but with presence of normally conducted QRS complexes of different shape to the LBBB pattern.
- 7-2-1 Complete right bundle branch block (RBBB) -- suppressed by 6-1, 6-4-1, 6-8, 8-2-1 or 8-2-2 QRS duration greater than or equal to 0.12 seconds in a majority of beats (of the same QRS pattern) in any of leads I, II, III, aVL, aVF, PLUS R greater than R in V1 or V2 OR QRS mainly upright plus R peak duration greater than or equal to 0.06 seconds in V1 or V2 OR S duration greater than R duration in all beats of either leads I or II, 7-2 suppresses 1-2-8, all 2, 3, 4 and 5 codes, 9-2, 9-4, 9-5.
- 7-2-2 Intermittent right bundle branch block -- same as 7-2-1 but with presence of normally conducted QRS complexes of different shape to the RBBB pattern.
- 7-3 Incomplete right bundle branch block: QRS duration less than 0.12 seconds in each of leads I, II, III, aVL, aVF, and R prime greater than R in either of leads V1, 2. (To be reported as 3-2 if those criteria are met.) 7-3 suppresses 1-3-8 code.
- 7-4 Intraventricular block (in absence of 6-4-1, 7-1-1, or 7-2-1): QRS duration 0.12 seconds or more in a majority of beats in any of leads I, II, III, aVL, aVF.
- 7-5 R-R prime in either of leads V1 or V2 with R prime less than or equal to R.
- 7-6 Incomplete left bundle branch block: QRS duration at least 0.10 seconds and less than 0.12 seconds in the absence of codable Q or QS waves, in the majority of beats in each of leads I, aVL, and V5 or V6.
- 7-7 LAH (Left-Anterior Hemiblock). QRS duration less than 0.12 seconds in the majority of beats in any of leads I, II, III, aVL, aVF, plus a Q wave that is greater than or equal to 1/4 mm amplitude and less than 0.03 seconds duration in lead I plus axis less than minus 45 degrees. In presence of 7-2, code 7-8 if axis is less than minus 45 degrees and Q wave in lead I meets the above criteria.

7-8 Combination of 7-7 and 7-2.

7. Arrhythmias

- 8-1-1 Frequent premature atrial, or nodal beats (10% or more of recorded cycles).
- 8-1-2 Frequent premature ventricular beats (10% or more of recorded cycles).
- 8-1-3 Frequent premature atrial and/or junctional beats, and ventricular beats (so that individual frequencies are less than 1 per 10 cycles but combined premature beats are greater than 1 per 10 cycles). Not to be coded in the presence of 8-1-1 or 8-1-2.
- 8-1-4 Wandering atrial pacemaker.
- 8-1-5 Presence of 8-1-2 and 8-1-4.
- 8-2-1 Ventricular fibrillation or ventricular asystole.
- 8-2-2 Persistent ventricular (idioventricular) rhythm.
- 8-2-3 Intermittent ventricular tachycardia. Three or more consecutive ventricular premature beats occurring at a rate greater than or equal to 100.
- 8-2-4 Ventricular parasystole (should not be coded in presence of 8-3-1).
- 8-3-1 Atrial fibrillation (persistent in all leads).
- 8-3-2 Atrial flutter (persistent)
- 8-3-3 Intermittent atrial fibrillation (code if three or more clear-cut, consecutive sinus beats present in any lead).
- 8-3-4 Intermittent atrial flutter (code if three or more clear-cut, consecutive sinus beats present in any lead).
- 8-4-1 Persistent supraventricular rhythm. QRS duration less than 0.12 seconds. Absent P waves or presence of abnormal P waves (inverted or flat in aVF). Regular rhythm.
- 8-4-2 Intermittent supraventricular tachycardia. Three consecutive atrial or junctional premature beats occurring at a rate of greater than or equal to 100.
- 8-5-1 Sino-atrial arrest. Unexpected absence of P, QRS, and T. RR-interval fixed multiple of normal interval plus or minus 10%.

- 8-5-2 Sino-atrial block. Unexpected absence of P, QRS, and T preceded by progressive shortening of P-P intervals. (R-R interval fixed multiple of normal interval or plus or minus 10%.)
- 8-6-1 A-V dissociation with ventricular pacemaker without capture. P-R and R-R occur at variable rates with ventricular rate as fast or faster than the atrial rate. Variable P-R intervals. No capture beats.
- 8-6-2 A-V dissociation with ventricular pacemaker with capture.
- 8-6-3 A-V dissociation with atrial pacemaker and with no capture beats.
- 8-6-4 A-V dissociation with atrial pacemaker with capture beats.

## 8. S-T Segment Elevation

(Not to be coded in the presence of codes 6-4-1, 6-8, 7-1-1, 7-2-1, or 7-4.)

### a) Anterolateral site (leads I, aVL, V6)

- 9-2 S-T segment maximum elevation of 1 mm or more in any of leads I, aVL, or V6.

### b) Posterior (inferior) site (leads II, III, aVF)

- 9-2 S-T segment maximum elevation of 1 mm or more in any of leads II, III, or aVF.

### c) Anteroseptal site (leads V1, 2, 3, 4, 5)

- 9-2 S-T segment maximum elevation of 1 mm or more in lead V5 or S-T segment maximum elevation of 2 mm or more in any of leads V1, V2, V3, V4.

## 9. Miscellaneous Items

- 9-1 Low QRS amplitude: QRS peak-to-peak amplitude less than 5 mm in all beats in each of leads I, II, III, or QRS peak-to-peak amplitude less than 10 mm in all beats in each of leads V1, 2, 3, 4, 5, 6.
- 9-3 P wave amplitude of 2.5 mm or more in any of leads II, III, aVF on a majority of beats.
- 9-4-1 QRS transition zone at V3 to the right (on the chest) of lead V3. (Not to be coded in the presence of 6-4-1, 7-1-1, 7-2-1, or 7-4.)
- 9-4-2 QRS transition zone at lead V4 or to the left of V4 on the chest. (Not to be coded in the presence of codes 6-4-1, 7-1-1, 7-2-1, or 7-4.)

- 9-5 T wave amplitude greater than 12 mm in any of leads I, II, III, aVL, aVF, V1, 2, 3, 4, 5, 6. (Not to be coded in the presence of 6-4-1, 7-1-1, 7-2-1, or 7-4.)
- 9-8-1 Technical problems present and interferes with coding.
- 9-8-2 Technical problems present but ECG codable.

Figure 15.1  
PROPER FOLDING OF ECG TRACINGS FOR EDIC

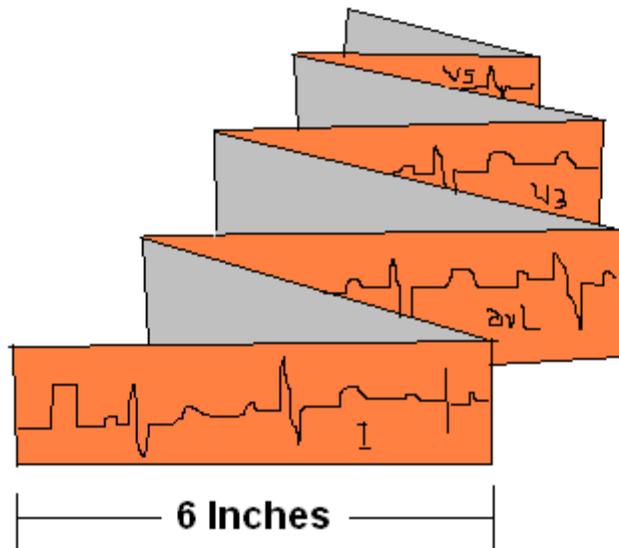


Figure 15.2  
Limb and Chest Electrodes

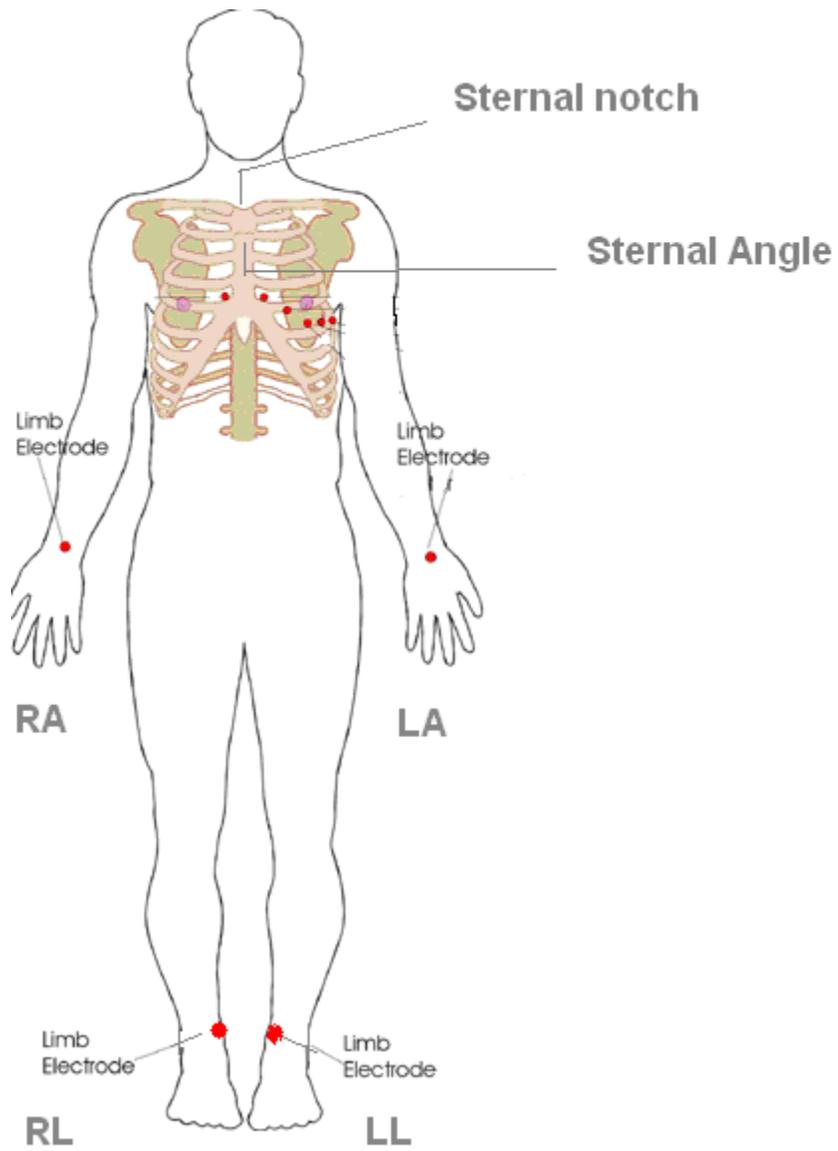
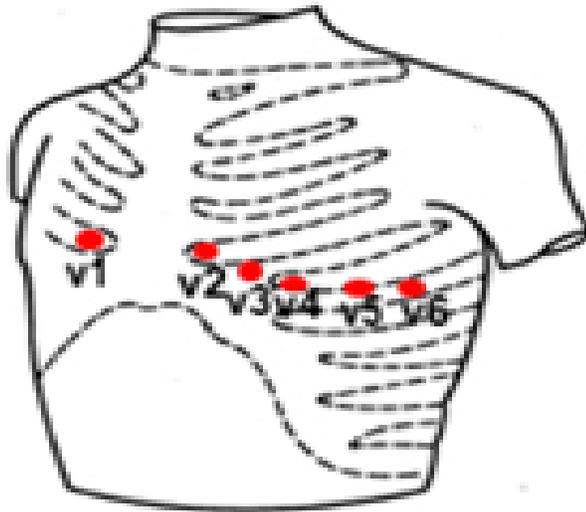


Figure 15.3



15.3.A Chest Electrodes

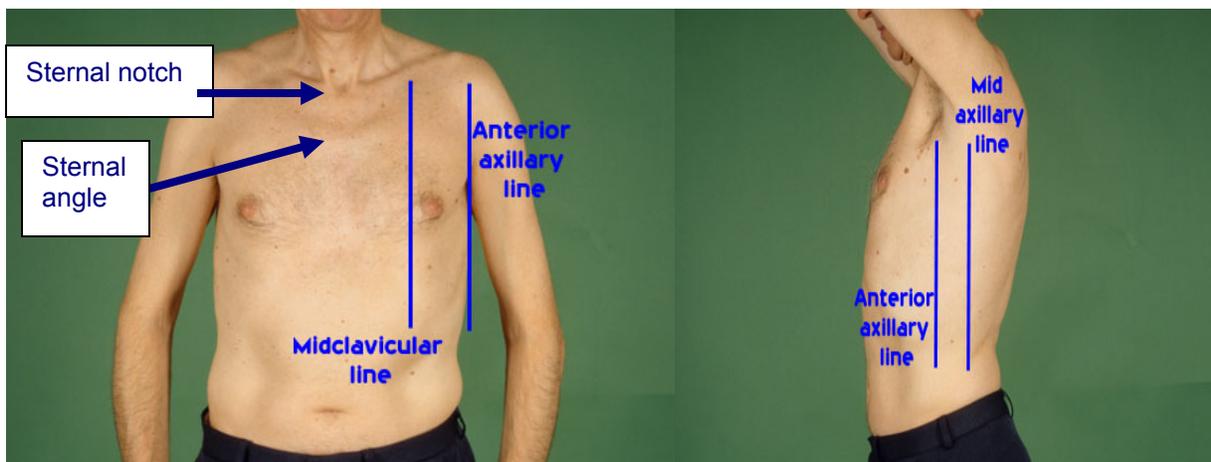


Figure 15.3B. Mid-clavicular, Anterior Axillary and Mid-axillary Lines

Figure 15.4

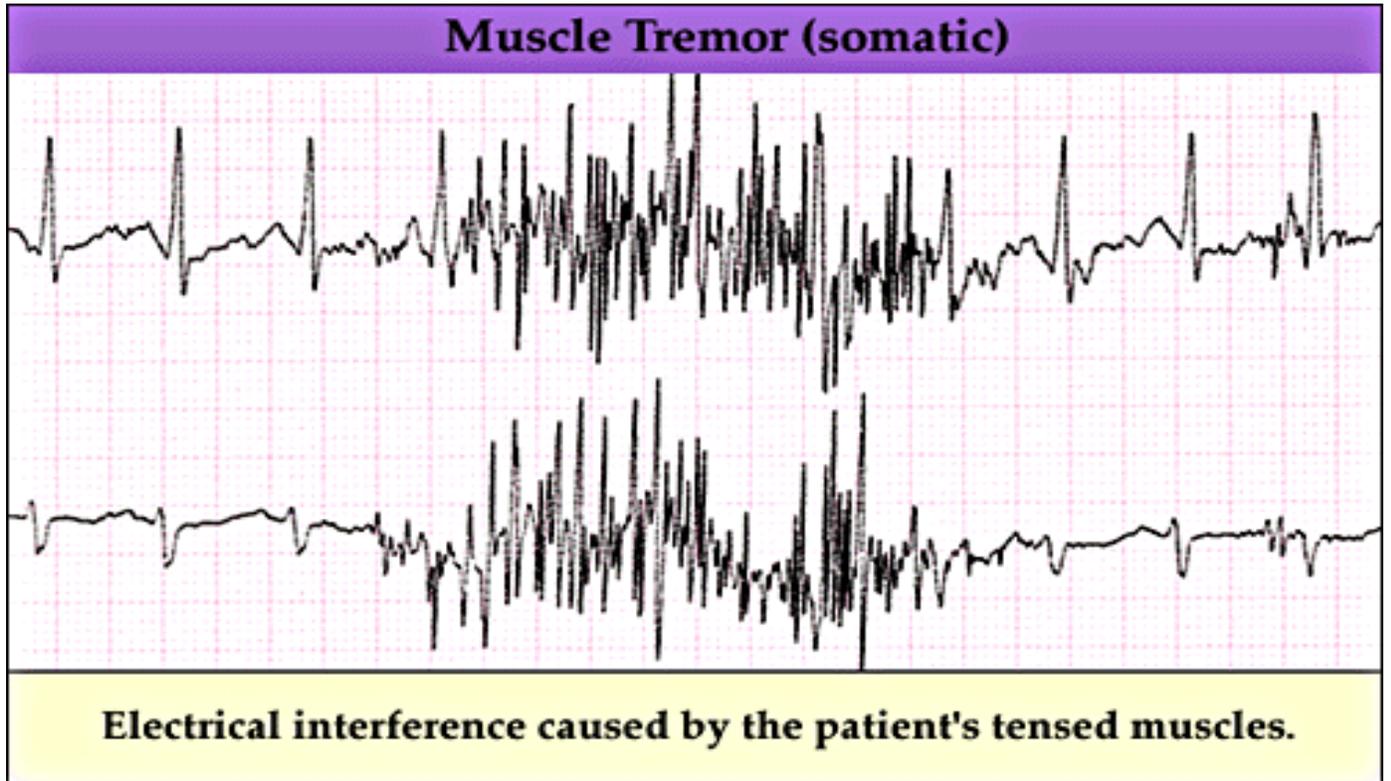


Figure 15.5  
Baseline drift due to participant movement

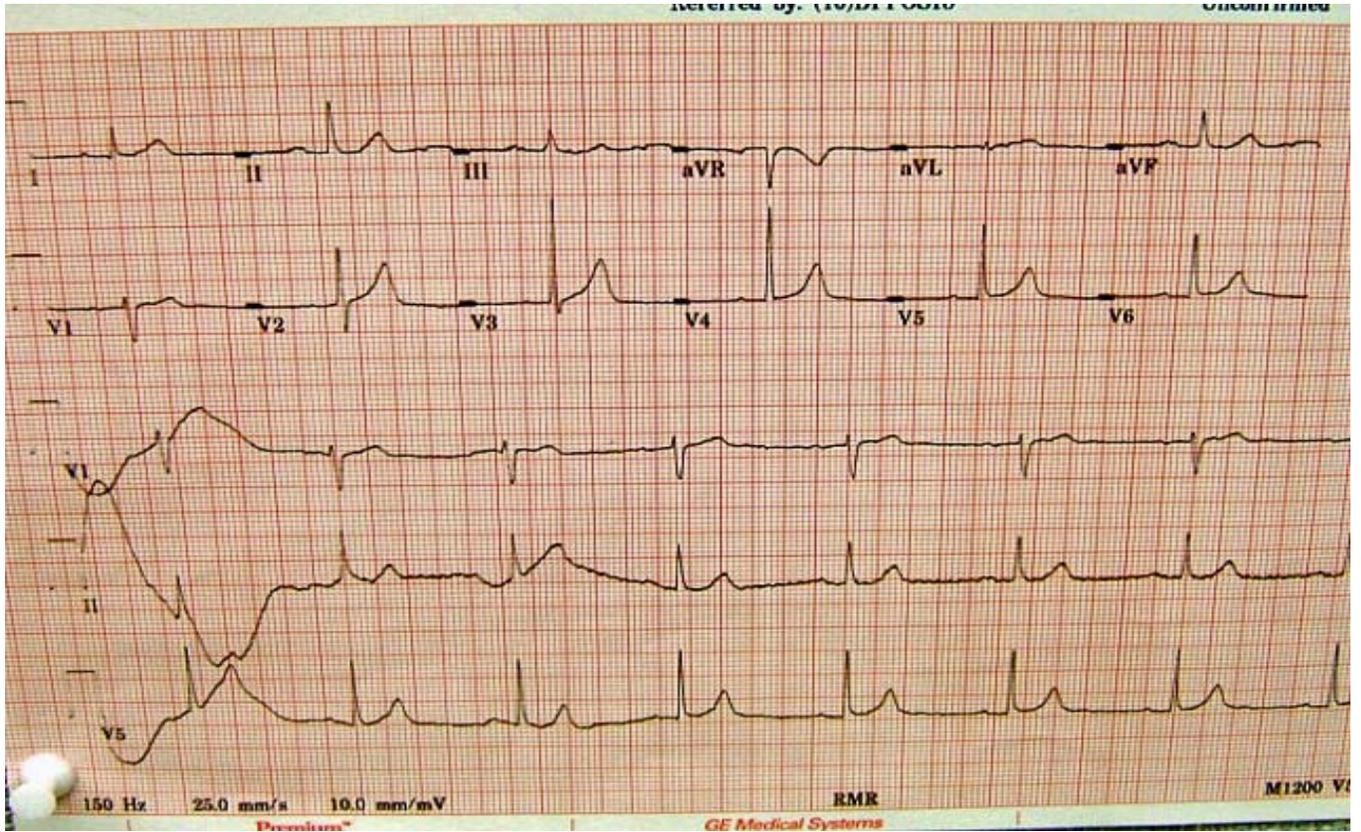


Figure 15.6

Improper application of V1 Electrode

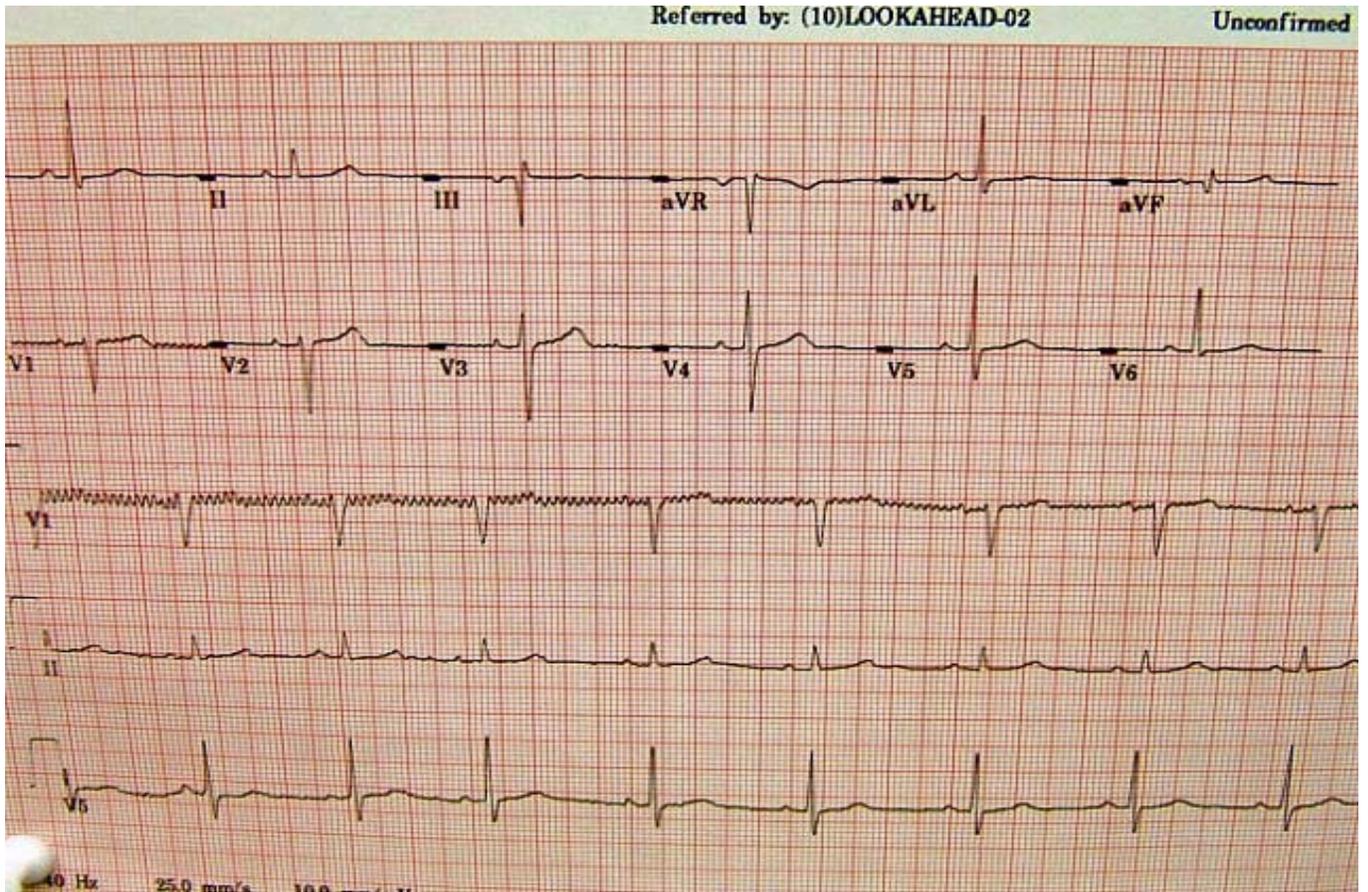
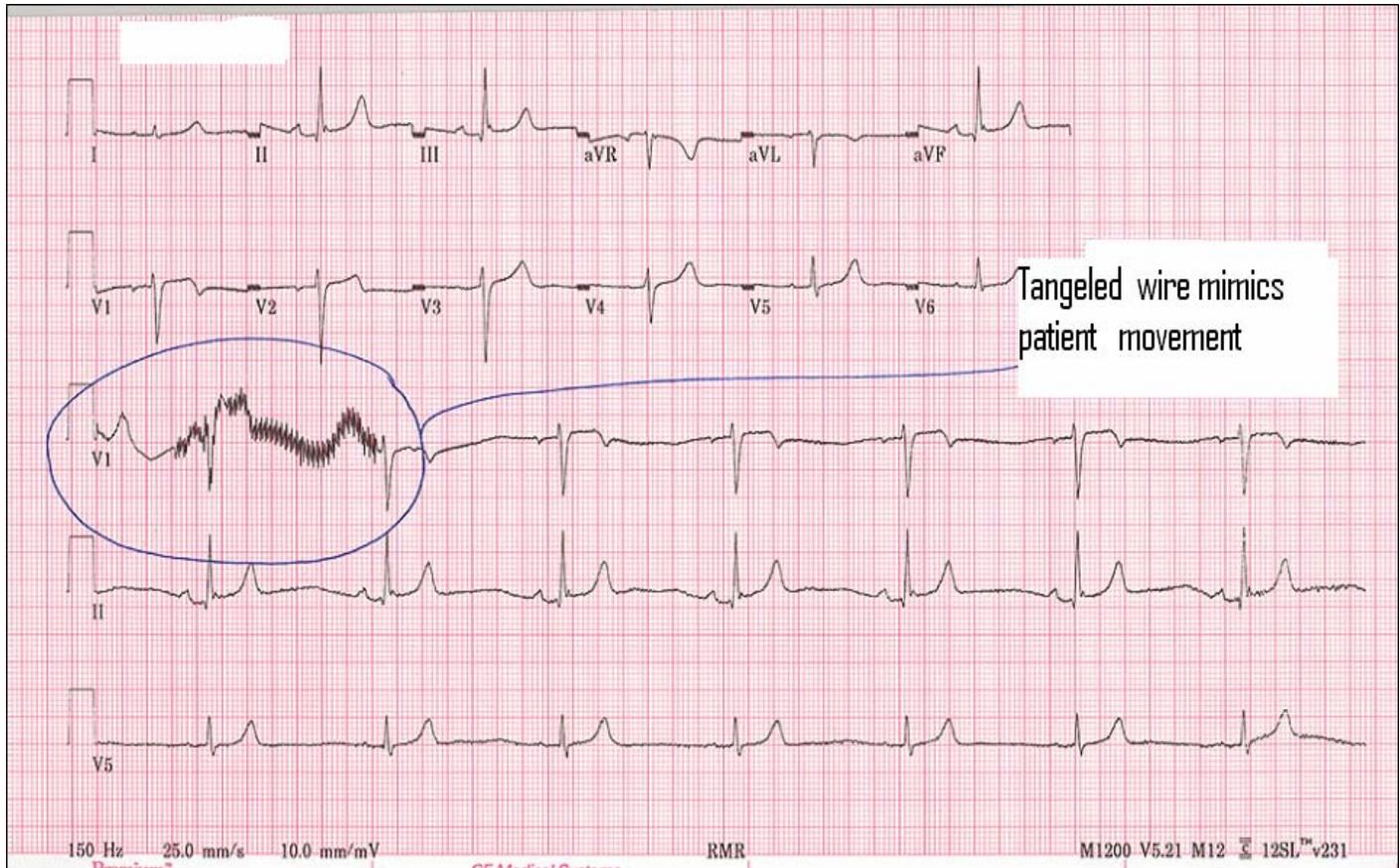
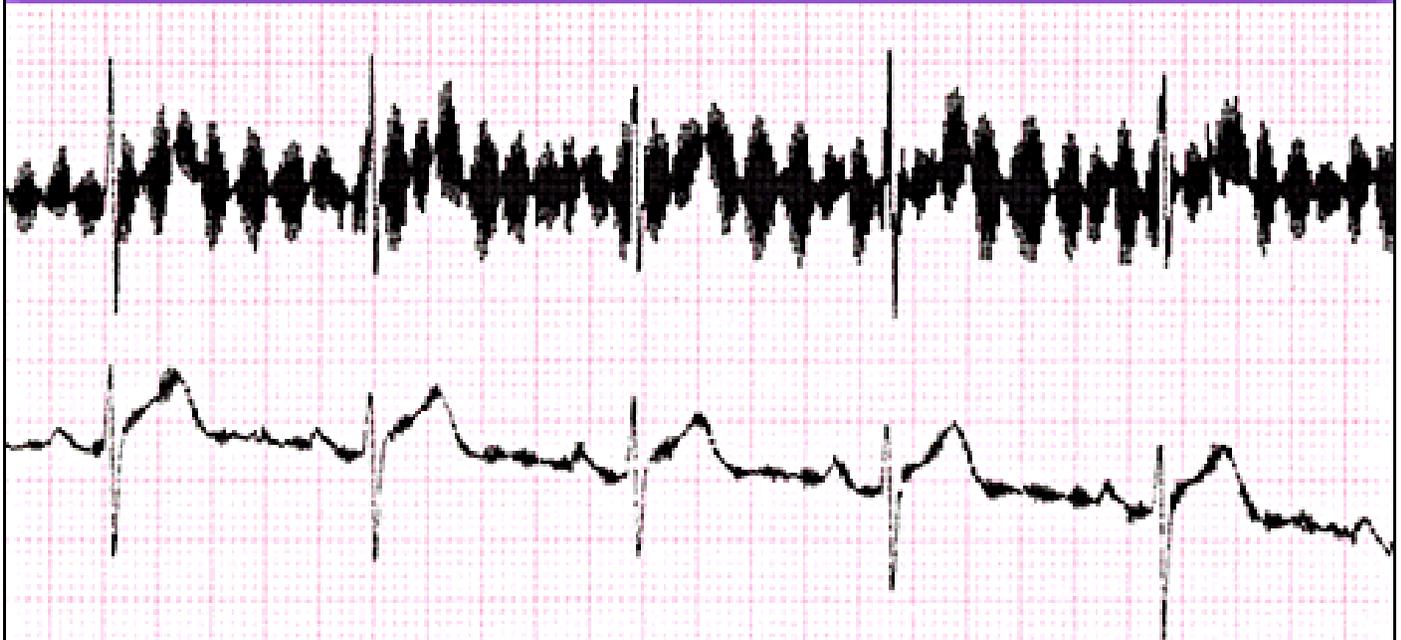


Figure 15.7

Tension on lead wires



## AC Interference (60 cycle)



**Sixty even, regular spikes in a 1 second interval caused by electrical current near the patient**

## 16. ANKLE/ARM INDEX BY DOPPLER

### 16.1 Introduction

Leg blood pressure determination is a method for detecting the development of obstructive changes in the arteries to the leg or calcification in their walls. Occlusive changes are almost invariably due to atherosclerotic plaques. Leg blood pressure determination therefore is a technique capable of early detection of diabetes-associated atherosclerosis. Advanced arterial calcification occurs predominantly in mid-life diabetic males, but mild artery wall calcification is a feature of developing diabetic kidney disease. In the case of arterial occlusion, a low-pressure ratio is found (ankle to arm systolic pressures) while this ratio is higher than normal when calcification is present.

### 16.2 Equipment

Because gravity has an effect on arterial pressure, the study is performed with the subject in the supine position. A table capable of supporting both the head and the legs and feet that is essentially level must be used. Since the patient should be comfortable, it should be satisfactorily cushioned. One should be able to lie on the table comfortably enough to go to sleep.

The procedure requires the normal arm blood pressure cuff, whose air bladder should measure 13 cm from top to bottom, and an ultrasound stethoscope. In 2006, the decision was made to use a large size blood pressure cuff if the extremity circumference exceeds the upper limit of a normal size cuff. The Medasonic Model BF4B is probably the most suitable for clinical screening. In the vascular laboratory, a blue cuff longer than the normal arm cuff, but measuring only 10 to 11 cm from top to bottom is used. A somewhat more sensitive ultrasound system is also used there. But commonly the vascular laboratory blood pressure gauge will only go up to 230 or 250 mm Hg. These differences create an inexact comparability between vascular laboratory and diabetes clinic determinations. But the mid-range (normal) values are usually essentially the same except in obesity. Failure to detect one or more pulses is more likely with a Medasonic than with a vascular laboratory stethoscope, but a high ankle to arm systolic pressure ratio (associated with extreme calcification) is easier to determine using the 13 cm cuff and a blood pressure gauge that goes up to 300 mm Hg. The same cuff(s) and ultrasound stethoscope should be used at all like extremity sites on the patient. The six systolic pressures should be gathered in a rapid but orderly manner.

In addition to the ultrasound stethoscope, an acoustic gel that allows for good sound transmission from below the skin surface to the ultrasound stethoscope is needed. ECG gel is conducting and should not be substituted for ultrasound acoustic gel; the ECG paste can corrode the ultrasound stethoscope head.

### 16.3 Technique

The patient should be in the supine position and psychologically at rest. The rest period to obtain this state should be at least 5 minutes. Additionally, it is important that the patient not undertake any emotionally distressing conversations or tasks during the leg blood pressure determination. The study should be between 5 and 10 minutes altogether. The blood pressure cuff is placed just above the ankle at the lowest site that allows listening at the dorsalis pedis site in front of the ankle. For the EDIC, we will evaluate the right ankle first. Once the cuff is in place, 0.5 to 1 ml acoustic gel is placed over the sites of the dorsalis pedis (anterior ankle to

upper dorsal foot) and the posterior tibial below the (medial malleolus) arteries. The ultrasound stethoscope is placed on the expected site of the dorsalis pedis pulse. An attempt is made to identify its presence by detecting a whooshing sound of arterial flow. The pitch of this sound is engineered into the ultrasound continuous Doppler stethoscope. When this site is identified, the blood pressure cuff is inflated. Care must be taken not to allow the ultrasound stethoscope head to migrate while this is done. The cuff is inflated to 250 mm Hg to make sure that the sound disappears. Occasionally, it may have to be inflated higher than this because of the persistence of a flow sound at 250 mm Hg, but this should be very unusual in the EDIC subjects. The applied pressure is then lowered slowly (as with arm pressure determinations) until the sound of flow is heard again. This is the systolic pressure. Deflate the cuff once this is heard; the diastolic pressure is not needed. Once the cuff has fully deflated, repeat systolic pressure assessment once more to be assured that a satisfactory value has been obtained. The average of these two measurements is then recorded to the nearest even number on the Form 002. Digit preferences will be monitored by the study group in the evaluation of quality control of this procedure. The same procedure is then carried out over the posterior tibial site below and/or behind the medial malleolus. After the two right ankle studies are completed, the right arm pressure should be examined at the antecubital fossa with the cuff applied at mid arm in the usual position. The left ankle is then studied in the same way as the right ankle, followed by the left arm. Six systolic pressure values have now been recorded and the study is complete. The acoustic gel is then removed from all sites using facial tissue or equivalent.

#### 16.4 Interpretation

Ascertainment of ankle to arm pressure ratios can be achieved by averaging the two brachial pressures and dividing this average into each of the four systolic ankle pressures. It is more common to use the higher arm pressure than the average of the two, but the average strategy is more supported by studies in diabetes. The systolic pressure is typically about 10 percent higher in the leg than in the arm. This is true because systolic arterial pressure is actually a reflected wave that slows the flow of blood as it arrives at more distal positions. This means that systolic pressure is higher further from the heart both in the leg and in the arm (unless there is occlusive disease). The mean dorsalis pedis ratio is slightly lower than the posterior tibial, and men have a slightly higher ratio than women. But the 10 percent rule (1.10 as an average) is not a bad one. One begins to suspect occlusion when an individual ankle pressure is below 90 percent of the arm pressure (0.89 or less). A ratio that exceeds 1.3 suggests that the arterial wall is not collapsing effectively under the blood pressure cuff and that calcium is likely to be present in the arterial wall.

Four ratios are achieved with each determination. The risk of finding a marginally low or marginally high value is therefore significant. A second set of abnormal pressures has recently been adopted, to avoid a more clinical reaction to marginal values. The values are below 0.8 and above 1.4. In the Epidemiology of Diabetes Interventions and Complications, we don't have specific plans for an active intervention. Unless we find a major defect in pressure, a ratio below 0.7, we will not be carrying out the early follow-up recommended for pressure ratios below 0.8 or above 1.4. Ratios that are outside the recommended range (below 0.8 or over above 1.4) should be called to the attention of the physician following the patient. They are sometimes the only sign of developing atherosclerotic arterial disease. A ratio below 0.6 threatens the integrity of the feet in the presence of infection and can signal future gangrene.

## 17. CAROTID ARTERY ULTRASOUND PROCEDURES AND CENTRAL ULTRASOUND READING CENTER

### 17.1 Introduction

The primary objective of the carotid ultrasound study is to acquire four standardized B-Mode images and a Doppler flow measurement from both the right and left sides of the neck in all EDIC subjects. The scanning protocol calls for eight images from each subject, four images from each side of the neck. The first image is of the distal common carotid artery and the three others are centered on the site of maximum near or far wall thickening (lesion) in the proximal internal carotid artery or the carotid bulb. The images at the site of maximum thickening are obtained at three different angles. Pulse Wave Doppler measurements are taken at the site of maximum flow acceleration in the distal common carotid artery, bulb, or internal carotid artery.

### 17.2 Subject Position

The subject is supine during the carotid artery examination and is made comfortable in a position that allows head rotation to either side. The sonographer is seated at the end of the exam table near the subject's head.

### 17.3 Selection of Anatomical Sites

The extracranial carotid arteries are divided into four anatomically defined segments:

Distal Common Carotid Artery

Carotid Bulb

Internal Carotid Artery

External Carotid Artery

The lateral extent of each segment is defined relative to the tip of the flow divider, which is typically the most clearly defined anatomical reference in the carotid system. The three segments of interest are the Distal Common Carotid Artery, the Carotid Bulb, and the Internal Carotid Artery. No external carotid artery images will be recorded.

(1) Distal Common Carotid - This is the segment of the common carotid artery immediately proximal to the origin of the carotid bulb, where the near and far walls of the artery are parallel to one another. The end of the distal common carotid artery is marked by the dilatation of the vessel walls, which is the carotid bulb.

(2) Carotid Bulb - The inferior extent of the bulb is the beginning of dilatation or 8 mm below the tip of the flow divider. The superior extent of the bulb is defined by the very tip of the flow divider.

(3) Internal Carotid Artery - The caudal, or inferior, extent is defined by the tip of the flow divider. The vessel then ascends in the neck and enters the base of the skull. For the purposes

of this protocol, the ultrasound study will be limited to the initial 10 mm of the internal carotid artery.

#### 17.4 Baseline Image Review

Baseline carotid IMT images for each EDIC subject have been distributed to the clinical centers. The baseline images are to be used by the sonographers during scanning to facilitate the collection of follow-up images that match the baseline in magnification (*scale*), anatomic position, and image perspective. It is of utmost priority to match the **magnification (*scale*)** of the baseline scan.

The image files are in a standard file format, bitmap \*.dib, that can be recognized by most digital imaging software including "Imaging" and "Paint", programs which are typically installed with the Windows operating system. The images are most efficiently viewed on a laptop or other computer that can be viewed while scanning. Alternatively, the pictures can be printed onto 8 ½ by 11 paper by any standard printer and brought into the scanning area.

Most EDIC participants were scanned during the first carotid ultrasound exam cycle in 1994; however, a few were not scanned until the second carotid ultrasound exam cycle in 1998. There will also be a few Subjects for whom one or more images may be missing.

The image file names will reflect the year of the scan, the subject ID, and the image label, which indicates the side, anatomic location, and perspective. The image file names used are the same as the image labels: RCC, RAO, RLO and RPO. These refer to right common carotid, right anterior oblique of ICA/bulb, right lateral oblique of ICA/bulb, and right posterior oblique of ICA/bulb. Images from the left side are thus named: LCC, LAO, LLO and LPO. The image file names include the year of the exam cycle, the participant's subject ID number and the letter "R" or the letter "L" to indicate the right or left artery. For example, the digital image of the left common carotid for the Subject ID # 51619 who was first scanned in 1994 is named 9451619\_LCC.DIB and the file containing the anterior view of the right internal for the same subject is named 9451619\_RAO.DIB. The RCC image of a subject who was first scanned in 1998 such as Subject ID # 13298 will be named 9813297\_RCC.dib

If the image file cannot be found or the imprinted Subject ID is does not match, please notify the Ultrasound Reading Center immediately.

<b><u>URC Contact</u></b>	<b><u>Telephone</u></b>	<b><u>E-mail</u></b>	<b><u>Fax</u></b>
Thao Ho <i>Primary EDIC Reader</i>	617.636.0036	<a href="mailto:THo@tufts-nemc.org">THo@tufts-nemc.org</a>	617.636.0064
Jason Coole <i>Reader</i>	617.636.0036	<a href="mailto:JCoole@tufts-nemc.org">JCoole@tufts-nemc.org</a>	617.636.0064
Laurie Funk <i>Project Manager</i>	717.228.3750	<a href="mailto:lrcfunk@comcast.net">lrcfunk@comcast.net</a>	717.274.0133

### 17.5 Scanning Summary

The scanning protocol includes a transverse sweep from the base of the common carotid up through the internal carotid, a pulse wave Doppler measurement at the site of maximal wall thickening, and static grayscale images of both the common carotid and the internal carotid arteries. The internal carotid artery images are taken at the site of maximal wall thickening.

Magnification and zoom, the terminology and the steps necessary to adjust the size of the anatomical area that is imaged vary amongst the ultrasound machine manufacturers. Because this is a progression study, the sonographers will try to match the level of magnification and position that was used at baseline. To accomplish this, the EDIC 3 images will be captured while viewing the baseline images.

#### Scanning Protocol Summary with GE Logiq 700 or 9 magnification notes

The carotid ultrasound images are collected and videotaped in this order:

IMAGE DESCRIPTION	IMAGE LABEL	TO BE VIDEOTAPED
<b>PATIENT INFORMATION PAGE</b> Complete the demographic information page with Study and Subject Identifiers		5 seconds
<b>RIGHT SIDE</b>		
1. Transverse (short-axis) sweep	R Trans	15 second scanning sweep
2. Pulse Wave Doppler ICA	R PW	5 seconds of frozen, measured image
<i>Magnification "On" to an approximately 3 cm field-of-view.</i>		
Baseline images are examined and the same (or similar magnification) is used		
3. Common Carotid Artery	RCC	5 seconds of frozen image then the cine loop
4. Anterior ICA or Bulb	RAO	5 seconds of frozen image then the cine loop
5. Lateral ICA or Bulb	RLO	5 seconds of frozen image then the cine loop
6. Posterior ICA or Bulb	RPO	5 seconds of frozen image then the cine loop
<i>Magnification "Off"</i>		
<b>LEFT SIDE</b>		
1. Transverse (short-axis) sweep	L Trans	15 second scanning sweep
2. Pulse Wave Doppler ICA	LPW	5 seconds of frozen, measured image
<i>Magnification "On" to an approximately 3 cm field-of-view.</i>		
Baseline images are examined and the same (or similar magnification) is used		
3. Common Carotid Artery	LCC	5 seconds of frozen image then the cine loop
4. Anterior ICA or Bulb	LAO	5 seconds of frozen image then the cine loop

5. Lateral ICA or Bulb	LLO	5 seconds of frozen image then the cine loop
6. Posterior ICA or Bulb	LPO	5 seconds of frozen image then the cine loop

### Scanning Protocol Summary with Philips or ATL HDI 5000 magnification notes

The carotid ultrasound images are collected and videotaped in this order:

IMAGE DESCRIPTION	IMAGE LABEL	TO BE VIDEOTAPED
<b>PATIENT INFORMATION PAGE</b> Complete the demographic information page with Study and Subject Identifiers		5 seconds
<b>RIGHT SIDE</b>		
Transverse (short-axis) sweep	R Trans	15 second scanning sweep
Pulse Wave Doppler ICA	R PW	5 seconds of frozen, measured image
<i>Press Zoom Toggle once</i>		
Baseline images are examined and the same (or similar magnification) is used		
Common Carotid Artery	RCC	5 seconds of frozen image then the cine loop
Anterior ICA or Bulb	RAO	5 seconds of frozen image then the cine loop
Lateral ICA or Bulb	RLO	5 seconds of frozen image then the cine loop
Posterior ICA or Bulb	RPO	5 seconds of frozen image then the cine loop
▪ Zoom "OFF"		
<b>LEFT SIDE</b>		
1. Transverse (short-axis) sweep	L Trans	15 second scanning sweep
2. Pulse Wave Doppler ICA	LPW	5 seconds of frozen, measured image
<i>Press Zoom Toggle once.</i>		
Baseline images are examined and the same (or similar magnification) is used		
3. Common Carotid Artery	LCC	5 seconds of frozen image then the cine loop
4. Anterior ICA or Bulb	LAO	5 seconds of frozen image then the cine loop
5. Lateral ICA or Bulb	LLO	5 seconds of frozen image then the cine loop
6. Posterior ICA or Bulb	LPO	5 seconds of frozen image then the cine loop

#### NOTE:

THE DEFAULT FIELD OF VIEW (MAGNIFICATION) IS 3 CM IN MOST CASES, VERIFY THE FIELD-OF VIEW ON BASELINE IMAGES.

#### 17.6 Verification of Image Location and Scaling

If it is available, review the appearance of the Exam 1 CCA image on laptop computer screen. Note the scaling factor, the location and orientation of the bulb, artery wall and if visible the tip of the flow divider. Document the visibility of the landmarks and assess the quality of the Exam 1

image on the videotape log sheet. The concordance of the baseline images with the set of images captured during this exam cycle is also scored on the log sheet.

Most importantly, attempt to match the degree of image magnification or field-of-view. See the examples of the way scales are displayed from the baseline ultrasound examination images in Section 1.0.2, Machine Set-up. The distance scale on the Ultramark-9 is on the right side. A major tick is 1 cm. Acuson and Toshiba machines display the scale on the left.

### 17.7 Initial Scan

The carotid ultrasound scan requires images from both the right and the left sides of each subject. The steps outlined in sections 17.4 and 17.5 are completed for the right side and then repeated on the left. The purpose of the initial scan is to orient the sonographer to the carotid anatomy to locate the bifurcation and distinguish which vessel is the internal and which is the external carotid artery. Color Doppler and pulse wave Doppler can be used as an identification aid. Once oriented to the pertinent anatomy and prior to obtaining the standard images described in detail below the sonographer should record on videotape a transverse scan of the length of the carotid artery to help orient the reader. Move the probe up and down the length of the carotid artery in the short axis view.

### 17.8 Standard Carotid Artery Ultrasound Images

After the initial scan, the sonographer takes pulse wave Doppler measurement at the point of peak velocity and videotapes it. Then the four standard views of the carotid are obtained (videotaped). The order of videotaping is as follows:

1. Peak systolic velocity - Pulse Wave Doppler Measurement
2. Lateral View of the Distal Common Carotid
3. Anterior-oblique view at the site of maximal thickening in the internal or bulb
4. Lateral oblique view at the site of maximal thickening in the internal or bulb
5. Posterior-oblique view at the site of maximal thickening in the internal or bulb

#### Image 1: Pulse Wave Doppler

The Doppler sample gate should be placed in the center of the distal common carotid artery. The sample gate will be 2 mm. The angle of transducer placement should permit easy movement of the sample volume through the bulb into the proximal internal carotid artery. The critical information required is peak velocity at peak systole at the site of maximum flow acceleration. If there is no site or zone of disturbed or turbulent flow, the Doppler recording should be taken from the first cm. of the internal carotid artery. The audible signal should be used to aid in the placement of the Doppler sample volume. *Angle correction should never exceed 60°.* The frozen image of the Doppler measurement should be recorded on videotape for five seconds.

## Image 2: Distal Common Carotid Artery

Image 2 is a view of the distal 10-mm of the common carotid artery in the lateral projection. The carotid bulb is displayed on the left side of the monitor (when facing the screen). If the bulb cannot be identified, but the tip of the flow divider can, this may substitute as the internal landmark on this view. After locating the tip of the flow divider and centering it on the screen, the probe is rotated into the lateral plane and moved downward 2 cm. The probe is then centered on the upper one cm. of the common carotid artery.

## Images 3, 4, & 5: Site of Maximum Thickening in Internal or the Bulb

The other three images are centered on the site of maximum wall thickness in the internal carotid artery or the carotid bulb. The objective is to obtain images of the segment of vessel that contains the single largest wall abnormality—either near or far wall—in any one view. These images should never be centered on the common carotid artery, even when it is the site of maximum disease. The location of the site of maximum wall thickness should be determined during the initial scan. It is not the site of average maximum wall thickness in multiple views, nor is it the site of maximum near plus far wall thickness, but rather it is the single site of maximum wall thickness in any single view. The sonographer can use any available technique to make this decision including long axis views, short axis views, color Doppler, and gated pulse Doppler.

The three images obtained at this site are taken from three different scanning angles, the anterior-oblique, the lateral, and the posterior-oblique, to provide as much circumferential information at the site of maximum wall thickness as possible. The point of maximal wall thickening should be centered in the middle of the screen for each image. The sonographer should adjust the probe to maximize lesion and wall interfaces in each projection so as not to exaggerate the size of the focal plaque by scanning across the vessel on an oblique axis. The Readers are dependent upon the sonographer to provide an accurate display of a plaque.

The anterior-oblique, lateral and posterior-oblique projections or scanning angles are defined as follows:

Anterior-oblique - the arch on the surface of the neck from the midline (trachea) to 55° to a line drawn from the mid-trachea to the center of the back of the neck.

Lateral - the arch along the lateral surface of the neck, from 55° to the perpendicular to 100° (hence 45°). The sternocleidmastoid muscle can be palpated beneath this portion of the skin's surface.

Posterior-oblique - the arch from 100° to the perpendicular to 145°. The probe almost always lies just behind the posterior margin of the sternocleidmastoid muscle.

If the sonographer considers the health of the artery to be normal, center the images on the initial 10-mm of the internal carotid artery. Use the tip of the flow divider as the point that identifies the most caudal portion or inferior boundary of the internal carotid artery. It will not always be possible to identify the tip of the flow divider in the digitized image. In such situations, the priority is to display the wall interfaces of the proximal internal carotid artery and not the tip of the flow divider.

### 17.9 Criteria for Satisfactory Images & Imaging Priorities

The criteria for optimal B-mode ultrasound images of the carotid arteries is defined on the basis of clear visualization on long axis views of arterial interfaces, internal arterial landmarks, and lesions.

Near wall - arterial wall nearest the probe

- (a) adventitia - medial boundary
- (b) intima - lumen boundary

Far wall - arterial wall furthest from probe

- (a) lumen - intimal boundary
- (b) medial - adventitial boundary

The area of interest will be centered in the middle of the image and the probe will be aligned to show as much of the vessel cephalad and caudad as is possible. The sonographer should maximize the visualization of interfaces by proper adjustment of gain settings, beam steering, and probe placement.

#### Priorities

- (1) Lesion - if a focal lesion is present, the visualization of the lesion should be optimized.
- (2) Far wall interfaces
- (3) Near wall interfaces

### 17.10 Videotaping

When the sonographer considers an image optimal, he touches the "Freeze" button on the ultrasound machine memory panel. If the unit is equipped with a cine (or memory) loop, page through the cine loop and select the best image. Videotape 5 seconds of the frozen frame and 5 seconds of the cine loop. If the unit does not contain a cine loop, first record a frozen image for 5 seconds. Then rescan and again obtain the same image. Then record in real time for 5 seconds. It is important that the sonographer wait for the mechanical delay of the VCR engaging before timing the recording. A few seconds of over recording is infinitely more desirable to the Carotid Ultrasound Reading Unit than a non-recording. If at any time during the examination of a subject, a better image of a previously recorded view is found, do not attempt to erase the video recording. Simply add the new images to the videotape and make a note the Reader in the Comments section of the log sheet.

### 17.11 Sonographer Response to the Presence of a Significant Stenosis

A significant vascular abnormality is defined as a percentage lumen diameter stenosis of 80% or greater in the common or internal carotid artery. The only criterion to be used to arrive at this estimate of stenosis is the finding of a significantly elevated Doppler shift at peak systole. A pulse Doppler measurement of a flow velocity equal to or greater than 2.5 m/sec in the common, bulb, or internal carotid artery suggests a significant vascular abnormality. Imaging data should **not** be used in arriving at this conclusion; its role is limited to the accurate determination of the flow abnormality site.

If a sonographer believes a significant vascular abnormality is present, this information should be relayed to the EDIC Trial Coordinator immediately after the subject has left the scanning area. An inquiry is thereby triggered at the EDIC clinic regarding the presence of relevant symptoms in the subject, whether he/she is under care for those symptoms, and appropriate referrals. Under no circumstances should this information be conveyed either directly or indirectly by the sonographer to the subject.

### **17.12 Suggestions for the Sonographer**

1. Acquire only high quality images. Remember the interfaces are the priority.
2. It is expected that the sonographer will always videotape the images in the order spelled out in the protocols. A study that is videotaped out of order is not as easy for the Readers at the Central Carotid Ultrasound Reading Unit to analyze.

#### Carotid Protocol Summary

R Pulse Wave Doppler  
 R Common Carotid  
 R Anterior Oblique  
 R Lateral Oblique  
 R Posterior Oblique  
 L Pulse Wave Doppler  
 L Common Carotid  
 L Anterior Oblique  
 L Lateral Oblique  
 L Posterior Oblique

3. Annotate; label the images and use arrows or other marks to distinguish the vessels. Don't make the Readers guess which vessel is the internal and which is the external carotid.
4. Use the Comment space on the Log Sheet! If there is a plaque note it, if the artery appears healthy note it. Use this space also to communicate any problems. If a scan is canceled, or if there are images missing, or out of order, write it down.
5. Videotape both the frozen image and the corresponding cine loop for 5-10 seconds, any shorter than that makes the study difficult to analyze efficiently and longer is simply too long.
6. Take the time to check the ID's entered into the ultrasound unit, recorded on videotape, and written on the Log Sheets. If the number entered is wrong, tell us. It is often difficult for the Central Carotid Ultrasound Reading Unit and the Data Coordinating Center to sort out erroneous ID's. Watch for transpositions.
7. Contact the EDIC Central Carotid Ultrasound Reading Unit immediately whenever questions and problems arise. The telephone number is 617.636.0036 and the Fax number is 617.636.0041. Dr. Daniel O'Leary, the Principal Investigator's e-mail address is [daniel.o'leary@caritaschristi.org](mailto:daniel.o'leary@caritaschristi.org) and Laurie Funk, the Project Manager's e-mail address is [lrcfunk@comcast.net](mailto:lrcfunk@comcast.net).

**17.13 Mailing Videotapes to the Central Carotid Ultrasound Reading Unit (CURU)**

The Central Carotid Ultrasound Reading Unit functions in the EDIC as a subcontractor of the Biostatistics Center of The George Washington University. Each EDIC clinic is expected to send a package once a month during the clinic's designated mailing week, to the CURU containing the Super VHS tape and a hard copy packing slip. The package should be shipped via Federal Express using the Data Coordinating Center's government rate account: **1095-6832-5**.

The package should be sent to:

EDIC Central Carotid Ultrasound Reading Center  
25 Stuart Street, 2<sup>nd</sup> Floor  
Boston, MA 02116

Be sure to include your return address on the mailing slip.

## 18. CLINIC OPHTHALMOLOGIC PROCEDURES AND THE CENTRAL OPHTHALMOLOGIC READING UNIT

### 18.1 Ophthalmic Examination

A complete ophthalmic examination is scheduled every four years (8<sup>th</sup>, 12<sup>th</sup>, 16<sup>th</sup>, etc) based on the patient's DCCT randomization date, and ideally should be done on the same day of the fundus photographs. The sequence of testing usually starts with the determination of best corrected acuity, subjective refraction, anterior segment examination and intraocular pressure measurements. These measurements are recorded on the EDIC form 30, *Ophthalmic and Visual Acuity Examination Form*.

The ophthalmoscopy examination can then be accomplished after adequate pupil dilation. It is important that the ophthalmoscopy examination be done in a systematic and thorough fashion by an EDIC-certified ophthalmologist. The ophthalmoscopy examination is carried out to detect changes in retinopathy, particularly development of characteristics for which photocoagulation treatment might be considered necessary. The ophthalmologist records his/her findings also on EDIC form 30, *Ophthalmic and Visual Acuity Examination Form*. See Appendix 18-A for common ophthalmologic abbreviations.

Visual acuity is one of the response variables used in the evaluation of treatment effects in the EDIC. It is therefore essential that a standard procedure be used to obtain visual acuity measurements in each of the participating clinics and that precautions be incorporated in the procedures for obtaining visual acuity measurements so as to minimize the effects of examiner and patient bias. The visual acuity measurements must be obtained by a certified EDIC visual acuity examiner at the beginning of each eye examination before the patient's pupils have been dilated.

If the patient wears contact lenses and has corrective lenses as well, he/she should be instructed to refrain from wearing the contact lenses on the day of each examination. In the event that the patient either has no glasses or has forgotten the instructions and has reported for examination wearing contact lenses, these should be removed and at least ½ hour should elapse before refraction and visual acuity testing is done. In this latter event, careful attention should be given to the cornea on slit-lamp examination and any abnormalities should be noted in the patient's clinic record.

#### 18.1.1 Subjective Refraction

The frame is placed and adjusted on the patient's face so that the lens cells are parallel to the anterior plane of the orbits and centered in front of the pupils. The left eye is occluded and the beginning approximate refraction as determined above is placed in the right anterior lens cells with the cylindrical correction anterior. The patient is asked to look at and read any standard chart or EDIC Refraction Chart R to determine the best lens correction. The standard chart at a distance of 10 to 20 feet may be used directly or with a mirror, or a projecto-chart may be used for the refraction. Note that the EDIC Visual Acuity Charts 1 and 2 are not used for this purpose but only to test the visual acuity under the prescribed conditions after the best refraction is determined. A +0.50 sphere is held in front of the right eye and the patient is asked if the vision is improved while looking at the smallest line read well. If the patient responds that it is not improved, he/she is asked if vision is made worse. If vision is improved or there is no change, the sphere in the trial frame is replaced with a sphere that is one-half diopter more plus. The +0.50 sphere is held in front of the right eye again and the patient is asked if the vision is improved or worsened. The process of increasing the plus sphere in the trial frame is repeated until the patient says that the +0.50 sphere held in front of the trial frame makes the vision worse. When this occurs, the +0.50 sphere is removed from in front of the trial frame. By this process the highest plus or least minus sphere that will produce a minimum blurring of the patient's vision is determined.

After determining the highest plus or least minus sphere, the patient is asked to read the smallest line possible. A -0.37 sphere is held in front of the trial frame and the patient is asked if the vision is improved. If it is not, the +0.50 sphere is tried again to see if the patient will still accept more plus. If the patient reports that the vision is improved by the -0.37 sphere, the patient is requested to read the smallest

line possible. If the examiner is convinced that the vision is improved, the sphere in the trial frame is replaced by a sphere that is 0.25 diopter less plus. Minus spherical power is added by -0.25 diopter increments in the above fashion until the patient shows no further improvement in vision. The patient's acuity is then recorded on EDIC Form 30 *Ophthalmic and Visual Acuity Examination Form*.

For purposes of this discussion only plus cylinder techniques will be presented. If the beginning approximate refraction contains a cylinder correction, changes in cylindrical axis are tested by adding a 0.25, 0.37, or 0.50 diopter cross cylinder, first with the positive axis 45 degrees to one side of the cylinder axis, and then with the positive axis 45 degrees to the opposite side of the cylinder axis. Since neither position may produce a clear image the patient is encouraged to select the position of least blur while fixing on a single round letter on the line above the line on the chart he/she is able to read when the cross cylinder is not held up before the trial frame. If the patient cannot choose between the two positions of the cross cylinder at the beginning of this test, the axis of the cylinder is moved five degrees to 15 degrees, first in one direction and then in the other, with the cross cylinder being checked in each position to confirm that the original axis was indeed correct. If the patient does prefer one position of the cross cylinder to the other and the cylinder in the trial frame is plus, the axis of the cylinder is moved five to 15 degrees axis of the cross cylinder when in the position which the patient said was better. The cross cylinder is tried again with the positive axis 45 degrees to one side of the new cylinder axis and then with the positive axis 45 degrees to the opposite side of the new cylinder axis and the patient is asked which position he/she prefers. If the patient prefers one position to the other, the axis of the plus cylinder is moved toward the positive axis of the cross cylinder. Testing for change of axis is repeated until the patient cannot decide that one position of the cross cylinder is better than the other.

Change in cylinder power is now tested by adding the cross cylinder, first with the positive axis and then with negative axis coincident with the cylinder axis. For this test, the patient is requested to focus attention on a round letter on the lowest line on the chart he/she is able to read. If the patient prefers the positive axis coincident with the cylinder axis, the power of the correcting plus cylinder is increased by an additional plus 0.25 diopter. If the patient prefers the negative axis coincident with the cylinder axis, the total power of the correcting plus cylinder is reduced by 0.25 diopter. The process is repeated until the patient cannot choose one of the cross cylinder positions as better than the other, i.e., until both positions are equally bad. If 1.00 diopter of cylinder should be added, 0.50 diopter of sphere of opposite sign should be added as well, and, similarly, 0.25 diopter of sphere of opposite sign added for each additional 0.50 cylinder.

If the beginning refraction is a sphere, the presence of astigmatism is tested by arbitrarily placing a 0.25 cylinder at 180 degrees in the trial frame, after having determined the highest plus or least minus sphere producing minimal blurring of vision as described above. The refraction is then continued by using the cross cylinder to test for cylinder axis and power. In this situation, or in any situation when testing for cylinder power with the cross-cylinder technique and when 0.25 cylinder is present, if the preference with cross-cylinder indicates that this 0.25 cylinder should be removed, before doing so rotate the 0.25 cylinder 90 degrees from its original position and test for cylinder power once again. At this point, if additional power is preferred, it should be added. If, on the other hand, the preference is to remove the 0.25, this should be done and the final refraction would be purely spherical.

#### Example:

Starting refraction:  $-2.50 + 0.25$  axis 37 degrees. Use of the cross cylinder to check cylinder axis indicates that the patient prefers the 37 degrees axis. If on using the cross-cylinder to check cylinder power one finds that the patient wants the 0.25 cylinder removed, rotate the cylinder to 127 degrees and test for cylinder power once again. If additional power is preferred, add it. If the preference is to remove the 0.25 cylinder, this should be done.

If 0.50 or more diopters of cylinder have been added, the cylinder axis should be refined, if possible, by using the cross cylinder as described above.

Minus cylinders may be used instead of plus cylinders to determine the best correction for the power and axis of the cylinder. If minus cylinders are used, the procedure described above must be revised to reflect this change in sign.

When neither the power nor the axis of the cylinder can be improved, the power of the sphere is rechecked by adding +0.37 and -0.37 spheres and changing the spherical power by quarter diopter increments of the appropriate sign until the patient can perceive no improvement in vision. If the sphere is changed at this point, the cylinder should be rechecked. This process is repeated until no further significant lens changes are made. The lens corrections obtained in this way for the right eye are recorded on the examination form in the section for visual acuity measurements as the corrections obtained by subjective refraction for the right eye. The entire process is repeated for the left eye and both lens corrections are recorded on EDIC Form 030.

If a site other than the actual EDIC refraction lane at 4 meters and/or a chart other than EDIC Refraction Chart R are utilized for the refraction, a final check of the sphere, as outlined above, should be carried out just prior to the actual visual acuity testing, using the EDIC refraction lane at 4 meters and EDIC Refraction Chart R and light box. Similarly, if a phoropter has been used for the subjective refraction, a final check on the sphere, as described above, should be performed with a trial frame using the EDIC refraction lane at 4 meters and the EDIC Refraction Chart and light box.

### **18.1.2 Refraction for Patients with Poor Visual Acuity**

If it is not possible to perform a subjective refraction at the 10-20 foot distance because the patient's visual acuity in one or both eyes is too poor to see the largest letters on the refraction chart at that distance, then the refraction should be attempted at the 1 meter distance in the eye(s) in question. If the subjective refraction can be successfully performed at the 1-meter distance, then a +0.75 sphere should be subtracted from the 1-meter refraction, in order to make the correction appropriate for the 4-meter visual acuity test distance. It is the latter correction that should be entered in the appropriate space on the form provided for distance subjective refraction. The visual acuity should always be tested first at the 4-meter distance, even if the patient could not be refracted at the 4-meter distance. If the number of letters read correctly at 4 meters is less than or equal to 20, the visual acuity must also be tested at the 1 meter distance, in which case the +0.75 sphere should be replaced (see Section 18.1.5 Best Corrected Visual Acuity Measurements).

#### Example:

Refraction could not be performed at 10-20 feet in the right eye because the patient could not see any letters on the refraction chart at that distance. When the distance was reduced to 1 meter, the following was obtained:

+ 2.00 + 1.00 x 180 degrees

In order to make this appropriate for visual acuity testing at 4 meters, a +0.75 sph must be subtracted from the above result.

+ 2.00 + 1.00 x 180 degrees

- +0.75 sph

---

+1.25 + 1.00 x 180 degrees

This value is entered on the form for distance subjective refraction and used to test the visual acuity at 4 meters.

#### Example:

In another patient, the refraction could not be performed at 4 meters and the following refraction was obtained at 1 meter in the left eye:

-1.75 + 0.50 x 90 degrees

The appropriate correction for 4 meter visual acuity testing is:

-1.75 + 0.50 x 90 degrees

- +0.75 sph

---

-2.50 + 0.50 x 90 degrees

If the subjective refraction cannot be performed at either the 4-meter or the 1-meter distance because the patient's visual acuity is too poor to see the largest letter on the refraction chart at both of these distances, then the most recent distance subjective refraction obtained at a previous EDIC visit should be used for visual acuity testing.

### **18.1.3 EDIC Visual Acuity Chart EDIC Adaptation (Modified Baily-Lovie)**

The EDIC uses the charts and procedures developed for the Early Treatment Diabetic Retinopathy Study (ETDRS), a multicenter clinical trial of diabetic retinopathy (See Appendix 18-B for examples of the charts). The chart should be hung so that the lower edge measures between 21 and 33 inches from the floor. Such hanging should provide that the charts are displayed in a plane parallel to the wall and perpendicular to the line of viewing. If new charts are required, the EDIC Clinical Coordinating Center should be contacted.

Two EDIC Visual Acuity Charts are used for the measurement of visual acuity, each with a different letter sequence. The right eye will always be tested with Chart 1 and the left eye with Chart 2. Testing of all patients begins at 4 meters. The EDIC Refraction Chart R or any other visual acuity chart *except* EDIC Visual Acuity Chart 1 or 2 may be used to determine the best distance lens correction, at 10 to 20 feet or for poor visual acuity at 1 meter for each eye. The visual acuity equivalents for 20 feet are indicated in the margins of the charts.

### **18.1.4 Illumination of the EDIC Visual Acuity Charts and Room Illumination**

Room illumination should be at a level of 50 to 100 foot-candles as measured with a photometer held 4 feet from the floor and directed toward the ceiling. This is equivalent to the room lighting in most office buildings or schools. Illumination should be within the stated limits at all points along a line from the patient to the chart except for the 3-foot segment closest to the chart, where the limit may be exceeded. The chart itself should be illuminated by an incandescent light or other source directed towards the chart in such a way to evenly illuminate it and not create shadows or glare.

### **18.1.5 Best-Corrected Visual Acuity Measurements**

With the lens correction obtained by subjective refraction in the refracting frame, the patient is asked to read EDIC Visual Acuity Chart 1 from the top with the right eye. It is emphasized to the patient that each answer will be scored so that adequate time should be allowed for each letter in order to achieve the best identification.

When the patient cannot read a letter, he/she is encouraged to guess if at all possible. If the patient states that a letter is one of two letters, he/she is asked to choose only one letter and, if necessary, to guess. It may be suggested that the patient fixate eccentrically or turn or shake his/her head in any manner if this improves visual acuity. If the patient employs these maneuvers, care must be taken to insure that the fellow eye remains covered. Only one reading is allowed for each letter. When the patient attempts to read the chart and comes to a level at which he/she cannot even guess, the examiner may stop the test for that eye provided that the patient has previously made some errors which indicate that the best possible acuity level has been reached.

The examiner records each letter identified correctly by the patient as he/she reads the chart by circling the corresponding letter on EDIC form 30, *Ophthalmic and Visual Acuity Examination Form*. Letters read incorrectly, or for which no guesses are made, are not marked on this form. Each letter read correctly is scored as one point. The score for each line (including zero if no letters were read correctly on that line) and the total score for that eye must be recorded on the form after the testing has been completed.

If the number of letters read correctly at 4 meters is less than twenty, the test should be repeated at 1 meter and both the 4- and 1-meter totals should be recorded on EDIC form 030 for this visit. Both eyes should be tested at 4 meters before the patient is moved up to the 1-meter test distance. Prior to actual testing at 1-meter, +0.75 spheres should be added to the correction already in the trial frame to compensate for the new distance. The patient may stand or sit for the visual acuity test at 4 meters, but must sit for the 1-meter distance.

If the patient's visual acuity is so poor that he/she cannot read the largest chart letters when tested at 1 meter (i.e., the number of letters read correctly at 1 meter is zero), then the patient's ability to count fingers, detect hand motion, or have light perception should be evaluated. If the examiner is not convinced that the patient can count fingers or detect hand movements, this eye should be tested for light perception (see Section 18.1.9)

The same procedure for obtaining visual acuity for the right eye is used for the left eye, except that EDIC Visual Acuity Chart 2 is used.

If the patient's visual acuity in either eye is less than 4/20 (20/100 equivalent) with the patient's present distance glasses (or without correction, if the patient does not have glasses), retinoscopy and refraction should be carried out by an examiner proficient in these procedures. The lens corrections obtained are used as the beginning approximate refraction in the procedure outlined below for determination of best-corrected visual acuity. If the patient's visual acuity is 4/20 (20/100) or better with the patient's present distance glasses, the glasses are measured with a lensometer and these measurements are used as the beginning approximate refraction. If the results of the subjective refraction from a previous EDIC visit are available, these results should be used as the beginning approximate refraction. If the patient's visual acuity is 4/20 (20/100) or better and the patient does not have glasses for distance vision, the beginning approximate refraction is no lens correction or plano.

#### **18.1.6 Safeguards to Avoid Bias**

Every effort is made to obtain an accurate measure of visual acuity for both eyes of each patient. Both examiner and patient bias may affect these measurements. The examiner must urge, cajole, and encourage the patient to keep trying to read each smaller line on the chart to ensure that the patient makes a maximal effort with each eye. Furthermore, the refraction (outlined in Section 18.1.1) should be carried out meticulously without hurrying the patient and each answer should be checked to be certain that the best possible refraction has been obtained for each eye.

#### **18.1.7 Calculating the Visual Acuity Score**

After each measurement of visual acuity, the visual acuity score for the visit is calculated. The visual acuity score is defined as follows:

1. If four or more letters are read correctly at the 1-meter test distance, the visual acuity score is equal to the number of letters read correctly at 4 meters plus 30; or
2. If fewer than four letters are read correctly at the 4-meter test distance, the visual acuity score is equal to the number of letters read correctly at 1 meter; or
3. If no letters are read correctly at either the 1-meter distance or the 1-meter distance, the visual acuity score is 0.

### **18.1.8 Proposal for Conversion from Visual Acuity Examination Record Form to Visual Acuity Value**

One may obtain a "fractional" visual acuity by noting the last full line read correctly and adding to it the number of letters read correctly beyond this line; for example, if a patient were to read all the letters on the 4/10 line and above and four of five letters on the 4/8 line, the acuity could be expressed as 4/10 + 4 (20/50 + 4).

For purposes of statistical analyses, conversion to Log MAR units may be done. (1) Each line of letters has a corresponding Log MAR value. It is assumed that each letter on the chart has a Log MAR value of 0.02, as each line of five letters has a total value of 0.10. One may therefore arrive at a Log MAR value for each test by the calculation  $(1.70 - 0.02N)$  where N is the total number of letters read correctly. For patients tested at the 4-meter test distance, 30 letters will be considered as having been read correctly prior to testing, in order to have scores attained at 4 meters and 1 meter correspond. In the example, by this method,  $N = (30 + 39) = 69$  and the Log MAR value would be  $1.70 - (0.02 \times 69) = 0.32$ . In other words, it is assumed, for scoring purposes, that the patient could read the 30 largest letters at 1 meter without actually testing this ability.

It should be noted that this method of conversion to Log MAR units has the difficulty of assigning the same 0.02 value to each letter read correctly, no matter which line the letter is from. Therefore, any letter on the 4/6.25 (20/32) line is given the same 0.02 value as any letter on the 4/8 (20/40) line, or any other line for that matter. While some accuracy may be lost by this method, the error is estimated to be small and the advantage of giving some credit for all correct answers probably outweighs this disadvantage.

### **18.1.9 Testing Light Perception**

If the number of letters read correctly at 1 meter was zero and the examiner is not convinced that the patient can count fingers or detect hand movements, the eye is tested for light perception with the indirect ophthalmoscope as the light source. Room lighting should remain at the level of normal visual acuity testing. The patient should close the opposite eye and occlude it by making a tight seal with the palm around the orbit and the bridge of the nose. The indirect ophthalmoscope light should be in focus at 3 feet, and the rheostat set at six volts. From a distance of 3 feet, the beam should be directed in and out of the eye at least four times; the patient should be asked to respond when he/she sees the light. If the examiner is convinced that the patient perceives the light, vision should be recorded as light perception, otherwise as not light perception.

### **18.1.10 Anterior Segment Examination**

The examination of the anterior segment of each eye is performed to detect any changes in ocular status during the course of the study. The examination should be performed in a dimly illuminated room; a slit-lamp biomicroscope should be used in the standard fashion starting anteriorly and working posteriorly.

The corneas are examined and abnormalities in the epithelium, stroma, and endothelium are noted (but not recorded on Form 030). The depth of the anterior chamber is assessed to determine if there is any danger in dilating the pupil. If the angle is thought to be closeable, the eye should not be dilated until appropriate provocative tests are performed. The presence of cells, flare, or other abnormality is recorded on EDIC form 030. The presence of new vessels on the iris is recorded. The lens is evaluated after the pupil is dilated and opacities or aphakia are noted. The clarity of the lens is assessed. In general, mild to moderate axial, posterior subcapsular opacities (PSC), or 2+ nuclear sclerosis may be expected to reduce visual acuity but not to less than 20/100. Severe PSC or severe nuclear sclerosis or a combination may be expected to reduce acuity to less than 20/100.

### **18.1.11 Intraocular Pressure**

The intraocular pressure is measured in both eyes before the pupils are dilated. A Goldmann applanation tonometer mounted on a slit-lamp is used for the measurement.

After a brief explanation of the procedure, the patient receives one or two drops of local anesthetic in each eye. A combination anesthetic-fluorescein drop may be substituted. The patient places chin and forehead firmly in the headrest, and directs his/her gaze straight ahead (with or without a fixation target).

The tonometer is brought into position and the tip illuminated with a wide-open slit and blue filter from approximately 45 degrees to the side. A magnification of ten power is recommended. The examiner brings the tonometer prism to within 5 to 10 millimeters of the center of the cornea while looking around the side of the microscope. If the patient has a tendency to blink as the tonometer approaches, the examiner may need to hold the lids apart. Care must be taken to keep from exerting pressure on the globe through the lids as this may affect the accuracy of the measurement. The examiner then looks through the oculars and, with the measuring scale set at one (10 mm Hg), gently brings the tip of the tonometer into contact with the center of the cornea by moving the joystick forward. At contact, the examiner will see a bright yellow-green spot that will break into two separate semicircular arcs. These arcs should be in sharp focus and be of equal circumference above and below the horizontal dividing line. If they are not of equal circumference the joystick is pulled back, removing the tonometer from the cornea, and the elevation changed in the appropriate direction (towards the larger arc). Only then is the tonometer replaced on the cornea by pushing the joystick forward. Pulsation of the arcs indicates proper contact of the tonometer. If the arcs start to overlap before pulsation is noted, the joystick has been pushed too far forward and the examiner should back off slightly. The width of the arcs should be about one-tenth their diameter. If greater, excess fluid should be wiped from the tonometer.

The force applied to the cornea is increased until the inner borders of the two fluorescein arcs just touch each other. The inner border of the arc represents the demarcation line between the cornea flattened by applanation and the cornea not flattened. The joystick is then pulled back just far enough to lose the image and then moved gently forward again to check the measurement. If the inner borders of the two arcs are still just touching, the measurement is rechecked as before. If the arcs do not overlap enough, the force is increased and again the measurement is rechecked.

The reading taken from the scale is multiplied by ten to convert to intraocular pressure in mm Hg. A measurement of two on the scale corresponds to 20 mm Hg. intraocular pressure. Each scale division between the numbers is equal to 2 mm Hg.

#### **18.1.12 Indirect Ophthalmoscopy**

Once the pupils have adequately dilated (see Section 18.2.1), indirect ophthalmoscopy is performed to obtain an overall stereoscopic view of the fundus and vitreous including the posterior pole and an anterior view that extends at least to the equator in all quadrants. The examination should be performed with a head-mounted indirect ophthalmoscope and handheld condensing lens (a 14 or 20D Nikon Aspheric lens is recommended) with the patient sitting or lying down if necessary. If the patient has had a vitreous hemorrhage, the sitting examination should always be done first.

#### **18.1.13 Direct Ophthalmoscopy**

Direct ophthalmoscopy is performed to obtain a detailed evaluation of the disc and macula as well as to confirm lesions seen by indirect ophthalmoscopy. Particular attention is placed on evaluating the presence of microaneurysms, or other lesions of diabetic retinopathy. Of particular clinical importance is the identification of new vessels on the disc (NVD) and distinguishing new vessels elsewhere (NVE) from intraretinal microvascular abnormalities (IRMA), as these lesions may indicate that clinical intervention may be necessary. The examination should be performed with a transformer-powered direct ophthalmoscope or a halogen bulb handheld ophthalmoscope. See Appendix 18-A for common ophthalmologic abbreviations.

## **18.2 Fundus Photography—Digital and Film Procedures**

In the EDIC study, color stereo fundus photographs of each eye are required every four years based on each patient's DCCT randomization date. The EDIC study uses the University of Wisconsin Fundus Photograph Reading Center as the EDIC Central Ophthalmologic Reading Unit or EDIC CORU. The following sections provide instruction for the photography, labeling the photographic media, and shipping the media to the CORU. All instructions are taken from the CORU's manual "Fundus Photograph Reading Center (FPRC) Imaging Procedures" which can be accessed on the EDIC website under "Resources."

Photographs may be taken digitally (7Std-Digital, preferred) or using color slide film (7Std-Film). The photographer(s) and digital camera systems must be certified by the CORU before study participant photography is performed. A photographer certified for the 7Std-Film procedure will need to certify for the 7Std-Digital procedure. Photographers and digital imaging systems that were previously certified to perform color digital imaging for the EDIC Film/Digital Ancillary Study are automatically certified for digital color imaging for EDIC as long as there have not been camera or software changes. Any new digital systems and photographers not previously certified will need to be certified.

The EDIC website's directory lists the CORU's personnel to contact with any questions related to fundus photographs, photographic equipment, photo labeling and shipment.

### **18.2.1 Pupillary Dilation**

Adequate dilation of the pupil is important to permit good quality stereo photography. Sufficient time should be allowed for dilation to at least 6 mm, repeating drops, if necessary, to achieve and maintain a pupil of at least this size during photography. Only if repeated instillation of drops and passage of at least 45 minutes after the last drops fail to produce dilation of 6 mm should photographs be taken through a smaller pupil (no smaller than 4 mm). Notation of inadequate pupil dilation (between 4 and 6 mm) should be made by the photographer on EDIC Form 031, *Fundus Photography Quality Review*, which is sent to the CORU with each patient's photographic media. If the pupil will not dilate to at least 4 mm, do not perform the fundus photography, as images will not be adequate for grading.

### **18.2.2 Cameras and Equipment—Both Digital and Film Photography**

The Topcon TRC-50 series (50VT, 50X, 50EX, 50IA, 50IX, and 50DX) used at the 35° setting, and the Zeiss FF450-plus, FF4, and Visucam digital camera models used at the 30° settings can be used for the EDIC study. The Canon fundus cameras (UVi or similar models) used at the 40° setting are also suitable. Additionally, some models of Kowa and Nikon fundus cameras with 30° or 35° settings may be used.

All cameras used for the EDIC photographs should be certified by the CORU (see Section 18.2.3.1). Cameras other than these may be substituted upon approval of the CORU. Approval may be obtained by sending sample photographic sets, taken according to the EDIC procedure, to the CORU, Attention: Imaging Services. Address for the CORU is available on the EDIC website.

Digital fundus photography requires recordable CD/DVD (discs) if the photos will be submitted by someone other than the photographer. Film fundus photography requires 35mm color slide film and plastic slide sheets. Specifications for the handling, labeling and shipping of either media to the CORU will be discussed in the following sections. Effective 2011, all clinical sites began using digital photography.

### **18.2.3 Fundus Photography—Digital Procedure**

#### **18.2.3.1 System Certification**

Any digital system to be used for the EDIC study must be certified for color capture capability before any patient images may be taken. Effective May 2012, requests for system certification must be made by the requesting photographer and are submitted via the Imaging Request and Information System (IRIS – <https://iris.opth.wisc.edu>). If a digital system has been previously certified for digital color capture capability by the CORU for another study and no software or hardware changes have been made since the time of certification, submission of additional images may not be needed. However, if the CORU has not received images from a study site within the past two years, additional images will be necessary to verify system settings.

If hardware or software changes occur during the life of the EDIC study, re-certification of the system will be needed. Requests for re-certification and required images should be submitted by the photographer via the IRIS. For digital systems which have been previously certified for FA capture capability, an abbreviated set of images is typically required to certify for color capture capability. For Zeiss Visupac®, Topcon IMAGENet® and Escalon Digital Solutions (using MRP OphthaVision® software) systems, one color image (centered on the posterior pole taken at the correct degree angle) is required to verify settings. For Escalon (using Escalon software), OIS Winstation® and Digital Healthcare, one color and one red free image (centered on the posterior pole and taken at the correct degree angle) of a common eye are required.

Please refer to Appendix 18-C for the details about the specific software requirements and contact information to certify the system if required. See Appendix 18.E for specific instructions from the CORU (Fundus Photograph Reading Center) regarding submission of certification requests via the IRIS.

The system certification process is complete for color capture capability after the CORU staff ensures that image quality is acceptable and that the files can be successfully viewed and analyzed.

### **18.2.3.2 Photographer Certification**

Any photographer taking photographs (or digital images: the terms will be used interchangeably in this procedure) for the EDIC Study must be certified by the CORU. Effective May 2012, requests for photographer certification must be submitted by the requesting photographer via the Imaging Request and Information System (IRIS – <https://iris.opth.wisc.edu>).

The Certification process consists of (1) review of study synopsis/protocol and imaging procedures and (2) demonstration of the ability to perform the imaging procedure(s) by submission of images of acceptable quality. The second requirement may be waived if the photographer has prior certification at the CORU using an identical procedure, and has been actively taking images, judged to be of good quality by the CORU, during the past 12 months. Photographers who are certified for a similar procedure also may be asked to submit sample photographs to become certified. All photographs required for Certification are submitted via the IRIS.

Photographers who are not eligible for certification on the basis of previous CORU certification should submit color images of four (4) eyes (two right eyes and two left eyes) taken using this procedure. The color images may be taken of patients with whom photography is being carried out for clinical purposes or of normal volunteers.

Photographers previously certified for this procedure on film (7Std-F) electing to perform this procedure digitally (7Std-D) must submit stereo color photographs of two (2) eyes (one right eye and one left eye) via the IRIS. This allows the CORU to check image quality (stereo effect, color quality and image resolution) and to determine whether the image files can be opened and archived. This requirement may be waived if a photographer has current digital color certification with the CORU for another procedure.

For certification images, comply with HIPAA regulations by masking patient identifiers on the digital files. Photographers are encouraged to submit complete submissions via the IRIS for each procedure for

which he/she is requesting certification (i.e., if four eyes are required for certification, send all four eyes in one submission).

Photographers who meet certification criteria will receive confirmation of certification from the CORU. Those who do not meet these criteria will receive feedback via the IRIS from the CORU imaging consultants and may be required to submit additional sets of images. A plan for improving image quality may be necessary after three complete unsuccessful certification submissions.

Once a photographer is certified for EDIC, he or she is certified for the duration of the study, even if inactive for more than 12 months. However, if a certified photographer consistently fails to meet study standards, certification may be suspended.

On those rare occasions when a patient who has come a long distance attends the clinic for a visit requiring photographs and all photographers certified for the EDIC (provisionally or fully) are ill or on vacation, the clinical center may have no alternative but to submit photographs taken by an uncertified photographer. The name of the uncertified photographer should be entered on the EDIC Form 031, *Fundus Photography Quality Review*, and the space for the photographer's certification number left blank. Special effort should be made to follow the EDIC photography protocol and to obtain photographs of satisfactory quality. Effective 2011, submission of Form 031 is no longer required by the CORU. However, a copy should be submitted to the Data Coordinating Center, with a copy maintained locally.

See Appendix 18.E for specific instructions from the CORU (Fundus Photograph Reading Center) regarding submission of certification requests via the IRIS.

#### **18.2.4 Seven Standard Fields of the Fundus—Digital Procedures**

The 7 standard fields specified by this procedure are identical to the fields used in the Early Treatment of Diabetic Retinopathy Study (ETDRS). These fields are illustrated below in Figures 18.1 thru 18.3.

A tutorial of the Modified 7-Standard Field Photography” from the CORU can be accessed on the EDIC website under “Resources” to review acquiring the 7 fields in a quick and easy manner (keep in mind that fields 1 and 3 will have a different field definition for the EDIC study than what is in the tutorial).

The following descriptions of the standard fields assume that there are two cross hairs in the camera ocular, one vertical and the other horizontal intersecting in the center of the ocular fields used in the Early Treatment of Diabetic Retinopathy Study (ETDRS). Fields 1, 2, and 3 of the right and left eyes are illustrated in Figures 18.1 and 18.2.

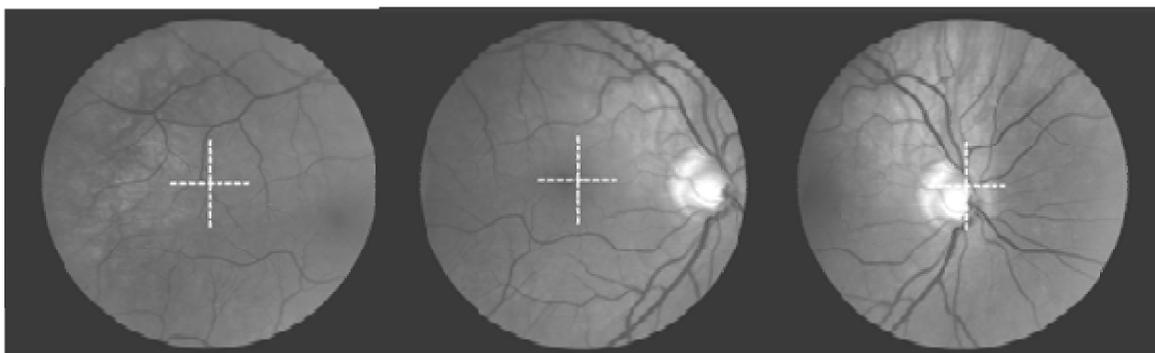


Figure 18.1 Right Eye fields 3, 2, and 1

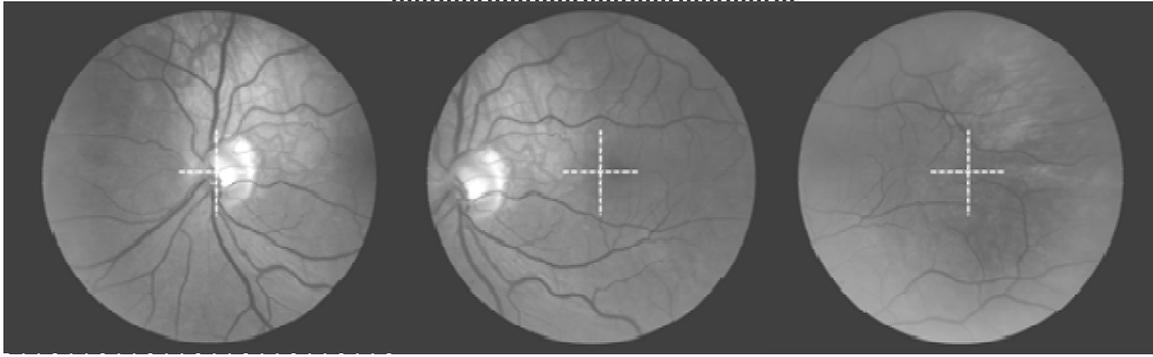


Figure 18.2 Left Eye fields 1, 2 and 3

**Field 1-Disc:** Center the optic disc at the intersection of the cross hairs in the ocular.

**Field 2-Macula:** Center the macula near the intersection of the cross hairs in the ocular. A suitable position can often be obtained by rotating the camera temporally from the Field 1 position, without vertical adjustment.

**Field 3-Temporal to Macula:** Position the macula so it is bisected at the nasal edge of the field. If Field 2 was centered above the center of the macula, as suggested above, Field 3 may be easily obtained by rotating the camera without making any vertical adjustment or movement of the fixation device.

Tips on field definition: The peripheral fields are only 1 DD (disc diameter) away from the optic nerve. Fields 4 and 6 abut without an overlap or gap between these two fields. This is true for Fields 5 and 7 also.

The following descriptions of the standard fields assume that there are two cross hairs in the camera ocular, one vertical and the other horizontal intersecting in the center of the ocular. Fields 4, 5, 6, and 7 of the right and left eyes are illustrated in Figure 18.3.

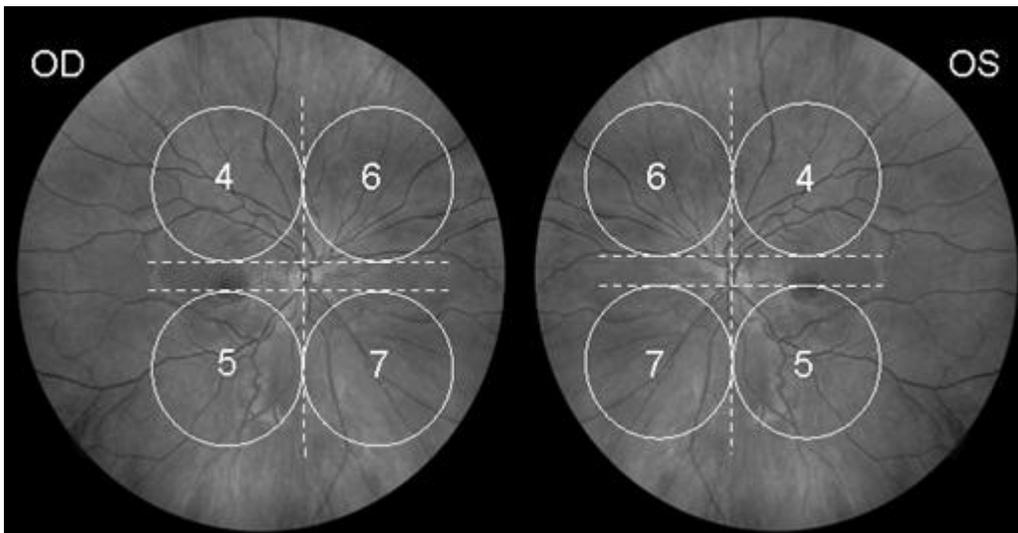


Figure 18.3

**Field 4-Superior Temporal:** The lower edge of the field is tangent to a horizontal line passing through the upper edge of the optic disc, and the nasal edge of the field is tangent to a vertical line passing through the center of the disc.

TIP: It is convenient to take Field 6 immediately after Field 4 by rotating the camera nasally.

**Field 6-Superior Nasal:** The lower edge of the field is tangent to a horizontal line passing through the upper edge of optic disc, and the temporal edge of the field is tangent to a vertical line passing through the center of the disc.

**Field 5-Inferior Temporal:** The upper edge of the field is tangent to a horizontal line passing through the lower edge of the optic disc and the nasal edge of the field is tangent to a vertical line passing through the center of the disc.

**Field 7-Inferior Nasal:** The upper edge of the field is tangent to a horizontal line passing through the lower edge of the optic disc and the temporal edge of the field is tangent to a vertical line passing through the center of the disc.

If any fundus details can be seen through the fundus camera, all seven fields should be photographed, even though no details may be visible in some fields. If extensive lens opacities or vitreous hemorrhage make it impossible to see any fundus details with the fundus camera, an attempt should be made to photograph only standard Fields 1 (disc) and 2 (macula); the other standard fields do not need to be taken. If no fundus reflex can be seen with the camera, a single non-stereo photograph of the anterior segment (lens) is taken.

It is the responsibility of each photographer to review fundus photographs for quality, and to make the decision to perform retakes of some or all fields when the first attempt at photographs is unsatisfactory. The following criteria should be used to determine when photography should be repeated: if Fields 1 or 2, or more than one of the five remaining fields are partially or totally missing, or if the photographer judges the photographs to be of poor quality for technical reasons that can be corrected (such as poor field definition, focus or stereo or photographic artifacts), the set should be retaken, if possible, prior to submission to the CORU.

The CORU will continue to formally monitor fundus photographs for quality, and will ask for retakes when sets submitted are inadequate.

#### **18.2.4.1 Fundus Reflex ("Lens") Photograph—Digital Procedures**

At all photo visits, stereoscopic fundus reflex images should be taken to document media opacities. If no opacities are present, focus on the pupil margin of the iris. If opacities are present, focus deeper on the lens opacities. The magnification of these images should match that of the image in Figure 18.4. The patient is asked to open his/her eyes very wide, or the lids should be gently retracted if necessary, so that the entire cornea is visible. The best stereo effect is obtained by moving the camera laterally about 3mm between exposures. The lateral shift can be obtained by moving the joystick. A fixation target should be positioned to direct the patient's gaze in the primary (straight ahead) position, so the optic nerve does not appear directly behind the lens.

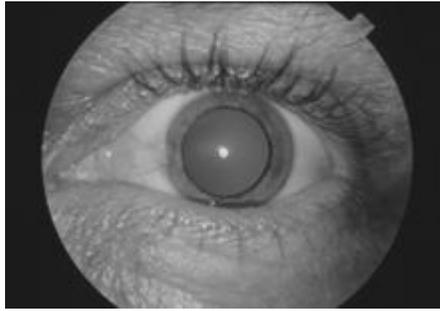


Figure 18.4 Fundus Reflex

During follow-up, if fundus photography is not possible because of opacities in the media, a bound-down pupil, previous enucleation, or for any other reason, a fundus reflex photograph should be taken. The photographer then can note the reason on the EDIC Form 031, *Fundus Photography Quality Review*, which is sent to the CORU attached to each patient's photographic media, noting the fields 1 through 7 are missing.

#### **18.2.4.2 Pointers on Photographic Technique**

Since the CORU analyzes photographs for quality in terms of (1) field definition, (2) focus/clarity, and (3) stereo effect, the comments presented here on photographic technique are organized under those headings.

##### **General**

Digital: When shooting the fields digitally, shoot the study eye images first, followed by fellow eye. Stereo pairs should be taken shooting the left member of the pair first, followed by the right member of the pair. All digital images should be reviewed for quality at the time of photography and the photographer should select the best stereo pairs for each field, deleting extra, unnecessary images. A stereo viewing aid is recommended (SCREEN-VU™, Eye Supply USA Inc.; Tampa, FL).

Film: A 4X or 5X magnification stereoscopic viewer for examining film stereo fundus photographs is required, so that the photographer can critically examine his/her work and make appropriate corrections in technique, as well as correctly label the right side and left side of stereo pairs.

##### **Patient Cooperation**

Photography of the photophobic patient can be challenging for the photographer and uncomfortable for the patient. Minimizing the number of flashes and the length of time the eye is exposed to a bright viewing lamp are two things that can help make the photography procedure more comfortable. Additionally, keeping the view lamp as low as possible (maybe even dimming the room lights) can help make the photography procedure more tolerable. Patients should be asked to blink to help keep the cornea clear.

##### **Field Definition**

When the 7 standard stereo fields are taken, the following sequence is recommended: disc (Field 1), macula (Field 2), temporal to macula (Field 3), superior temporal (Field 4), superior nasal (Field 6), inferior temporal (Field 5), inferior nasal (Field 7). Fields 1, 2, and 3 may be taken on the same horizontal plane.

The following technique may be used for attaining proper definition of Field 4: (1) move the camera from the center of the disc upwards until the upper edge of the disc meets the bottom of the photographic field, (2) take note of some landmark at the intersection of the cross hairs (e.g., a small vessel or microaneurysms), (3) swing the camera temporally until this landmark is at the nasal border of the

photographic field (at this point, the lower edge of the field will fall on the same plane as the upper edge of the disc). This is the proper position for Field 4.

To locate Field 6 rotate the camera nasally until the landmark is at the temporal edge of the field. A similar approach can be used to obtain Fields 5 and 7.

### **Focus/Clarity**

Remember that the best image quality can be acquired if corneas are not disturbed by prior examination with a diagnostic contact lens.

Perhaps the most common error in fundus photography is poor focus, which can be avoided if the photographer develops a constant awareness of the need to keep the cross hairs in the ocular of the camera in sharp focus by adjusting the ocular as often as necessary. The cross hairs must be in sharp focus at all times -- having the fundus in focus and the cross hairs blurred results in an out-of-focus photograph.

If it is not possible to get the entire photographic field in crisp focus, please concentrate on getting the center of the field in focus, sacrificing a bit on the periphery if necessary. This is especially important in Fields 1 and 2. Frequently the CORU sees photographs showing the fovea to be slightly out of focus while the periphery of Field 2 is in focus. (This may be due to the fact that when the photographer moves to Field 2, having just taken Field 1, he or she does not refocus on the foveal area.)

A common problem is focusing too deep. Photographs which include the disc (Fields 1, 1F, and often 2) sometimes show clear focus on the bottom of the cup, while the retina is slightly out of focus. It appears that some photographers use the disc margin or the granular pattern of the pigment epithelium for focusing. Instead, it is desirable to focus on the fine vascular branches as they approach the macula. Since the depth of focus is greater posterior to the plane of absolute focus than anterior to it, it makes sense to err on the side of focusing slightly above the retina rather than too deep. This should keep both the anterior surface of the retina and the pigment epithelial background in focus. Such a strategy is of special importance when macular edema is present.

In all fields except Field 2, when elevated structures are present such that the depth of field cannot encompass both the most posterior detail of retina and the elevated lesion at the same time, it is usually advisable to take one side of the stereo pair focused on the plane of the flat retina (near the anterior surface) and the other side of the pair focused near the top of the elevated structure. It should be remembered, however, that the focus should not be so far anterior that all landmarks below disappear. Some recognition of these must be possible in order to be able to fuse the two sides comfortably when looking at them binocularly.

In Field 2, focus both members of the stereo pair on the small blood vessels near the center of the fovea. When there are elevated structures other than macular edema, they can nearly always be seen in another field because of the overlapping of the fields.

Photographers should periodically determine if their cameras need cleaning, and clean them when necessary. Photos marred by dust on the lenses often provide ambiguous evidence. The CORU cannot differentiate if a superficial lightish spot is a soft exudate or a dust spot.

### **Stereoscopic Effect**

Adequate dilation of the pupil is important to permit good quality stereo photography. When photographs are taken before dilation is complete or after the pupil has started to come down, the maximum stereo separation cannot be obtained. Sufficient time should be allowed for dilation to at least 6 mm, repeating drops if necessary to achieve and maintain a pupil of at least this size during photography.

Many photographers use the Allen stereo separator. If it is used, a setting between 2.25 and 2.50 is recommended. Please be careful about overriding the separator, i.e., moving the camera too far back toward the first member of the pair when taking the second member.

The technique described by Allen\* is used for taking non-simultaneous stereo fundus images. The camera should not be rotated or pivoted; instead, it should be moved laterally from left to right with the joystick (or by sliding the camera base on its table, if preferred). About 2mm is the minimum separation between members of the stereo pair is the goal when moving the joystick or sliding the camera.

It is customary to take the left member of the pair first, followed by the right member of the pair, but this is optional. When obtaining stereo pairs, care should be taken that at least one member of the pair is of good technical quality with crisp focus. In many cases, it will be possible to obtain good quality in both members of the pair, but if this is not the case, the aim should be to obtain good quality in one member and some stereo separation between the members, accepting somewhat poorer quality in the second member of the pair, if necessary.

### **Exposure, Gain and Flash**

It is important that photographers use flash, gain, and gamma changes to obtain optimal exposure, as well as to avoid severe over or under exposure to avoid loss of image detail. We recommend that photographers become familiar with using the camera and software controls available to ensure optimal exposure and good color balance. The CORU Imaging staff is available to assist in recommending acceptable settings.

Most digital systems have a wide variety of image enhancement tools to adjust image contrast, brightness or sharpness after image capture. Enhancement tools should not be used at the clinical site to adjust image quality. Pay careful attention to obtaining optimum exposure and image sharpness so that enhancements are not necessary. For more information from the CORU on color balance for retinal images, refer to the EDIC website under “Resources.”

#### **18.2.4.3 Exporting and Labeling Digital Images --Digital Procedures**

Digital images for the left and right eye should be saved to one CD/DVD at full resolution, using no compression or lossless compression (.png). Loosely compressed (standard .jpg) images may be accepted but will be evaluated by the CORU on a case-by-case basis.

Only the standard methods existing in the capture software of the imaging system should be used to isolate images for submission. Specific image handling procedures are outlined by accessing the links listed in Appendix 18-D. Digital images should be “burned” to a CD/DVD before being archived on the computer system (a process that often compresses the images for storage). The CORU recommends confirming that the images were successfully burned to a CD/DVD by checking the CD/DVD on another computer.

Replace	With	EDIC Specific
Patient’s ID#	Clinic# Patient ID#	1212345
Patient’s Last Name	Study Name	EDIC
Patient’s First Name	Clinic#- Patient ID#, Initials	12-12345, ABC
Patient’s Date of Birth	mm/dd/yyyy	Must be mm/dd/yyyy

For study submissions the CD/DVD should be labeled using the circular CD/DVD labels. These pre-printed labels are provided by the EDIC Data Coordinating Center and include the study name, site ID, patient ID number, initials and visit information (See Figure 18.5) The CD/DVD label also includes a space for date of photography, the photographer’s name(s) and the serial number of the fundus camera used

(located on the head of the fundus camera). The date of the photos should be written on the label as mm/dd/yy.

A full resolution (uncompressed) duplicate set of images of each submission should be retained at the site.

Please note these directions when labeling the CD/DVD:

- Only use black permanent ink for both forms and labels.
- Do **not** use correction fluid or tape.
- Do **not** obliterate data.
- If an error is made:
  - Use a single line to cross-out the error.
  - Write the correct information next to the error.
  - Initial and date the correction.
- Do **not** use labels with incorrect information, use blank labels and fill in all the blanks.
- Do **not** put a new label on top of a label.
- Only use labels provided by EDIC.
- Always ensure information is consistent and correct before sending photos.



Figure 18.5 Example of CD/DVD label

The CD/DVD should be prepared and labeled as described above. The CD/DVD of images should be sent together with a completed EDIC form 107 *Fundus Photograph Mailing List*, to the CORU as soon as possible after being taken. It is advisable to mail or ship the photos with a method that provides a tracking number in case the media did not arrive to the CORU when expected. If a commercial carrier is not used, either send a copy of the mailing list (Form 107) to CORU separately, or fax to them: 608-263-0525.

Send photos to:  
Sherri L. Neill, Project Manager  
Fundus Photo Reading Center  
8010 Excelsior Drive  
Madison, WI 53717

CORU will fax your site a copy of the mailing list as confirmation of receipt for each submission. The submission will then be reviewed for completeness. IF a submission is not complete, the CORU will also send a query at a later date (See Figure 18.7 for an example of the Query Form).

If digital images are submitted via the CORU portal, confirmation of receipt will be automatically be sent to the sender via the email on file at the CORU. A copy of Form 107 is not submitted to the CORU if photos are submitted via the portal. However, Form 107 should be completed and sent to the Data Coordinating center and a copy kept locally.

Effective 2011, it is no longer necessary to submit a completed EDIC form 107 *Fundus Photograph Mailing List* to the CORU. However, completed EDIC form 107 should be sent to the Data Coordinating Center and a copy kept locally.

#### **18.2.4.4 Query Overview**

If you receive a query (via fax or email, example in Figure 18.6), please make the necessary corrections within 7 days of receipt and fax, email, or ship your responses back to CORU. If corrections are not made promptly, CORU reserves the right to ship the materials back to your site for correction.

##### **Examples of why you may receive a query are:**

- Missing information on the Mailing List and/or CD labels
- Blank CD
- Color images saved in the wrong file format
- The wrong subject's images were submitted

# FUNDUS PHOTOGRAPH READING CENTER

University of Wisconsin Medical School  
Department of Ophthalmology and Visual Sciences  
406 Science Drive, Suite 400  
Madison, WI 53705

Phone: 608.263.0789  
Fax: 608.263.0525  
jdingledine@rc.ophth.wisc.edu  
http://eyephoto.ophth.wisc.edu

Date: January 13, 2009  
Expiration Date: April 13, 2009

**If this query is not resolved by the expiration date, the image will be disqualified and evaluation data will be reported as Cannot Grade.**

To: Clinic 20

From: Jeannette Dingleline, Project Manager  
Re: EDIC

## **ACTION REQUIRED**

Will you please submit the requested items within the next 7 days along with a new Transmittal log if submitting new images. Thank you.

---

Clinic: 20  
Patient: 20282  
Initials: MRT  
Visit: YEAR 15  
Photo Date: 23-Sep-2008  
Photographer/Operator:

This shipment was received without the item(s) listed below:

Comments: Please resubmit the COLOR images for this visit, exporting from OIS as 'No Loss Tiff'. The CD received contained JPEG (in TIFF) files that appear all black.

---

Figure 18.6 Example Query Form

### **18.2.5 Seven Standard Fields of the Fundus—Film Procedure**

The same procedure is utilized for obtaining the 7 Standard Fields of the Fundus with film as when using the digital systems. Please refer back to Sections 18.2.4, 18.2.4.1 and 18.2.4.2 for specific instructions. Effective 2011, film photographs were replaced by digital photographs at all clinical centers.

#### **18.2.5.1 Film Processing**

Kodachrome (ASA25 or 64), Ektachrome (ASA 100) or Fujichrome (ASA 50 or 100) film is recommended. Kodachrome may be processed in routine fashion at any Kodalux processing laboratory; Ektachrome and Fujichrome may be processed in routine fashion at any reliable local professional laboratory utilizing the E6 process. A different color film may be used, if necessary, to expedite processing, but only on approval of quality by the CORU. It is strongly preferred to use the same film type and development procedures for the duration of the study.

It is important that the processing laboratory correctly orient each transparency in the readymount and correctly number the readymounts. Transparencies processed by Kodak are in the proper position when the frame number is visible and right side up.

#### **18.2.5.2 Mounting and Labeling of 35mm Images**

The transparencies (slides) returned from the processing lab are mounted in standard 2X2 inch plastic mounts.

Labels for each slide are pre-printed by the EDIC Data Coordinating Center for each patient. If pre-printed labels are not available for certification images please hand-label using a permanent felt-tip marker. The individual slide labels must indicate which eye, the field location and which member of the stereo pair (e.g. RE-F1-LS). The plastic sheet page labels should indicate the patient's study ID, initials, date of photography in mm/dd/yy, and the name of photographer with their certification number. Figure 18.7 shows how the slides are labeled and placed in the plastic slide sheets.

Slides of each eye should be placed in an individual plastic sheet with 20 pockets. The CORU recommends Bardes 20-pocket pages, product #62022C available from Bardes Products, Inc., 5245 West Clinton Avenue, Milwaukee, WI 53223-9839, phone 800-223-1357. The plastic sheets should be constructed so that the pockets open at the side rather than at the top; that is, the open side of the left pocket should face the open side of the right pocket. A page identification label is completed and attached to the front of each plastic sheet.

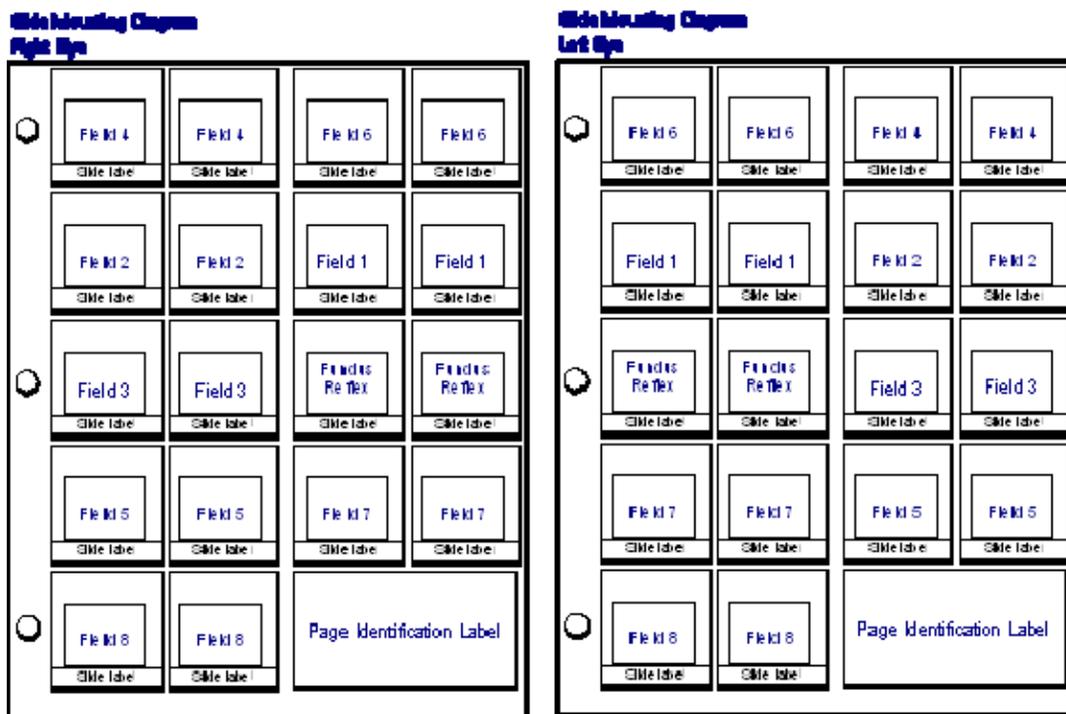


Figure 18.7 Slide Mounting Diagram

The plastic slide sheets should be sent together with a completed EDIC Form 031, *Fundus Photography Quality Review* and a completed EDIC Form 107, *Fundus Photograph Mailing List* to the CORU as soon as possible after being taken. It is suggested, but not required, that duplicates of the photographs be retained at the clinical center for patient management. Copies of photographs are not required for data backup in the EDIC. If the clinic chooses to make copies of the photographs, the method of copying (whether to make true copies of the original set sent to CORU or to shoot two sets during the photographic session) is left to the discretion of the clinical center and is at the clinic's expense.

Please note these directions when labeling the CD/DVD:

- Only use black permanent ink for both forms and labels.
- Do **not** use correction fluid or tape.

- Do **not** obliterate data.
- If an error is made:
  - Use a single line to cross-out the error.
  - Write the correct information next to the error.
  - Initial and date the correction.
- Do **not** use labels with incorrect information, use blank labels and fill in all the blanks.
- Do **not** put a new label on top of a label.
- Only use labels provided by EDIC.
- Always ensure information is consistent and correct before sending photos.

### 18.2.5.3 Photographic Quality

Color images of each eye are reviewed and assigned a grade for overall quality. Feedback will be provided to the photographers as needed to help with resolution of any problems. Special attention will be given to photographers having difficulty meeting study photo quality standards. If a certified photographer consistently fails to meet study standards, certification may be suspended.

Each set of fundus photographs should be assessed for quality before the photographs are sent to the CORU. The photographer taking a set of photographs should grade them carefully for quality, using EDIC Form 031, *Fundus Photography Quality Review*. All photographs are graded in detail for quality at the CORU and feedback is provided to photographers as necessary to help solve any problems that may be found.

The CORU staff carries out only an abbreviated overall quality grading on photographs taken by fully certified photographers. If overall quality is less than "fair" for reasons attributable to photographic technique, a detailed quality grading is carried out, with only the fields and photographic characteristics causing the grade to be lowered recorded on the form. When the grader deems it necessary, comments on the set are returned to the clinical center. If overall quality of photographs taken by any photographer consistently fails to meet study standards, his/her certification will revert to the "provisional" category; all photographs must then be graded in detail for quality and recorded on the EDIC Form 031, both by the photographer and the CORU staff, until problems are resolved and full certification is restored.

In grading photographic quality, a three-step confidence scale is used. The grading levels, designated "high", "adequate", and "inadequate" are defined below as they apply to a single photographic field:

<b>STEP</b>	<b>FIELD DEFINITION</b>	<b>FOCUS AND CLARITY EFFECT</b>	<b>STEREOSCOPIC</b>
Good	less than one half DD from definition	Crisp (at least centrally)	Satisfactory
Fair	one half to one DD from definition	Fuzzy, but better than standard #14	Less than satisfactory but useful for grading
Poor	more than one DD from definition	Clarity no better than standard #14	Little or no stereoscopic effect

A photographic field will be considered "good" if all three characteristics listed above are graded "good"; "fair" if one of the conditions listed as "fair" is present and the other two are "fair" or "good"; and "poor" if one or more of the conditions listed as "poor" is present.

A set of photographs will be graded "excellent", "good", "fair", "acceptable", or "inadequate" according to the criteria listed below:

### GRADE

- Excellent = E      Beyond meeting criteria for "good," set is outstanding for its high quality.
- Good = G      Fields 1 and 2 are of good quality; of remaining five fields (3 through 7) at least two are of good quality and not more than one of poor quality, with good focus in at least four of these five fields.
- Fair = F      Field 2 is of good quality, and Field 1 and at least four of Fields 3 through 7 are at least fair in quality, with good focus in at least four of these six fields.

### Acceptable, Borderline

Set does not meet criteria for "fair" but is judged to provide adequate documentation of retinopathy and can be graded.

- B<sup>1</sup>      From lens photo included with the set, CORU grader confirms that media opacities account for problems in set.
- B<sup>2</sup>      In opinion of CORU grader, lens photo does not show substantial opacity, but photographer noted on form that media opacities caused problems.
- B<sup>3</sup>      Photographer noted on form that extreme photophobia, poor fixation, excessive tearing, or similar condition caused problems.
- B<sup>4</sup>      None of above descriptions apply, therefore quality problems in set are unexplained.

### Inadequate

Quality of set is too poor to allow reliable grading. One of four grades (I<sub>1</sub>, I<sub>2</sub>, I<sub>3</sub>, I<sub>4</sub>) is assigned in such cases. These are differentiated just as the four grades for "acceptable, borderline" described above.

## **18.3 The Central Ophthalmologic Reading Unit**

### **18.3.1 Organization**

The Central Ophthalmologic Reading Unit (CORU) is a unit of the Department of Ophthalmology in the Medical School of the University of Wisconsin. It is located on the Madison campus of the University of Wisconsin system. Composing the staff of the CORU are the following personnel: Director, Associate Director, Assistant Director, Project Associate (senior grader), Graders, Systems Analyst/Programmer, Biostatistician, Coordinator, and clerical assistants. The CORU functions in the EDIC as a subcontractor of The Biostatistics Center of The George Washington University.

### **18.3.2 Goals**

The objectives of the CORU in the EDIC are to perform the following functions:

- a. Grade color film / digital photographs in detail using an adaptation of the Modified Airlie House Classification of Diabetic Retinopathy;
- b. Monitor photographs submitted in the EDIC for satisfactory quality, providing feedback and compiling statistics as appropriate;
- c. Review the performance of photographers seeking EDIC certifications;
- d. Enter grading data into computerized files, edit and summarize the data, and transmit the results to the Data Coordinating Center;
- e. Take measures to assess the quality of the grading programs as they are carried out;
- f. Serve as a repository for the photographs submitted in the EDIC, providing safe physical storage and an adequate inventory system;

Collaborate with the EDIC Research Group in preparing manuscripts describing ophthalmologic procedures and results.

### **18.3.3 Detailed Grading of Color Fundus Photographs**

Sets of color stereoscopic fundus photographs of each eye taken are evaluated for presence and severity of various retinal abnormalities. This grading is performed in duplicate by two graders working independently, with significant differences being resolved if possible through re-grading of the problematic lesions, and if necessary through adjudication by a third, more senior grader.

Color detailed grading is carried out under an adaptation of the Modified Airlie House Classification of Diabetic Retinopathy, with the results recorded on EDIC Form 032 *Detailed Color Grading Form*.

All editing of data is accomplished using a computerized system that checks for omissions and large discrepancies in the gradings. Re-grading and adjudication forms are issued by the computer as necessary, and completed by the original graders or the adjudicator without reference to previous assessments.

Graders are masked to patient ID and clinic as they make their assessments. The order in which photo sets are examined is determined by a randomized reading list arranged so that right and left eyes are not included in the same batch of photographs. The coordinator assembles packets of photos for grading using the reading list as a guide.

Results of the detailed grading are maintained in a computer file. Before transmission of information to the Data Coordinating Center, completed gradings are further processed to summarize the lesion-by-lesion, field-by-field detail that they contain. Data transfer is accomplished by sending a magnetic computer tape.

### **18.3.4 Preliminary Assessment of Follow-up Color Photographs**

As follow-up visit color photographs are received at the CORU, they are given a preliminary examination for satisfactory quality and for development of retinopathy severe enough to require treatment or at least more frequent observation by the local ophthalmologist.

Any data emanating from this preliminary grading for retinopathy are separate from the information produced by the color detailed grading program. The latter data are to be used for any data analysis; the former are maintained solely to help clinics monitor possible development of retinopathy that may be treatable with laser photocoagulation. Graders performing the subsequent detailed assessment do not have access to any preliminary evaluation.

### **18.3.5 Monitoring of Photographic Quality**

The CORU program for monitoring photographic quality has two components: (1) an assessment of each photo set received, with feedback to the clinic as appropriate, and (2) a two-step certification program.

As photographs are received at the CORU, each set is assessed for photographic quality. Photographs submitted during follow-up receive a preliminary examination for photo quality at the same time they are reviewed for development of retinopathy treatable with photocoagulation.

Summaries of the results of the evaluations are sent to the Data Coordinating Center monthly. Annually, similar summaries are sent to the clinical centers. Occasionally, the CORU mails additional information to the photographers and study ophthalmologists concerning points of the photography protocol.

Before photographers are allowed to submit photos in the EDIC, they are required to send samples of their work for certification review and approval by the CORU. Extensive comments are returned each time an application for certification is processed. See Chapter 24 for more details about certification procedures.

When photographers come into the study, they are "provisionally certified", meaning that their work is monitored in detail at the CORU. After they have submitted work of satisfactory quality for a specified period, their certification status is altered to "full", meaning that they no longer have to record a field-by-field quality assessment of their photos. At that time, the CORU shifts to a briefer overall evaluation of the work from those photographers.

Photographers whose work is not generally satisfactory are closely monitored, with suggestions for improvement made as appropriate. For those photographers having problems not remediable in a reasonable period of time, certification for EDIC photography will be revoked.

### **18.3.6 Handling of Data**

Data generated by the various grading programs are entered into computerized files, where all editing and further processing is carried out.

Data are entered by clerical assistants using interactive CRT terminals. To check the accuracy of manual entry, a second complete verification entry is made by another data enterer. After that entry is completed, an editing program compares the first and second independent entries, indicating the data fields needing resolution.

As requested by the Data Coordinating Center and other study leadership, the CORU maintains software to condense and summarize data from the various grading programs.

Transmission of data is accomplished by sending of a magnetic computer tape. This includes hard copy of the data encoded on the tape for checking.

All CORU data storage systems have provision for backup in the event of loss of a primary file. These procedures allow rapid and economical regeneration of any files needed, either from disk or tape media.

At the end of the EDIC or when requested, the CORU will provide the Data Coordinating Center with the originals of all data collection forms completed at the CORU.

### **18.3.7 Quality Control**

The quality control program to monitor and improve the quality of grading at the CORU has internal and external components.

Internally, the CORU provides feedback periodically to graders using programs that entail duplicate independent gradings. This information consists of a comparison of that grader's initial grades with the final "grades of record" resulting either from agreement of the two original graders or from adjudication by a third, more senior grader. Also, retraining sessions are held as necessary to deal with problematic lesions.

In addition to the feedback mechanism, the CORU compiles data and runs statistics on the reproducibility of grading. This effort includes comparisons between graders and between results of the system at different times. Some of these analyses entail the annual masked regrading of a small proportion of the photo sets handled by the system (usually 5%).

Periodically, the CORU coordinator is directed by the Data Coordinating Center to submit specified photographs to the CORU grading programs for a repeat reading. Insofar as possible, the grading personnel are not allowed to know that these masked specimens are being regraded.

### **18.3.8 Procedures for Handling Photographs**

Upon receipt of a package of photographs from a clinic, the CORU staff check the contents against the enclosed mailing list (EDIC Form 107, Fundus Photograph Mailing List). Identifying information is examined to see if all materials are present and appear correct.

If inconsistencies, omissions, or damage in shipping are noted, contact is made by phone, fax or email with the originating center. If the problem cannot be rectified in this manner, the package is mailed back to the clinic for resolution.

The photography forms accompanying the photo sets are separated from the photos to enable grading in a masked fashion. The information on the forms will be entered into the computer file separately.

Once photographs have been graded, they are filed permanently in clinic and patient order in steel filing cabinets. This collection is indexed in a computerized inventory system for easy access and retrieval. Digital photographs are archived on a secure system at the CORU.

### **18.3.9 Reports To the Data Coordinating Center**

The CORU is required to report periodically to the Data Coordinating Center regarding both its own performance and the performance of clinics in the EDIC.

## REFERENCES

1. The University of Wisconsin School of Medicine Fundus Photograph Reading Center (CORU) Imaging Procedures, July 2009.
2. Early Treatment Diabetic Retinopathy Study Research Group: Grading diabetic retinopathy from stereoscopic color fundus photographs - an extension of the Modified Airlie House classification. ETDRS Report Number 10. *Ophthalmology* 1991;98:786-806.

## APPENDIX 18-A

### Common Ophthalmologic Abbreviations

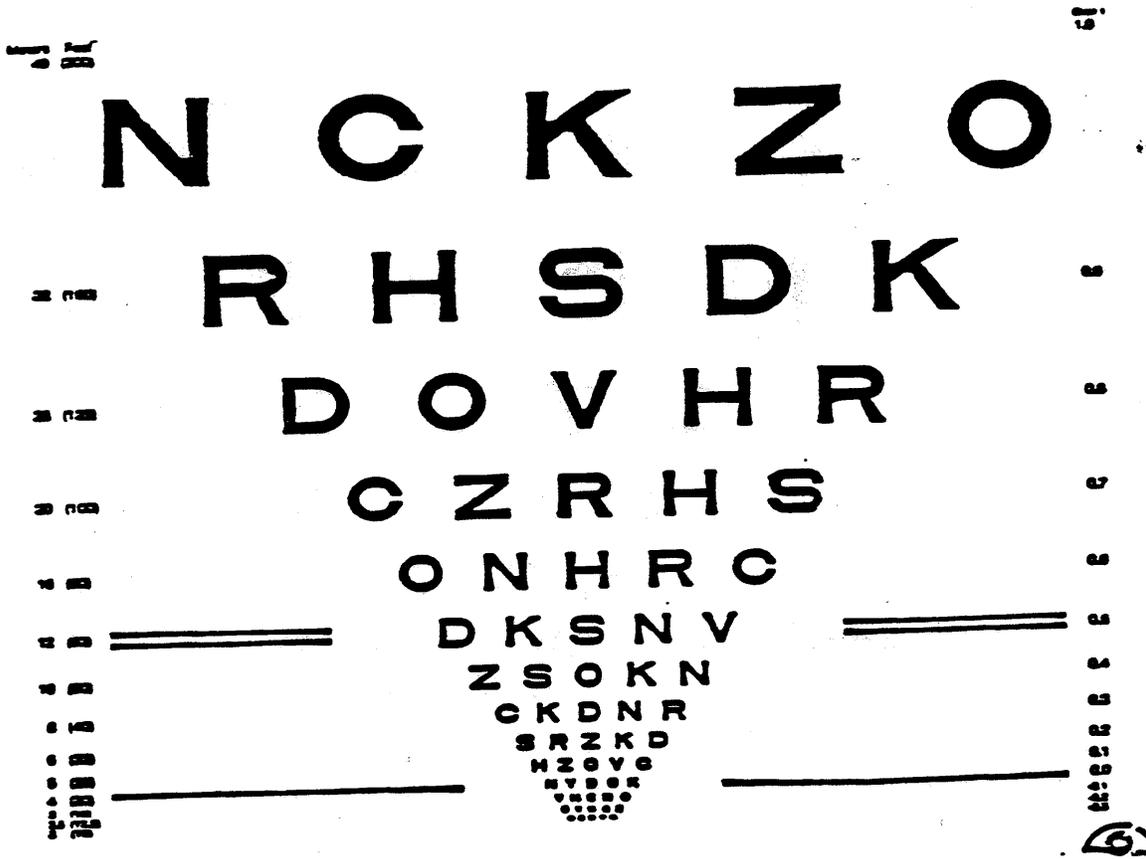
These might be used by the clinic's certified ophthalmologist and photographers notations on the forms:

<b>Δ</b>	Prism diopter
<b>A/C or AC</b>	Anterior chamber
<b>ACG</b>	Angle closure glaucoma
<b>ALPC</b>	Argon laser photocoagulation
<b>ALT</b>	Argon laser trabeculoplasty (for glaucoma)
<b>AMD</b>	Age-related macular degeneration
<b>APD</b>	Afferent pupillary defect
<b>BCC</b>	Basal cell cancer
<b>BDR</b>	Background diabetic retinopathy (outside the disc)
<b>BRVO</b>	Branch retinal vein occlusion,
<b>c or cc</b>	With refractive correction
<b>C/D</b>	Cup-to-disc ratio of the optic nerve
<b>CF</b>	Count fingers visual acuity
<b>CL, HC</b>	Contact lenses, hard
<b>CME</b>	Cystoid macular edema
<b>CRAO</b>	Central retinal artery occlusion
<b>CRVO</b>	Central retinal vein occlusion
<b>CSR / CSCR</b>	Central serous chorioretinopathy
<b>CVF</b>	Confrontation visual field
<b>cyl</b>	Cylinder (in refraction)
<b>D</b>	Diopter
<b>DCR</b>	Dacryocystorhinostomy
<b>DVD</b>	Dissociated vertical deviation (a form of strabismus)
<b>DVS</b>	Ductions, versions, saccades
<b>DWSCL</b>	Daily wear contact lenses
<b>ECCE c IOL</b>	Extracapsular cataract extraction with intraocular lens implantation
<b>EOG</b>	Electrooculogram
<b>EOM</b>	Extraocular motions
<b>ERG</b>	Electroretinogram RD Retinal detachment
<b>EOM</b>	Extraocular muscle ROP Retinopathy of prematurity
<b>ERM</b>	Epi-retinal membrane RP Retinitis pigmentosa
<b>ET,E(T),E,E'</b>	Esotropia, intermittent esotropia, esophoria, and esophoria at near
<b>EUA</b>	Exam under anesthesia
<b>Gonio</b>	Gonioscopic exam
<b>HM</b>	Hand motion vision
<b>HVF</b>	Humphrey Visual Field
<b>ICCE</b>	Intracapsular cataract extraction keratopathy
<b>IF</b>	1% Inflamase Forte 1%
<b>IK</b>	Interstitial keratitis
<b>IO</b>	Inferior oblique
<b>IOL</b>	Intraocular lens)
<b>IOP</b>	Intraocular pressure
<b>IR</b>	Inferior rectus
<b>K</b>	Keratometer reading (measures the curvature of the cornea), or abbreviation for cornea
<b>KCS</b>	Keratoconjunctivitis sicca
<b>KP</b>	Keratitic precipitate
<b>LPO</b>	Light perception, light perception only
<b>LR</b>	Lateral rectus
<b>LHoT, RHoT</b>	Left Hypotropia, right hypotropia

<b>LHT, RHT</b>	Left hypertropia and right hypertropia
<b>M&amp;N</b>	Mydriacyl & Neosynephrine mixture
<b>M</b>	Manifest (non-cyclopleged) refraction
<b>ME</b>	Macular Edema
<b>NVD</b>	Neovascularization of the disc
<b>NVE</b>	Neovascularization of the retina elsewhere
<b>NLP</b>	No light perception
<b>NS or NSC</b>	Nuclear sclerotic cataract
<b>NVI</b>	Neovascularization of iris
<b>OD, OS, OU</b>	Right eye, left eye, both eyes
<b>OHT</b>	Ocular hypertension
<b>P1, P2, P4</b>	Pilocarpine (with concentrations)
<b>PC</b>	Posterior chamber or posterior capsule
<b>PD</b>	Prism diopters
<b>PE, PHACO</b>	Phacoemulsification
<b>PEE</b>	Punctate epithelial erosions
<b>PEG</b>	Punctate epithelial granularity
<b>PEK</b>	Punctate epithelial keratitis or keratopathy
<b>PERL</b>	Pupils equal and reactive to light
<b>PF, PA</b>	1% Pred Forte eye drops, prednisolone acetate
<b>PH</b>	Pinhole
<b>PI 1/8</b>	Phospholine Iodine 1/8%
<b>PKP or PK</b>	Penetrating keratoplasty (cornea transplant)
<b>POHS</b>	Presumed ocular histoplasmosis syndrome
<b>POAG</b>	Primary open angle glaucoma
<b>PPDR</b>	Pre-proliferative diabetic retinopathy
<b>PRP</b>	Pan-retinal photocoagulation
<b>PSC</b>	Posterior subcapsular cataract
<b>PVD</b>	Posterior vitreous detachment
<b>RPE</b>	Retinal pigment epithelium
<b>s or sc</b>	Without refractive correction
<b>SCL, EWSCCL</b>	Soft and extended wear
<b>SLE or SLX</b>	Slit lamp exam
<b>SPH</b>	Sphere
<b>SPK</b>	Superficial punctate keratitis
<b>SR</b>	Superior rectus
<b>SRN,SRNVM</b>	Subretinal neovascular membrane
<b>TA</b>	Applanation tonometry
<b>T ½, T ¼</b>	Timoptic (with concentrations)
<b>Va</b>	Visual acuity
<b>VF</b>	Visual field
<b>vit</b>	Vitreous
<b>VTX</b>	Vitrectomy
<b>W4D</b>	Worth 4-dot test (in strabismus)
<b>X, X'</b>	exophoria, exophoria at near
<b>XT, X(T)</b>	Exotropia, intermittent exotropia
<b>YAG</b>	Neodymium-yttrium aluminum garnet laser

APPENDIX 18-B  
ETDRS CHARTS

EDIC VISUAL ACUITY CHART 1



EDIC VISUAL ACUITY CHART 2

120

100

80

60

40

30

20

15

10

5

3

2

1

D S R K N

C K Z O H

O N R K D

K Z V D C

V S H Z O

==== HDKCR =====

CSRHN

SVZDK

NCVOZ

RHSOV

—————

120

100

80

60

40

30

20

15

10

5

3

2

1

6

EDIC REFRACTION CHART R

15  
H V Z D S  
N C V K D  
C Z S H N  
O N V S R  
K D N R O  
Z K C S V  
D V O H C  
O H V C K  
H Z C K O  
N E R K D  
S H E R R  
A

VISUAL ACUITY FROM EDIC CHARTS AT FOUR METERS DISTANCE

ACTUAL VISUAL ACUITY	EQUIV. VISUAL ACUITY	LETTERS		LOG MAR*
		CHART 1	CHART 2	
4/40	20/200	NCKZO	DSRKN	1.0
4/32	20/160	RHSDK	CKZOH	0.9
4/25	20/125	DOVER	ONRKC	0.8
4/20	20/100	CZRHS	KZVDC	0.7
4/16	20/80	ONERC	VSHZO	0.6
4/12.5	20/62.5	DKSNV	HDKCR	0.5
4/10	20/50	ZSOKN	CSRHN	0.4
4/8	20/40	CKDNR	SVZDK	0.3
4/6.25	20/32	SRZKD	NCVOZ	0.2
4/5	20/25	EZOVC	RESDV	0.1
4/4	20/20	NVDOK	SNROH	0.0
4/3.12	20/16	VHCNO	ODMKR	-0.1
4/2.5	20/12	SVECZ	ZKCSN	-0.2
4/2	20/10	OZDVK	CRHDV	-0.3

VISUAL ACUITY FROM EDIC CHARTS AT ONE METER DISTANCE

ACTUAL VISUAL ACUITY	EQUIV. VISUAL ACUITY	LETTERS		LOG MAR*
		CHART 1	CHART 2	
4/160	20/800	NCKZO	DSRKN	1.6
4/125	20/640	RESDK	CKZOH	1.5
4/100	20/500	DOVHR	ONRKD	1.4
4/80	20/400	CZRES	XZVDC	1.3
4/63.5	20/320	ONERC	VSEZO	1.2
4/50	20/250	DKSNV	HDKCR	1.1
4/40	20/200	ZSOKN	CSREN	1.0
4/32	20/160	CKDNR	SVZDK	0.9
4/25	20/125	SRZKD	NCVOZ	0.8
4/20	20/100	HZOVC	RESDV	0.7
4/16	20/80	HVDOK	SNROH	0.6
4/12.5	20/62.5	VHCNO	ODEKR	0.5
4/10	20/50	SVHCZ	ZKCSN	0.4
4/8	20/40	OZDVK	CRHDV	0.3

## APPENDIX 18-C

### DIGITAL SYSTEM CERTIFICATION FOR COLOR CAPTURE CAPABILITY

#### SYSTEM REQUIREMENTS

Color digital images must be taken using Escalon Digital Solutions (MRP OphthaVision®), OIS Winstation®, Escalon Medical Imaging (EMI), Topcon IMAGENet®, Zeiss VISUPAC® or Digital Healthcare digital systems using a 3 mega-pixel or larger image sensor. Each color digital system must be certified by the CORU. The color balance of images is reviewed by CORU staff. If a system's color balance does not meet the CORU's requirements the system will not be certified until these issues are resolved.

It is preferred that the digital system contains software and hardware that allows remote access and operation. The CORU or a manufacturer's representative may inspect the digital camera system to assure that all capture settings are correct for accurate image analysis. This inspection may be performed via "dial-in" access or as part of a site visit. Inspection software may be used to verify and record system settings.

Each digital system with color capture capability used for the study must be certified by the CORU before beginning patient photography. See Appendix 18-D.

#### **Escalon Digital Solutions (MRP OphthaVision®)**

System Certification is handled through Escalon Digital Solutions and is a two step process. Those wishing to certify a camera should submit on film and digital 2 red free images, of the same patient, with the optic nerve head centered in the photograph. If a variable degree fundus camera is used, images should be taken at all magnifications. Send the processed film and a CD containing the digital images to:

Escalon Digital Solutions  
49 Blanchard Street  
Lawrence, MA 01843  
Attn: Matt Carnevale

Once the images are analyzed by Escalon Digital Solutions, the scale factor for that fundus camera will be sent to the study site. These factors will need to be entered into the preference files within the OphthaVision software. Please contact Escalon Digital Solutions (1-800-676-0043) when you have received the scale factors to ensure they are entered correctly.

Once the system has been approved, images will be requested from the CORU to verify image settings. CD/DVDs sent to the CORU must include a .dbf and a .tif file.

#### **OIS Winstation®, Escalon (using Escalon Software) or Digital Healthcare (DHC)**

Each system requires a calibration for certification. The calibration uses 10 color images, of 10 different eyes, at the acceptable image angle (determined by camera type). The color images should be centered on the posterior pole so that both the disc and macula are in view. If the center of the macula and the center of the disc are not clearly defined they cannot be used for calibration. The CORU would prefer that OIS Winstation® systems have software version 10.0 or higher. EMI systems must have RCPrep software version 1.4 or higher. DHC Classic systems must have software version 4.19 or higher.

If there are any hardware or software changes made to the system 10 more color images may be required to recalibrate the system. This requirement can be abbreviated if one of the 10 eyes used in the initial calibration is from someone who can be photographed in the future (i.e. the same staff member's eye photographed under 2 different system parameters). This way if the system changes, the patient can be re-photographed and the old and new photos can be sent to the CORU for calibration and recertification.

## **Topcon IMAGEnet®**

Run the Digital System Evaluation Software (DSES), which can be found on our website at <http://eyephoto.opth.wisc.edu/dses2.html> or it can be mailed to you by contacting the CORU. Follow the directions included with the software and send the results to [tony@cfsimaging.com](mailto:tony@cfsimaging.com) or via courier to:

Choices for Service in Imaging, Inc.  
233 Rock Road #249  
Glen Rock, NJ 07452

If you have any questions during the process please contact Tony Pugliese at 1-888-751-0141, [tony@cfsimaging.com](mailto:tony@cfsimaging.com).

Once Tony Pugliese has verified that the system settings are correct he will issue a document to the CORU. Upon receipt of this document the CORU will need to verify the system settings by reviewing recent images (taken after Tony's documentation has been issued).

## **Zeiss Visupac®**

Sample images are taken at 30 degrees and exported as DICOM (.dcm) files. The images can be anonymized manually prior to export (for certification and study submissions), or an 'anonymizing' license may be purchased from Zeiss.

## APPENDIX 18-D

### SYSTEM SPECIFIC LINKS FOR INSTRUCTIONS ON EXPORTING AND LABELING DIGITAL IMAGES

Please note if any of the links are out of date, please contact the CORU staff for up-to-date information listed on the EDIC website.

#### **Escalon Digital Solutions (MRP OphthaVision®)**

Please go to: <http://eyephoto.ophth.wisc.edu/Escalon%20export%20procedure.doc>

#### **OIS Winstation®, Escalon (using Escalon Software) or Digital Healthcare (DHC):**

Please see OIS Winstation® Export Procedure at <http://eyephoto.ophth.wisc.edu/DSES.html> to correctly export images to CD. To properly export images to CD:

Select CD (OISReview)  
Select file type from file format drop down  
Version 6.0 and lower = Standard File Format  
Version 10.0 and higher = TIFF or NO LOSS TIFF (not LOSSLESS TIFF)

#### **Topcon IMAGENet®**

Please go to: <http://eyephoto.ophth.wisc.edu/Imagenet%20Study%20Drive%20and%20CD.pdf>

#### **Zeiss Visupac®**

Please go to: [http://eyephoto.ophth.wisc.edu/VISUPAC\\_Measuring\\_tutorial.pdf](http://eyephoto.ophth.wisc.edu/VISUPAC_Measuring_tutorial.pdf)

**APPENDIX 18-E**

**Fundus Photograph Reading Center:**

**“Submitting Imaging Technician and Equipment Certification Requests Using IRIS”**



University of Wisconsin  
**SCHOOL OF MEDICINE  
AND PUBLIC HEALTH**

# **Fundus Photograph Reading Center**

## **Submitting Imaging Technician and Equipment Certification Requests Using IRIS**

**Effective Date: 07May2012**

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## 1. Overview

Sites can apply for FPRC certification using our upload utility known as IRIS. A username and password are required to login into IRIS. Typically your username is the unique email address that was provided to the FPRC. If you are unable to establish a password, it is most likely because the FPRC did not have your email address to enter into our system. If you feel this is the case, please contact the FPRC at [FPRC\\_IRIS@rc.opth.wisc.edu](mailto:FPRC_IRIS@rc.opth.wisc.edu) or contact the FPRC Project Manager for your study.

If you have not created a password click on the link “Establishing Username/Password” on IRIS’s main page.

If you have forgotten a previously created password, click the link “Resetting a Forgotten Password” on IRIS’s main page.

Java software is required to upload images. If you do not have Java installed on your computer click on the link “Get Java” on IRIS’s main page.

## 2. Logging into IRIS

- Enter IRIS’s URL into your web browser <https://iris.opth.wisc.edu/>
- Enter your username and password



FUNDUS PHOTOGRAPH  
**READING CENTER**

IMAGING REQUEST AND INFORMATION SYSTEM

User Name

Password

### 3. Creating a New Certification Request

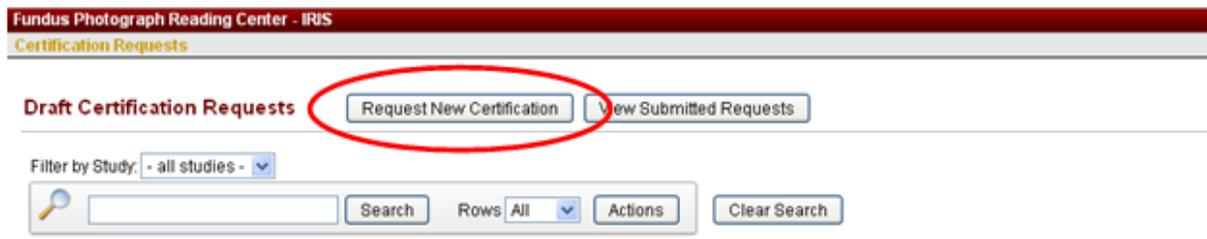
1. Select Certifications tab from the home page



#### Options from the Certification Tab

1. Create a new certification request
2. View draft certification requests report
3. View submitted certification requests report

2. Select the “Request New Certification” button



3. Select the “Certification Type”. It will be either
  - Imaging Technician
  - Equipment



4. Once the Certification Type is selected, fields for Study and Study Site with appear

**Fundus Photograph Reading Center - IRIS**  
Certification Requests > Entry

**Certification Entry**

Certification Type: Imaging Technician ▼  
Study: select - ▼  
Study Site: select - ▼  
Imaging Procedures:

Add Request Reset

5. Once Study and Study Site fields are selected, Imaging Procedures will appear. Note that you will not be able to select Imaging Procedures that have a grey check mark. This is because you are already certified for that procedure or a request for that procedure is currently in process.

**Fundus Photograph Reading Center - IRIS**  
Certification Requests > Entry

**Certification Entry**

Certification Type: Imaging Technician ▼  
Study: AAdave test ▼  
Study Site: testwiz02 ▼  
Imaging Procedures:  3M-D  3M-F  7M-D  AF-D  FA-D  OCT-3

Add Request Reset

Once Imaging Procedures are added the “Add Request” button becomes available.

**Fundus Photograph Reading Center - IRIS**  
Certification Requests > Entry

**Certification Entry**

Certification Type: Imaging Technician ▼  
Study: AAdave test ▼  
Study Site: testwiz02 ▼  
Imaging Procedures:  3M-D  3M-F  7M-D  AF-D  FA-D  OCT-3

Add Request Reset

6. Once the “Add Request” button is selected the requests are listed in the Summary of Requests section. Note: you have the option of adding as many requests as you would like before proceeding by repeating steps 1-4 for additional requests.

**Fundus Photograph Reading Center - IRIS**  
Certification Requests > Entry

**Certification Entry**

Certification Type:

**Summary of Requests**

Certification Type	Study	Study Site	Imaging Procedure	Equipment	Comments
✘ Imaging Technician	AAdave test	testwiz02	7M-D	-	add a comment
✘ Imaging Technician	AAdave test	testwiz02	FA-D	-	add a comment

- You may add multiple certification requests during one session.
- Click "Proceed to File Upload" if you will be uploading files.
- Click "Save as a Draft" if you are not ready to send your certification request(s).
- Click "Finalize Submission" if you are requesting certification(s) based on prior FPRC certification(s). You will not be able to upload images if "Finalize Submission" is selected.

At this point you have 3 options

- Upload any necessary files
- Save as a draft to complete at a later date
- Finalizing Submission by sending to the FPRC

### 3.1. Uploading Files

By selecting the “Proceed to File Upload” you will be taken to a page where you have the ability to include files with your certification requests.

Select the “Upload Files” button.

Fundus Photograph Reading Center - IRIS  
 Certification Requests > Upload Files

Certification Requests							Uploaded Image Files
Remove	Files Uploaded?	Submission ID	Study	Study Site	Imaging Procedure	Equipment	Type of Certification
✘		5315	AAdave test	testwiz02	7M-D		Imaging Technician
✘		5316	AAdave test	testwiz02	FA-D		Imaging Technician

A pop-up window will appear allowing you the opportunity to upload multiple groups of images, if necessary. A group of images can be associated with one or more procedures. It is not required to associate images with a procedure in which “auto certification” applies.

**Upload Files** ✘

You will have the opportunity to upload multiple groups of images, if necessary. A group of images can be associated with one or more procedures. It is not required to associate images with a procedure in which "auto certification" applies.

Which procedure(s) apply to the image group to be uploaded?

Request Type	Study	Imaging Procedure	Study Site	Equipment
<input checked="" type="checkbox"/> Imaging Technician	AAdave test	7M-D	testwiz02	-
<input type="checkbox"/> Imaging Technician	AAdave test	FA-D	testwiz02	-

After the “OK” button is selected the JumpLoader applet will appear, allowing you to add the necessary files by click the  Add... icon...

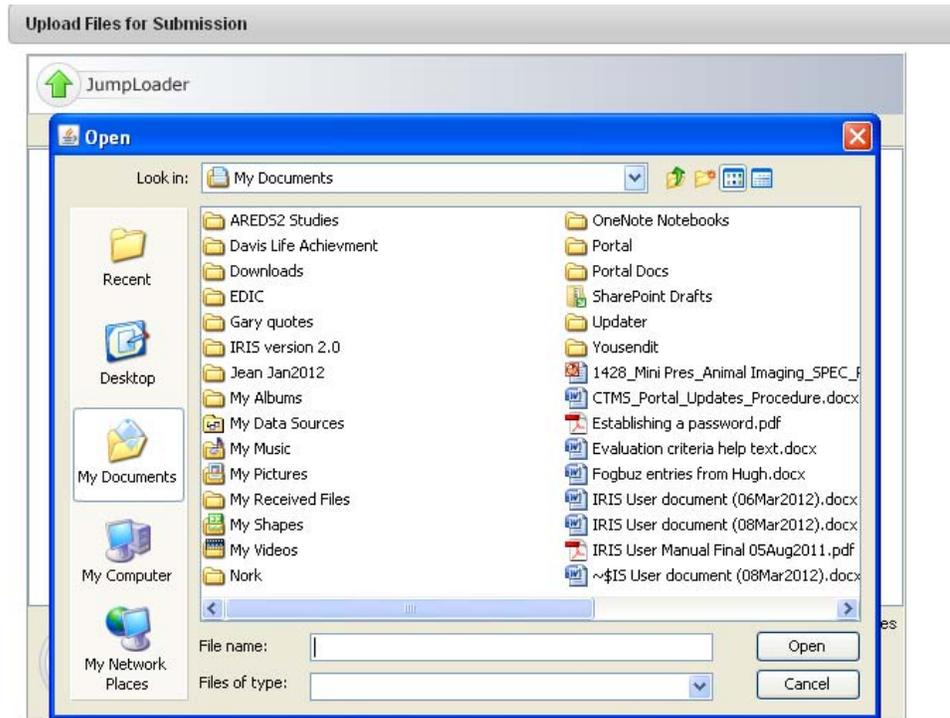
Upload Files for Submission

JumpLoader

Drop Files Here

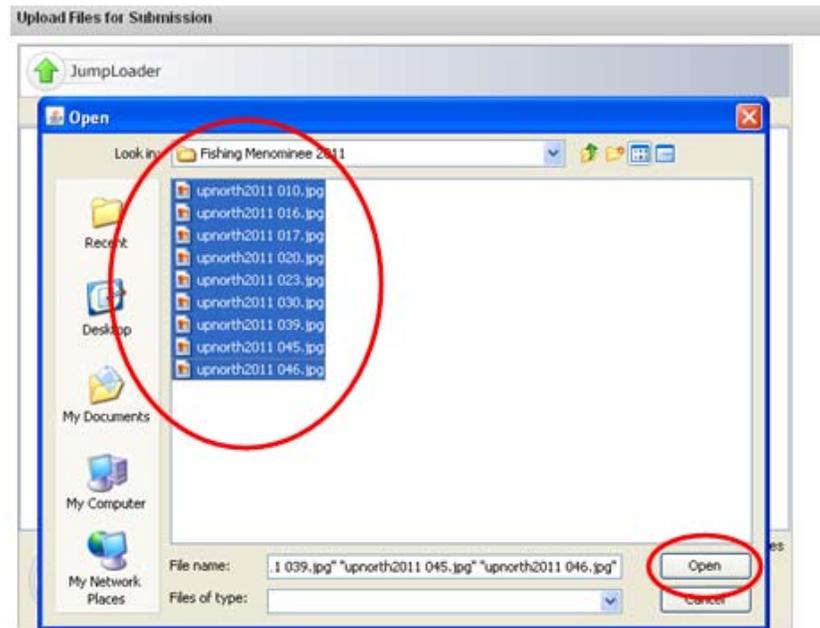
No files

and browsing to the location of the files.



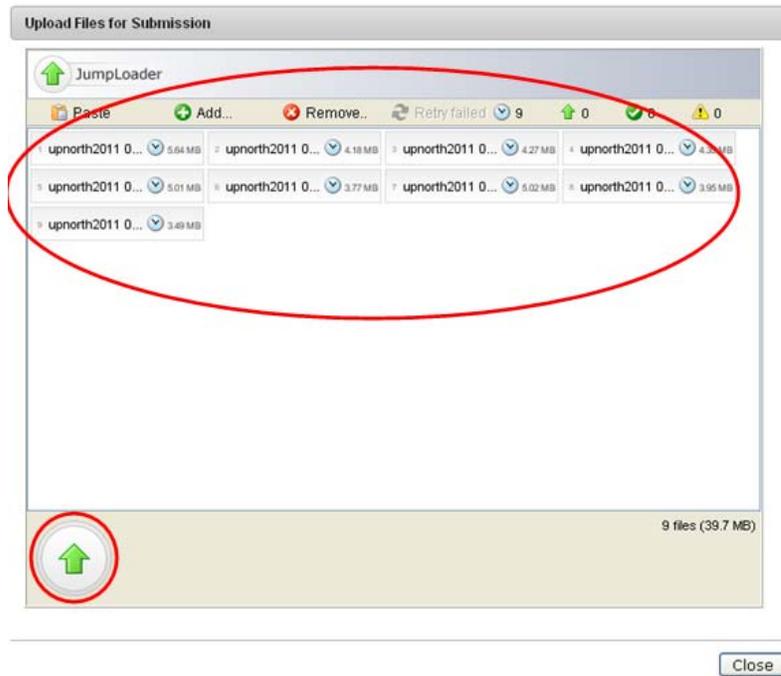
Close

Highlight the files and select the “Open” button.

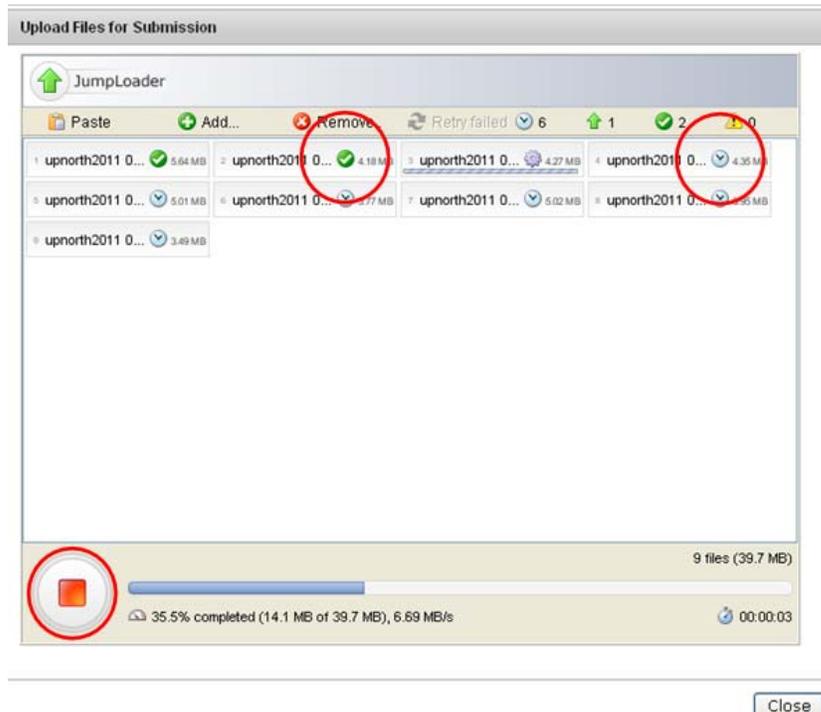


Close

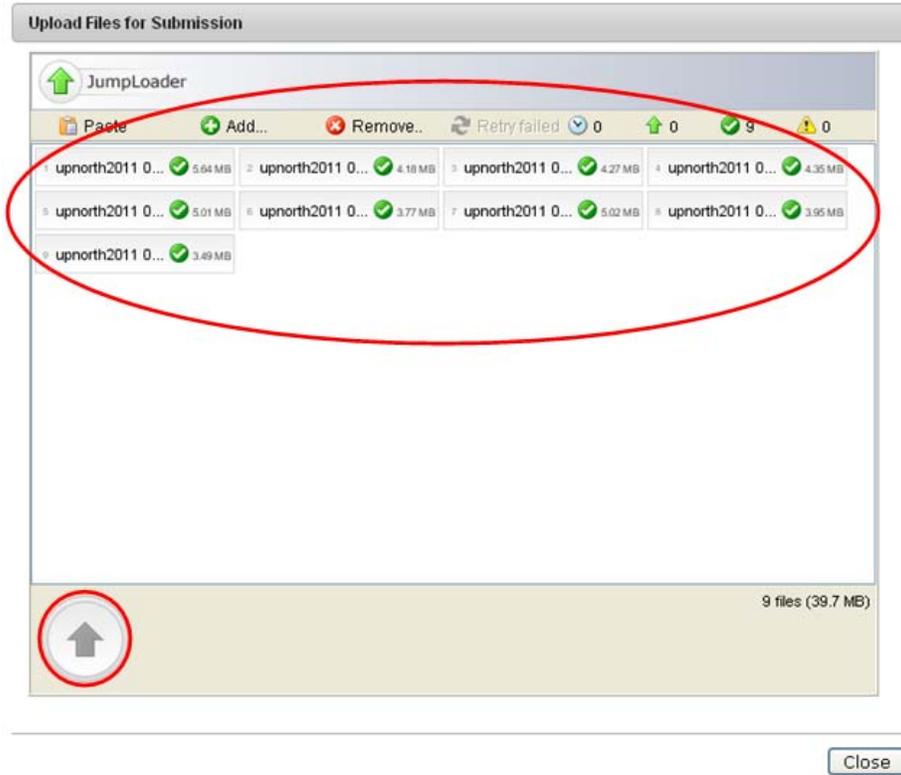
This will move the files to the JumpLoader application where you can click on the large green arrow near the bottom left corner to begin the upload process.



During the upload process the large green arrow will turn to a red box. Successfully loaded images will change from a light blue clock to a green check mark.

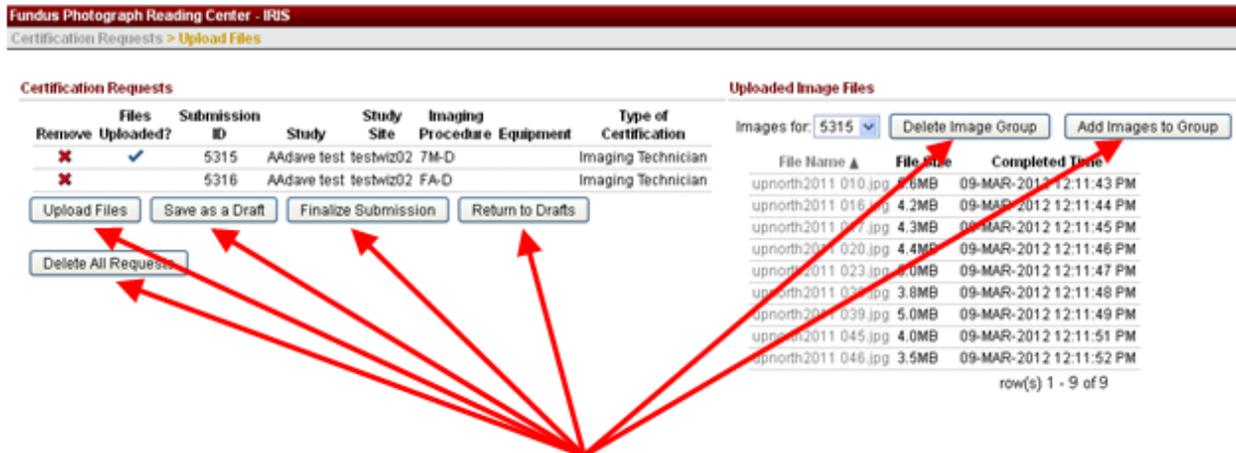


When the upload process is complete all files should have a green check mark next to them and the red box should turn into a grey arrow.



Once the “Close” button is selected the application returns you to a summary page where you can:

- Upload files for a new image group
- Save, to finalize at another time
- Finalize and send to the FPRC
- Delete the requests
- Delete *all* images for the selected procedure
- Add images to the selected image group



It is important to recognize that the images displayed in the Uploaded Image Files section are only for the submission ID selected. In the example below the images listed below are associated to submission ID # 5315

**Certification Requests**

Remove	Files	Submission	Study	Study	Imaging	Equipment	Type of
	Uploaded?	ID		Site	Procedure		Certification
<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	5315	AAadave test	testwiz02	7M-D		Imaging Technician
<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	5316	AAadave test	testwiz02	FA-D		Imaging Technician

**Uploaded Image Files**

Images for: 5315

File Name	File Size	Completed Time
upnorth2011_010.jpg	5.6MB	09-MAR-2012 12:11:43 PM
upnorth2011_016.jpg	4.2MB	09-MAR-2012 12:11:44 PM
upnorth2011_017.jpg	4.3MB	09-MAR-2012 12:11:45 PM
upnorth2011_020.jpg	4.4MB	09-MAR-2012 12:11:46 PM
upnorth2011_023.jpg	5.0MB	09-MAR-2012 12:11:47 PM
upnorth2011_030.jpg	3.8MB	09-MAR-2012 12:11:48 PM
upnorth2011_039.jpg	5.0MB	09-MAR-2012 12:11:49 PM
upnorth2011_045.jpg	4.0MB	09-MAR-2012 12:11:51 PM
upnorth2011_046.jpg	3.5MB	09-MAR-2012 12:11:52 PM

And in the next example below the images displayed are for both submission ID #s 5315 & 5316. This is because color and FA images were uploaded together in the same image group.

**Certification Requests**

Remove	Files	Submission	Study	Study	Imaging	Equipment	Type of
	Uploaded?	ID		Site	Procedure		Certification
<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	5315	AAadave test	testwiz02	7M-D		Imaging Technician
<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	5316	AAadave test	testwiz02	FA-D		Imaging Technician

**Uploaded Image Files**

Images for: 5315, 5316

File Name	File Size	Completed Time
001_3.JPG	415.5KB	09-MAR-2012 12:44:08 PM
002_4.JPG	342.9KB	09-MAR-2012 12:44:08 PM
003_5.JPG	340.8KB	09-MAR-2012 12:44:08 PM
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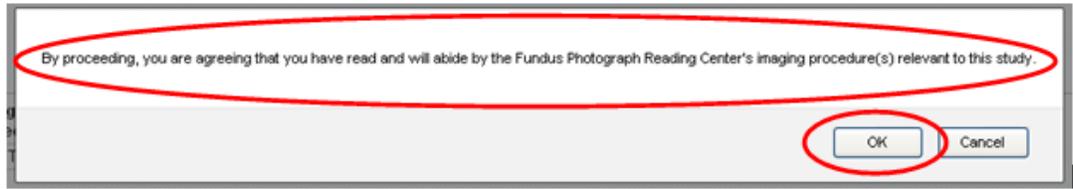
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	Uploaded?	ID		Site	Procedure		Certification
<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	5315	AAadave test	testwiz02	7M-D		Imaging Technician
<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	5316	AAadave test	testwiz02	FA-D		Imaging Technician

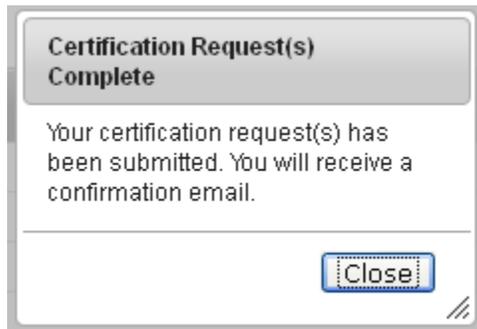
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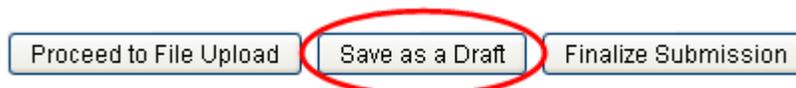
A pop-up window will be presented indicating that your requests have been submitted and that you will receive a confirmation email.



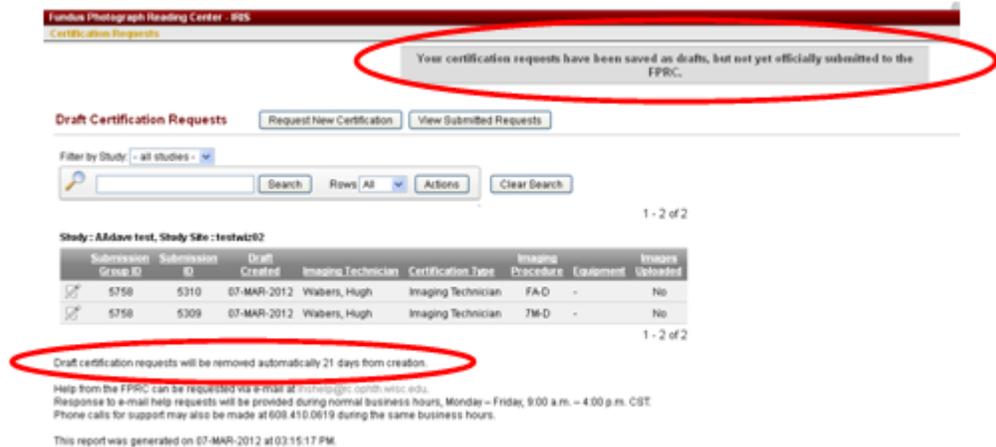
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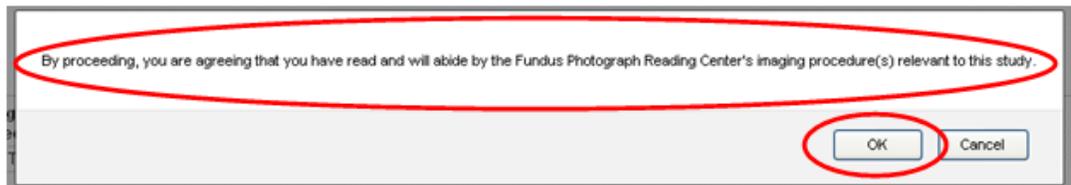


### 3.3. Send Request to the FPRC

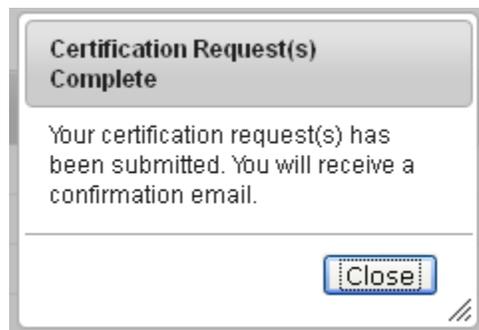
By selecting the “Finalize Submission” button you commit to sending your requests to the FPRC.



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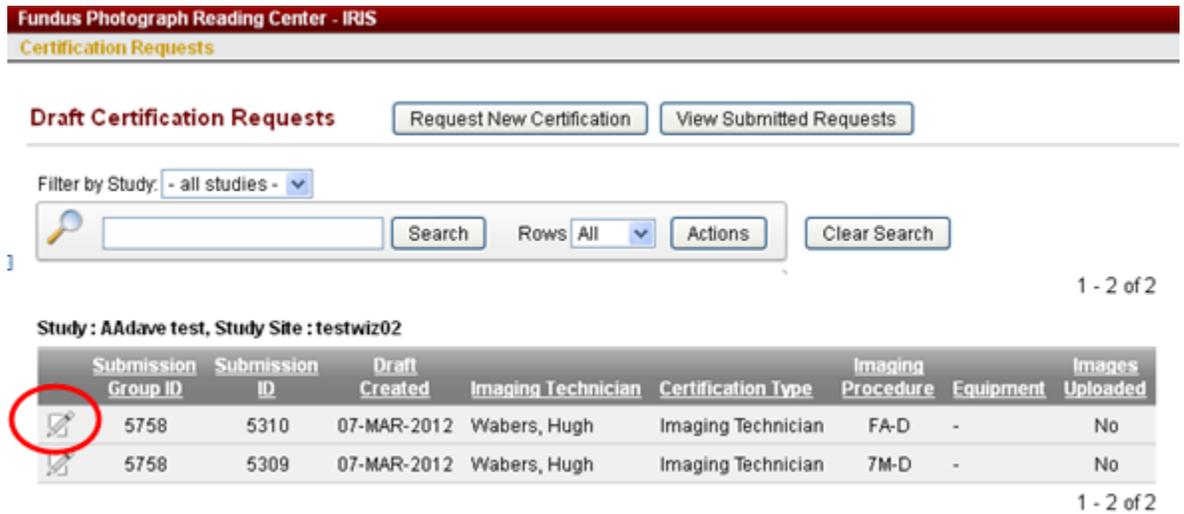


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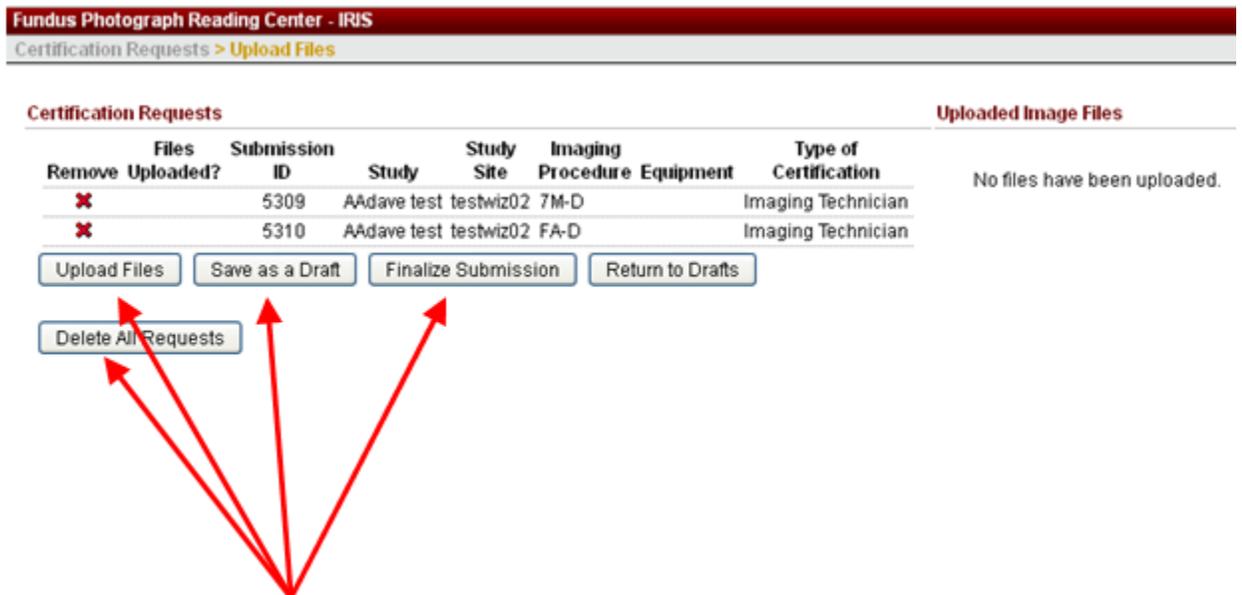
1 - 2 of 2

Study: AAdave test, Study Site : testwiz02

Submission Group ID	Submission ID	Draft Created	Imaging Technician	Certification Type	Imaging Procedure	Equipment	Images Uploaded	
	5758	5310	07-MAR-2012	Wabers, Hugh	Imaging Technician	FA-D	-	No
	5758	5309	07-MAR-2012	Wabers, Hugh	Imaging Technician	7M-D	-	No

1 - 2 of 2

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		5309	AAdave test	testwiz02	7M-D		Imaging Technician
		5310	AAdave test	testwiz02	FA-D		Imaging Technician

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## 5. View Submitted Certification Requests Report

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1 - 2 of 2

**Study : AAdave test, Study Site : testwiz02**

Submission Group ID	Submission ID	Draft Created	Imaging Technician	Certification Type	Imaging Procedure	Equipment	Images Uploaded
 5758	5310	07-MAR-2012	Wabers, Hugh	Imaging Technician	FA-D	-	No
 5758	5309	07-MAR-2012	Wabers, Hugh	Imaging Technician	7M-D	-	No

1 - 2 of 2

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Help from the FPRC can be requested via e-mail at [irishelp@rc.ophth.wisc.edu](mailto:irishelp@rc.ophth.wisc.edu).  
 Response to e-mail help requests will be provided during normal business hours, Monday – Friday, 9:00 a.m. – 4:00 p.m. CST.  
 Phone calls for support may also be made at 608.410.0619 during the same business hours.

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1 - 50 of 82

**Study : AAdave test, Study Site : testwiz02**

Details	Submission ID	Date Received	Imaging Technician	Certification Type	Imaging Procedure	Equipment	Images Uploaded	Certified By	Certification Approved	Certification Status	Draft Created
	5088		Carey, Randy	Equipment	7M-D	Fundus Camera 66292 (Capture#4)	No		Yes	Complete	24-JAN-2012
	5082		Carey, Randy	Equipment	3M-D	Fundus Camera 66292 (Capture#4)	No		Yes	Complete	24-JAN-2012

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**Fundus Photograph Reading Center - IRIS**  
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<b>Request</b>	<b>Uploaded Files</b>
Group ID <b>5088</b> Submission ID <b>5088</b> Status <b>Complete</b> Received Date <b>24-JAN-2012</b> Certification Type <b>Equipment</b> Study <b>AAave test</b> Site <b>testwiz02</b> Imaging Procedure <b>7M-D</b> Equipment <b>Fundus Camera 66292 (Capture#4)</b> Imaging Technician <b>Carey, Randy</b> Certification Approved <b>[Yes] 01-MAY-2008</b> Approved By  Comments	No files are uploaded for this certification request.  <b>Related Certification Request</b> There are no related certification requests

### 19.1 Introduction

The Harvard Food Frequency Questionnaire<sup>1</sup> was administered every 2 years in EDIC Yrs. 1-15 in conjunction with the lipid assessments. The potential importance of diet in the etiology of heart disease and unknown influence of protein intake on renal function highlighted the need for a method to measure individual dietary intake that was simple, reproducible, and accurate. The questionnaire was designed to be self-administered by nurses and other health professionals participating in epidemiologic cohort studies. The questionnaire was discontinued in EDIC Yr. 16.

### 19.2 Results from the Harvard Food Frequency Questionnaire

The dietary assessment consists of values obtained from the food frequency questionnaire that the patient completed. This assessment includes the percentage of total calories the patient gets from protein, various types of fat, carbohydrates, and sucrose, along with a recommended percentage of each, as well as the patient's actual intake of protein, carbohydrates, fats, cholesterol, iron, folic acid, thiamin, riboflavin, niacin, calcium, and vitamins A, C, D, E, B6, and B12.

<sup>1</sup> Willett WC, Sampson L, Stampfer MJ, Rosner B, Bain C, Witachi J, Henekens CH, Speizer FE. Reproducibility and validity of semiquantitative food frequency questionnaire. Am J Epidemiol. 1985; 122:51-65.

## 20. NEUROLOGICAL PROCEDURES

### 20.1 Introduction

The neurological history and examination, nerve conduction studies and autonomic nervous system testing performed during the DCCT will be repeated during EDIC in years 13 or 14 to evaluate the development and progression of distal symmetrical peripheral neuropathy and autonomic neuropathy in the EDIC. In addition, subjects will undergo quantitative sensory testing (QST) and will be asked to complete two questionnaires: a neurology symptom-specific quality of life questionnaire (NeuroQOL) and the autonomic symptom questionnaire (Autonomic Symptom Profile – ASP). Subjects will continue to have the Michigan Neuropathy Screening Instrument (MNSI) administered annually. Following years 13 and 14, Autonomic measures, **with the autonomic symptom questionnaire (Autonomic Symptom Profile – ASP)**, will be completed on each subject **once in years 16 or 17**.

The specific aims of the neuropathy measurement in EDIC are:

1. To determine whether the imprinting or “metabolic memory” phenomena observed for retinopathy and nephropathy also apply to peripheral and autonomic neuropathy by assessing the long-term effects of former DCCT intensive vs. conventional treatment on distal symmetrical peripheral neuropathy and autonomic neuropathy.
2. To identify factors that explain a long-term effect of former DCCT treatment group, in particular the level of glycemia observed during the DCCT.
3. To identify factors related to the progression of peripheral and autonomic neuropathy separately within the former DCCT intensive and conventional therapy groups, especially the role of hyperglycemia as reflected by the HbA<sub>1c</sub>.
4. To assess the impact of peripheral and autonomic neuropathy on health-related quality of life, and
5. To assess the association among autonomic neuropathy, cardiovascular outcomes, congestive heart failure, and sudden death.

#### 20.1.1 Background and Significance

Distal symmetrical peripheral neuropathy and autonomic neuropathy are well-recognized complications of diabetes.<sup>1,2,3</sup> Distal symmetrical peripheral neuropathy is a significant cause of pain, suffering, and disability, and accounts for the majority of non-traumatic lower extremity amputations in the United States. Although predominantly sensory in nature, distal symmetric peripheral neuropathy is associated with distal motor abnormalities and with autonomic dysfunction. Sensory deficits appear first in the toes and feet, and progress proximally. Diabetic autonomic neuropathy may affect virtually any sympathetic or parasympathetic function. Manifestations include abnormalities of heart rate control and vascular dynamics, pupillary dysfunction, gastroparesis, constipation, cystopathy, impotence, abnormal sweating, and reduced hypoglycemia awareness. Cardiovascular autonomic neuropathy may be associated with both parasympathetic and sympathetic denervation. Persons with cardiac denervation syndrome lack heart rate variation during deep breathing or during the Valsalva maneuver. Persons with advanced cardiac denervation may experience a deficient postural reflex with resultant orthostatic hypotension. Persons with cardiac denervation are believed to be at increased risk for painless myocardial ischemia, cardiac arrhythmias, and sudden death.<sup>4</sup>

The DCCT conclusively demonstrated that intensive diabetes therapy aimed at reducing blood glucose levels to as close to normal as possible, reduced the appearance and progression of retinopathy, nephropathy and neurological complications in persons with type 1 diabetes.<sup>5</sup>

Subsequently, DCCT subjects previously assigned to the conventional therapy group were converted to intensive therapy and intensive-group subjects were encouraged to maintain intensive therapy at the conclusion of the DCCT in 1993.

The EDIC study commenced in 1994. The primary goal of the EDIC study was to determine the long-term effects of previous glycemic separation on diabetic complications, based on an intention-to-treat analysis. The EDIC study follow-up has demonstrated that the differences in retinal and renal outcomes between the intensive and conventional treatment groups observed at the end of the DCCT have persisted and even increased for as long as 8 years, despite the narrowing of glycemic differences that appeared to explain the majority of the treatment differences during the DCCT.<sup>6,7,8</sup> The prolonged salutary effects of intensive therapy and the prolonged deleterious effects of conventional therapy were termed “imprinting” or “metabolic memory.”

It is unknown whether imprinting or metabolic memory apply to development of neuropathy. Abbreviated clinical measures have suggested that peripheral neuropathy outcomes remain different in the two DCCT treatment cohorts.<sup>8,9</sup> Unfortunately, no rigorous quantitative measures of peripheral nerve function and no measures of autonomic function have been performed on the DCCT/EDIC cohort since year 5 of the DCCT. Given the findings of metabolic memory effects for retinal and renal outcomes, it is imperative to determine whether these effects extend to neuropathic outcomes and, if not, to consider alternative hypotheses for the metabolic memory phenomena.

## **20.2 Evaluation of Peripheral Sensorimotor Neuropathy in EDIC**

The clinical and electrophysiological measures used to evaluate peripheral sensorimotor neuropathy in the DCCT will be performed either in EDIC year 13 or 14. These measures include assessment of neurological symptoms and signs by a neurologist, and conventional nerve conduction studies. Vibration threshold perception testing, a recognized and widely used Quantitative Sensory Test (QST) method, which was not included in the DCCT, will be added to the neuropathy assessment in the EDIC study. Together, these measures have good consensual validity among neuromuscular clinicians and are consistent with the consensus recommendations of expert groups asked to develop protocols for evaluating diabetic neuropathy.<sup>10,11</sup> To provide further clinical context, we will also carefully assess the impact of peripheral neuropathy on health-related quality of life.

### **20.2.1 Symptoms and signs of distal symmetrical peripheral neuropathy**

#### Neurological History and Examination

EDIC Form 051 will be used to record clinical symptoms and signs of distal symmetrical (sensorimotor) peripheral neuropathy. Questions relating to the definition of peripheral and autonomic neuropathy are identical to those used during DCCT. A focused neurological examination will be used to evaluate the neuromuscular system, and the combined results will be used to identify the presence of a distal symmetrical peripheral neuropathy (items related to the primary neurology hypothesis in the DCCT and the proposed hypothesis in the EDIC). Original DCCT items pertaining to the examination of mental status and cranial nerve function are not related to the specific aims of the project and are not included.

Each EDIC clinical center will be asked to identify a qualified, board-certified neurologist to perform the examination. Each neurologist will be asked to complete EDIC form 51 and each

will be certified to perform the study examination by James Albers, MD, PhD, from the University of Michigan.

### Nerve Conduction Studies

The same nerve conduction studies performed in the DCCT will be repeated. These nerve conduction studies are non-invasive and only slightly uncomfortable compared to, for example, the needle EMG examination, which is invasive and painful. The four nerves studied in DCCT (dominant side median motor, median sensory, peroneal motor and sural) will be studied again in the EDIC study.

Each EDIC study site will identify a qualified electromyographer to perform the nerve conduction studies. In most instances, this physician will be the same neuromuscular clinician who will perform the clinical neurological examination. The procedure used to certify the electromyographer will be identical to that used in the DCCT. All electromyographers identified to perform evaluations who did not perform evaluations in the DCCT will be contacted by the certifying EDIC electromyographer and, if deemed necessary, the site may be visited for training purposes prior to certification. If an appropriate individual(s) cannot be identified, the certifying neurologist will assist in the selection.

Nerve conduction studies will use standardized methods involving stimulation and recording sites and temperature control, all of which will be identical to those used in the DCCT. Consistent with the DCCT, electromyographers will be informed of the patient's previous temperature recordings (pre- and post-recording temperatures for each anatomical site), so that the studies can be performed under similar temperature conditions, to the extent that it is safe and practical to do so (see Temperature Control, section 20.4.3).

All electrophysiological responses will be recorded and independently reviewed by the certifying electromyographer using the same primary quality control algorithm used in the DCCT. All recordings will be examined by an independent reviewer to identify potentially correctable transcription, measurement, or calculation errors. The algorithm also includes an iterative inspection of amplitude, latency, and conduction velocity distributions to identify outlying or non-physiological values. If individual or systematic errors are found, the recordings will be returned to the investigator for re-measurement using the proper protocol technique.

### **20.2.2 Quantitative Sensory Testing**

Quantitative Sensory Testing (QST) has been added in response to recommendations of two consensus panels that were convened after the start of the DCCT. These panels were convened to standardize the nomenclature and assessment of diabetic neuropathy, particularly diabetic peripheral polyneuropathy. The first conference met in San Antonio in 1988. This conference, usually referred to as The San Antonio Conference on Diabetic Neuropathy, was endorsed by the American Diabetes Association and the American Neurological Association. The second conference, referred to as the Consensus Development Conference on Standardized Measures in Diabetic Neuropathy, met in 1992. Both panels supported classification of diabetic neuropathy based on categories of clinical symptoms, clinical examination results (signs), electrodiagnostic studies, quantitative sensory testing, and autonomic function testing. Quantitative sensory testing procedures were endorsed for longitudinal studies of diabetic peripheral polyneuropathy. Vibration perception threshold (VPT) testing was reported to be the most widely used and studied measure, with the most extensive normal and neuropathy databases.

A change in the ability to perceive vibration is recognized as an early and reliable sign of peripheral neuropathy. VPT was also identified as a surrogate for predicting long-term complications of ulceration and amputation.<sup>12</sup> VPT testing principally evaluates function mediated by large-diameter nerve fibers. Although smaller fibers are frequently involved in diabetic neuropathy, predominant or exclusive small fiber diabetic neuropathy is uncommon, and it is generally accepted that large nerve fibers are the first and the most prominently involved nerve fibers in diabetic neuropathy.

The study coordinator or study nurse at each site will be trained in a central session to perform VPT testing using the Vibratron II device (Physitemp Instruments, Inc.). Subjects will be assessed in conjunction with their annual EDIC assessment and testing should take not more than 10 to 15 minutes. VPT testing will be performed independently from the neurological examinations and the VPT results will not be made know to the clinician performing neurologist and NCS examinations. A forced-choice procedure will be used, in which the subject must determine which of two posts is vibrating. The coordinator/nurse administering the test will follow a specific algorithm for adjusting the position of the stimulus and amplitude of vibration in order to determine the threshold for perception for each great toe and for the dominant index finger.

All submitted studies will undergo a third party, centralized review to identify and correct, when possible, scoring errors and test administration errors (Figure 1). Normal reference values have been established for this procedure (Appendix A).

### **20.2.3 Neuropathy Specific Quality of Life Assessment**

Although diabetic peripheral neuropathy results in severe morbidity, few studies have assessed the quality of life of patients with diabetic neuropathy. The NeuroQOL is a validated instrument that assesses six primary domains: 1) painful symptoms and paresthesias; 2) symptoms of reduced/lost feeling in the feet; 3) diffuse sensory motor symptoms; 4) limitations in daily activities; 5) interpersonal problems; and 6) emotional burden. Other domains include overall impact of neuropathy and sleep disturbance.

Subjects will be asked to complete the NeuroQoL at the time of their neurology examination and nerve conduction study visit. This is a self-administered instrument that requires approximately 15 minutes to complete.

## **20.3 Autonomic Nervous System Testing (ANS)**

The quantitative measures of autonomic nervous system (ANS) function that were performed in DCCT will be repeated **once in year 13 or 14 and again in year 16 or 17**. These include assessment of RR variation, heart rate response to the Valsalva maneuver, and postural testing. **The Autonomic Symptom Profile (ASP) will be collected at the same visit at which ANS testing is performed.**

RR variation, a measure of sinus arrhythmia during quiet respiration, has been used as an index of cardiovagal autonomic function since 1973. Under carefully standardized conditions without sympathetic activation, RR variation primarily reflects parasympathetic function. The Valsalva ratio evaluates cardiovagal function in response to a standardized increase in intrathoracic pressure (Valsalva maneuver). The increase followed by a decrease in heart rate during and following the Valsalva maneuver is due to cardiovagal response to a reduction followed by an

increase in blood pressure.<sup>13</sup> The Valsalva Maneuver performed with the patient supine results in a variable reduction in venous return, being dependent on the volume status of intrathoracic and abdominal capacitance vessels. Although not as sensitive as RR variation, we will retain the test, since it might detect patients with more severe diabetic autonomic neuropathy. Postural testing involves measuring heart rate and blood pressure before and after assuming an upright posture. A normal response is dependent upon intact baroreceptors. Orthostatic hypotension occurring in the absence of volume depletion is an indication of an abnormal reflex arc involving vascular autonomic insufficiency. It is a marker of severe autonomic neuropathy. Postural hypotension can be affected by volume status of the patient; volume depletion can aggravate or precipitate orthostatic hypotension. A subnormal norepinephrine response to hypotension is indicative of orthostatic hypotension to autonomic neuropathy rather than to volume depletion. This test is relatively insensitive, requires repeat testing on a separate day, and adds little to the information obtained from measurement of heart rate and blood pressures. For this reason, we propose to do postural testing without measurement of catecholamine levels.

The EDIC study coordinator or nurse at each site will be certified to perform ANS testing at a central training session. Arrangements for certification of additional or replacement testers will be made as needed in coordination with the ANS reading center. Subjects may be scheduled for testing in conjunction with their annual EDIC visit, or on a separate date.

Autonomic nervous system measurements will be centrally reviewed for quality control purposes prior to submission for data entry, management, and analysis. The central review will be performed by the certifying EDIC autonomic nervous system tester.

### **20.3.1 Autonomic Symptom Profile (ASP)**

The Autonomic Symptom Profile is a questionnaire focused on autonomic symptoms. Higher scores indicate more or worse symptoms. The instrument has demonstrated an acceptable level of content and criterion validity in domains of orthostatic intolerance, secretomotor dysfunction, male sexual dysfunction, urinary dysfunction, gastroparesis, diarrhea, constipation, pupillomotor dysfunction, vasomotor dysfunction, reflex syncope, and sleep disorder. The ASP is administered in conjunction with ANS testing.

## **20.4 Specific Procedures for Neuropathy Assessment in the EDIC Study**

### **20.4.1 Neurologic History and Physical Examination**

The Neurological History and Physical Examination (EDIC Form 051) should be carried out in a quiet, comfortable room such as an outpatient examining room or an EMG suite. The neurologist's standard neurological examination should be performed. Special attention should be paid to the peripheral nervous system.

The recommended method for testing small-diameter sensory fibers is to begin with evaluation of cold perception. A dense metal object such as the weight at the end of a 128Hz tuning fork serves as a good cold stimulus. The neurologist should begin by asking the patient to compare the temperature of this object as perceived of the dorsum of the foot and the top of the thigh. If the more proximal stimulus is colder, then starting on the dorsum of the toes, the object is slowly moved proximally until the level of change to normal is found. Pinprick should be used to verify this level, since patients without neuropathy may report a change in temperature if they are

examined in a cool room. The level at which the pin prick feels normal (compared with the upper thigh or face), and not just “sharp”, should be recorded. To examine large fiber functions, the ability to detect the direction of the small upward or downward movement of the great toe should be determined, as well as the ability to perceive a low amplitude 128 Hz vibration at the first metatarsal-phalangeal joint—using the neurologist’s personal experience with individuals without neuropathy as a control.

For the most part, strength will be normal in this group of patients. To look for the earliest evidence of distal weakness, the neurologist should test the strength of great toe dorsiflexion (extensor hallucis longus muscle) and the strength of small toe dorsiflexion (extensor digitorum brevis). In addition, one should look for evidence of atrophy of intrinsic foot muscles and evaluate the size of the contracting EHL muscle for atrophy.

Reflexes should be elicited in the neurologist’s usual way. In this study, we will be especially interested in the knee and ankle jerks. Reflexes should be graded as ++++ (very brisk with clonus), +++ (brisk), ++ and + (normal), +/- (elicited only with the Jendrassik maneuver), or 0 (cannot be elicited).

#### **20.4.2 Nerve Conduction Studies**

The choice of EMG machine or electrodes is not standardized. Any modern equipment is accepted, provided that it includes an averager and that photographic or durable paper recording are available. The instrument for temperature measurements should include a surface thermistor and should preferably allow continuous monitoring.

The protocol comprises the following nerve segments:

1. Median nerve.
  - Distal motor latency from wrist to the abductor pollicis brevis muscle. Motor conduction velocity from the elbow to wrist. F-wave latency, stimulating at the wrist.
  - Orthodromic sensory conduction velocity from digit II to wrist. (Note that an orthodromic study, stimulating the digit and recording at the wrist is required, as per the original DCCT protocol.)
2. Peroneal nerve. Distal motor latency from ankle to the extensor digitorum brevis muscle. Motor conduction velocity from capitulum fibulae to ankle. F-wave latency, stimulating at the ankle.
3. Sural nerve. Antidromic sensory conduction study, stimulating the nerve 14 cm proximal to a recording electrode at the lateral malleolus.

#### **Stimulation**

Surface electrodes are used for stimulation. The cathode will be distal. The anode is placed to approximate the course of the nerve. The optimal location of the electrode is determined by moving the cathode in small steps while stimulating the nerve with sub-maximal current. The actual recording should be performed with supramaximal stimulus strength, but not higher than 30% above maximum as judged from the amplitude of the evoked response. A minimal number of stimuli should be applied. The site of stimulation is marked accurately with an easily removed marker.

## Recording

The evoked responses are recorded with surface electrodes. The electrode positions are described below (“Specific Methodology”). For muscle action potential recordings, the “active” electrode is placed so that the potential has a clearly defined negative onset and a maximal amplitude. Only use enough electrode paste to coat the electrode. If the electrode moves during the conduction study, it should be replaced and the entire procedure repeated. To reduce artifacts, the anode may be rotated, the skin dried, excess electrolyte paste removed, bad leads or pin-jacket contacts replaced, the skin under the recording electrode mildly abraded, or recording and stimulating wires kept apart. A ground electrode is placed conveniently between the distal site of stimulation and recording, and it should make an extensive contact with the skin as possible.

The frequency band is inclusive of 2 to 10,000 Hz for muscle potential recordings, and 20 to 20,000 Hz for sensory potential recordings. The time base should be set to give maximal accuracy in latency measurements, and should be the same for distal and proximal stimulation sites. The potential amplification (gain) should be adjusted to prevent clipping of the peaks, and so that amplitudes are at the least 1 cm. Sensory action potentials less than 5 uV in amplitude should be averaged, so that the amplitude is higher than 1 cm and the baseline less than 10% of the signal amplitude. Preferably, the gain should be the same for distal and proximal stimulation sites. F-waves are recorded with supramaximal stimulation and the minimal F-wave latency of eight responses is reported and recorded. The gain is adjusted to clearly identify the response. The site of stimulation and recording and time base and amplification should be clearly indicated on each photographic recording.

### **20.4.3 Specific Methodology - Temperature Control**

Temperatures are measured to the nearest 0.1 degree C after equilibration of the surface thermistor.

There were no significant surface temperature differences between DCCT baseline and the DCCT 5-year test temperatures, and most temperatures were between 31 and 34°C (median value of 33°C in the upper extremities and median temperature of 32°C in the lower extremities.<sup>14</sup> Review of the individual subject surface temperatures, however, revealed numerous outliers, particularly at baseline. Many of the outliers represent non-physiological values, such as temperatures of 16.0°C, a temperature probably representing room temperature, not limb temperature. At the other extreme, several temperatures were recorded as 38.0 °C, a temperature that may be difficult to obtain among this now older group of subjects with diabetic neuropathy. Extreme high temperatures were more frequent at baseline than at closeout. The literature contains several articles related to the effects of surface temperature on nerve conduction results, including one study showing the effects of warming the upper and lower extremities to 37°C among subjects with neuropathy.<sup>15</sup>

Consistent with the DCCT, each investigator will be given the DCCT closeout pre-test and post-test temperatures for each of the nerve conduction study sites.

#### Specific Instructions for Electromyographers related to EDIC limb temperatures:

Temperature measurements are performed with surface thermistors throughout. The temperature is recorded before (pre-test) and after (post-test) the actual nerve conduction study

in each nerve and both values are reported. As done in the DCCT, the pre-test and post-test temperatures for each site will be averaged.

Study coordinators at each site will provide the Electromyographer with limb temperatures (pre- and post-testing) from the DCCT closeout exam for each subject. Close-out temperatures for all subjects are available to study coordinators through the DCCT/EDIC web site. The warming (or passive cooling) instructions are as follow:

For DCCT closeout temperatures between **28.0 °C and 37.0 °C** (pre-test), individual studies in EDIC should be performed with pre-testing surface temperatures as similar as possible to prior (DCCT closeout) recordings, to the extent that it is safe and practical to do so. This may require passive cooling or warming using the technique used at the local site.

If the DCCT closeout temperature was **less than 28.0 °C** (pre-test) and the subject already exceeds that temperature, the subject can be allowed to passively cool as reasonable, but not below 28 °C. If the subject's temperature is below the DCCT temperature, the subject should be warmed to approximate the DCCT temperature.

If the DCCT closeout temperature **exceeded 37.0 °C** (pre-test) and the subject's temperature is lower, warm the limb if it is safe to do so, **but do not warm beyond 37.0 °C**. If the subject's current surface temperature already exceeds 37.0 °C proceed without additional warming, even if the DCCT closeout temperature was higher. The clarification is consistent with the intent of the original protocol but emphasizes care to avoid injuring the skin. In this context, the absolute temperature is not as relevant as the means of attaining that temperature (e.g., gradual warming by submerging the limb versus more rapid forms of warming by a heat lamp).

Note that the nerve conduction velocities should be reported as the actually recorded values without temperature corrections. A centralized temperature correction of data may be considered for final analysis. As done in the DCCT, the pre-test and post-test temperatures for each site will be averaged.

Temperatures are measured at the following sites:

1. Median nerve:
  - Motor - on the forearm over the nerve, midway between the wrist and elbow.
  - Sensory - on the palm between digit II and the wrist.
2. Peroneal Nerve: Over the anterior tibial muscle between the knee and ankle.
3. Sural nerve: On the calf midway between the sites of stimulation and recording.

#### **20.4.4 Specific Methodology - Measurements**

**Inter-electrode distances and pre-test temperatures should be recorded before the test is begun. Post-test temperatures should be recorded after the test is concluded, regardless of whether a response to stimulus was detected. Temperatures and distances should NEVER be reported as zero, and should be missing ONLY if the test was not attempted.**

Motor latencies are measured to the onset of the negative portion of the compound muscle action potential with an accuracy of 0.1 msec. Sensory latencies are measured to the onset of the negative peak of the compound nerve action potential with an accuracy of 0.1 msec. The amplitude of compound muscle action potentials is measured from the baseline to the peak of the negative portion of the potential.

The sensory potential amplitude is measured from the baseline (or the onset of the initial negative deflection) to the negative peak. The accuracy is 0.1 mV and 1  $\mu$ V for muscle and sensory nerve action potentials, respectively. All measurements of latency and amplitude in a given nerve are made with the same gain and sweep speed. In the sural nerve, absence of a response will mean that no potential could be detected despite stimulation in a series of contiguous steps along the postero-lateral half of the calf, and despite averaging of 32 responses.

**Amplitudes are reported in millivolts (mV) for motor nerves, microvolts ( $\mu$ v) for sensory nerves.**

Distances will be measured to the nearest mm with flexible tape, approximating the course of the nerve. The distance of proximal nerve segments is from the centers of the cathodes at the proximal and distal site of stimulation. The distance of distal nerve segments is from the center of the distal stimulation cathode to the center of the active recording electrode.

**All distances should be reported in millimeters. Distances should be measured as exactly as possible using a flexible tape measure and reported precisely as measured to the nearest millimeter (not rounded to the nearest 5 or 10 mm). The electrodes should be place as close as possible to the locations used the last time the patient was tested.**

**Reporting unelicitable responses:**

**If no response is detected in the test of conduction velocity and amplitude, enter “NR” for latency and conduction velocity and “0” (zero) for amplitude.**

**If no response is detected in an F-wave study, enter “NR” for F-wave latency.**

**In all cases, record the post-test skin temperature.**

**In summary, NO ITEMS SHOULD BE LEFT BLANK unless a test was not attempted, in which case ALL relevant items should be left blank. Zero is an acceptable value ONLY for amplitude.**

#### **20.4.5 Report of Data**

Data from nerve conduction studies are reported on EDIC Form 52. All spaces must be filled out at each examination. The form should be accompanied by photographic recordings of the evoked response, mounted on white paper. All sheets with recordings must be clearly identified with the patient's EDIC identification number and each recording should give the name of the nerve, the gain, and sweep speed. In addition, an extra set of recordings should be filed in each

laboratory. Reports and recordings are given to the EDIC study coordinator, who will forward the reports to the data coordinating center.

### **Rounding Instructions for EDIC Nerve Conduction Studies Values**

All nerve conduction study values are to be rounded to the level indicated on the data form (e.g., motor amplitudes to the nearest 0.1 mv, sensory amplitudes to the nearest microvolt, all latencies to the nearest 0.1 ms, conduction velocities (calculated from the properly rounded latencies) to the nearest 0.1 M/sec, and temperatures to the nearest 0.1 °C.

Proper rounding is performed after dropping all but one of the digits following the rounding digit; if the digit following the rounding digit is  $\geq 5$ , round up by adding one to the rounding digit; if the digit following the rounding digit is  $< 5$ , do not change the rounding digit

The rounding "rules" are as follow:

1. Find the place value you want (the "rounding digit") and look at the digit just to the right of it.
2. If that digit is greater than or equal to five, add one to the rounding digit and drop all digits to the right of it.
3. If that digit is less than 5, do not change the rounding digit but drop all digits to the right of it.

Examples:

1. Rounding 3.64999 to the nearest 0.1 is performed by reducing the number to 3.64 ("4" is the number to the right of the rounding digit) - the "rounded value is 3.6 (no reason to change the rounding digit).
2. Rounding 3.65999 to the nearest 0.1 is performed by reducing the number to 3.65 (in which case "5" is the digit to the right of the rounding digit) and then rounding up to 3.7 (by adding one to the rounding digit).
3. Rounding 3.4999 to the nearest integer is performed by reducing the number to 3.4 - the "rounded" value is 3
4. Rounding 3.5111 to the nearest integer is performed by reducing the number to 3.5 - the "rounded" value is 4

### **20.4.6 Specific Methodology – Electrode Placement**

#### *Median Nerve - Motor*

Stimulating electrodes: Distal – the cathode is placed two (2) cm proximal to the distal wrist crease and between the flexor carpi radialis and palmaris longus tendons (in cases where multiple wrist creases are identified, the cathode is placed relative to the most distal wrist crease). The anode is proximal and should be rotated laterally to minimize spread of current to the ulnar nerve. Proximal – the cathode is on the anterior surface of the upper arm between the biceps tendon and the medial epicondyle of the humerus, immediately over the brachial artery. The anode is proximal and should approximate the course of the nerve.

Recording electrodes: The "active" electrode is placed over the abductor pollicis brevis muscle one-third of the distance between the most distal wrist crease and the

metacarpal – phalangeal joint of the thumb. The “inactive” electrode is placed just distal to and on the anterior surface of the metacarpal-phalangeal joint of the thumb.

Ground electrode: A ground electrode is placed conveniently between the distal site of stimulation and the recording electrode.

#### *Median Nerve - Sensory*

Stimulating electrodes: Ring electrodes are wrapped around the index finger (digit II). The cathode is wrapped around the middle of the proximal phalanx of the index finger. The anode is wrapped around the middle of the middle phalanx of the index finger. Cotton is used to separate the index and middle fingers so that the stimulating electrodes do not touch the middle finger.

Recording electrodes: The sensory nerve action potential is recorded longitudinally with the same electrode position as used for stimulation of median nerve motor fibers at the wrist. (Again, if multiple wrist creases are present, the electrode is placed 2 cm proximal to the most distal wrist crease).

Ground electrode: Same as for median nerve - motor

#### *Peroneal Nerve - Motor*

Stimulation electrodes: Distal – the cathode is placed on the anterior aspect of the ankle, lateral to the tendon of the anterior tibial muscle and 5 cm proximal to the lateral malleolus. The anode is proximal along the course of the nerve. Proximal – the cathode is placed behind the neck of the fibula, just proximal to where the nerve enters the anterior compartment. The anode is proximal, approximating the course of the nerve.

Recording electrodes: The “active” electrode is placed over the extensor digitorum brevis muscle one cm distal to its bony origin. The “inactive” electrode is placed over the lateral aspect of the distal end of the fifth metatarsal bone.

Ground electrode: A ground electrode is placed conveniently between the distal stimulating electrode and the recording electrode.

#### *Sural Nerve - Sensory*

Stimulating electrodes: The cathode is placed on the calf 1 to 3 cm lateral to the midline, and 14 cm proximal to the center of the “active” recording electrode. The anode is proximal and the position adjusted to minimize the stimulus artifact.

Recording electrodes: The “active” electrode is placed immediately behind the lateral malleolus. The “inactive” electrode is placed 4 cm distal to the “active” electrode along the course of the nerve.

Ground Electrode: A ground electrode is placed between the stimulating and the recording electrodes, just proximal to the “active” recording electrode.

## **20.5 ANS Testing Procedures**

### **20.5.1 Subject Eligibility**

The study coordinator will complete the ANS testing eligibility form (EDIC form 55) when the subject arrives for testing (Figure 2). Because autonomic function is altered by a variety of factors including eating, coffee, smoking, hypoglycemia, and a variety of over-the-counter and prescription medicines including insulin, subjects will be asked to avoid these factors (save for their usual basal insulin regimen) for at least 8 hours before the ANS studies. If the answer to any question on the form is “yes”, the patient will be ineligible for ANS testing that day and must be rescheduled. See Appendix A for guidelines related to deviations from test eligibility requirements

### **20.5.2 Specific ANS Test Procedures**

Upon verification of eligibility, the subject is placed in the supine position and must remain supine for 30 minutes. During this time, the three ANS electrodes are placed on the subject’s upper torso and the recording device is activated to verify capture of the subject ECG. Test procedures are reviewed with the subject, who is also given the opportunity to practice using the respiration pacer.

After the subject has been supine for 30 minutes, the ANS testing may begin (note, the subject should be relatively undisturbed for at least 10 minutes prior to the start of ANS testing). Three tests are performed: RR variation during slow deep breathing, postural testing, and heart rate response to Valsalva testing.

#### **RR variation**

The RR heart rate variation measure is a 6-minute test during which the patient breathes at a fixed rate with the aid of the respiration pacer. The test is performed with the patient in the supine position the entire 6 minutes and is followed by the postural study, during which the patients stands for 10 minutes.

Before the RR variation study begins, the tester must fully complete the ANS Testing Eligibility Form (EDIC Form 55), and the patient must rest in the supine position for 30 minutes. During the 30 minutes, the patient will receive instruction on how to perform the test. S/He will be given the Respiration Pacer to be held at a comfortable angle for viewing and told to inhale as the lights are ascending on the pacer and to exhale as the lights are descending. The pacer is timed for five breaths per minute and the patient must be told to “pace” themselves with the lights – inhaling as the lights ascend and exhaling as the lights descend. S/He must be informed that the test will last for 6 minutes and inhaling and exhaling as the lights go up and down is mandatory for that time period. The patient must understand that s/he must stand after the 6 minutes to complete the 10-minute postural study. The patient will not need to breathe with the Respiration Pacer during the postural study, but must stand still and have blood pressure measurements at fixed time periods. After receiving instructions, the patient is allowed to practice breathing with the Respiration Pacer prior to the start of actual testing. The tester must ready all test equipment during the 30 minutes of rest.

When the patient understands the method of the test, s/he will begin the fixed breathing when prompted by the examiner.

Throughout the study, the patient must be watched carefully to insure s/he is always pacing his/her breathing pattern with the Respiration Pacer. The tester must be positioned so s/he can look across the patient's chest and see the pacer to watch that the rise and fall of the chest cavity matches the rise and fall of the lights on the pacer and be able to observe the computer screen to verify the ECG signal, and monitor the time of testing. Encouragement can be given to the patient to continue complying with the Respiration Pacer, and the patient can be told how much longer s/he has before the RR variation test is completed.

If at any time during the RR variation study the patient fails to inhale and exhale properly, (i.e., getting the inhaling and exhaling backwards, falling asleep, talking, etc), the test must be stopped and restarted. A rest period is not required for a restart of the RR variation test.

At the end of the 6 minutes, the patient blood pressure must be taken and recorded on form 55.

Blood pressure is measured while the patient is supine, just prior to the start of the 6-minute R-R variation test, and again just after the R-R test. Blood pressures are measured on the right arm, unless contraindicated.

### Postural Study

The postural study is a 10-minute test during which the patient stands in place while blood pressures are recorded at specified times. The postural test will always immediately follow the RR variation study.

Upon the completion of the 6-minute RR variation study, the patient is instructed to breathe ad libitum. She will not need to breathe with the respiration pacer during the 10-minute postural study. The patient must then stand when prompted by the examiner, being careful not to detach the ECG leads or their connectors. The examiner will mark the start of standing on the ANS recording. The tester should observe the ECG monitor to ensure that the heartbeat is being captured, and that the ECG leads have not been displaced. Heart rate is recorded only during the first minute of standing. Only blood pressure is monitored for the duration of the 10 minute test.

The patient's blood pressure is taken at 1, 2, 3, 4, 5, and 10 minutes into the study. Blood pressures are recorded on Form 55.

If the postural study is being done without the RR variation study preceding it, the patient must rest in the supine position for 30 minutes. Blood pressure should be measured and recorded just prior to standing. Recording should begin prior to standing, and the start of standing marked. Blood pressures are recorded 1, 2, 3, 4, 5, and 10 minutes after the start of standing.

The patient should be watched carefully during the postural test for signs of hypotension. The tester should have help available in case the patient faints. **IF A DROP OF MORE THAN 10 mmHg IN THE DIASTOLIC BLOOD PRESSURE OCCURS, AND THE PATIENT IS SHOWING OBVIOUS SIGNS OF POSTURAL HYPOTENSION, THE PATIENT MUST BE PLACED IN THE SUPINE POSITION IMMEDIATELY.** As soon as the patient is comfortable, the test can be stopped. Postural hypotension, if it occurs, is noted on form 55.

### Valsalva Maneuver

Following the RR variation and postural studies, the patient must rest in the supine position for 15 minutes. During this time, the Valsalva maneuver will be explained. The patient will remain in the supine position for two Valsalva studies, and the 5-minute resting period between the two studies. The first minute of the test the patient will lie still and breathe ad libitum. Then, the patient will be asked to blow into the mouthpiece of the Valsalva apparatus for 20 seconds, holding the gauge on the Sphygmomanometer at 40 mmHg. After the 20-second blowing period, the patient will again breathe ad libitum for 1 minute thus concluding the study. The patient is allowed to practice the blowing period before the first Valsalva is performed. During the test blowing period, the tester needs to watch the ECG monitor to ensure that the ECG is being captured, and make any adjustments.

When the patient is ready for the study, the tester will begin recording the heart rate for 1 minute. Just prior to the end of that minute, the tester will ask the patient to take a deep breath and begin blowing into the mouthpiece of the Valsalva apparatus. An event marker (spacebar) is placed to signal the start of blowing. After 20 seconds, the subject is instructed to stop blowing and another event marker is placed to signal the end of the 20-second period. An additional 1 minute of ad libitum breathing is recorded. Event markers are placed at the actual start and actual cessation of blowing by the patient, (even if the full 20 seconds has not elapsed).

During the blowing period, the tester must watch the gauge of the sphygmomanometer to ensure that once the pressure reaches the 40 mmHg, the patient keeps it as close to that mark as possible for the remainder of the blowing period. Praise and encouragement should be given to the patient to successfully complete the blowing period.

If a patient does not complete the full 20-second blowing period on both Valsalvas, the test should be restarted with a 5-minute rest period between attempts, until two good Valsalvas are recorded (Appendix C). See Appendix B for minimum acceptability requirements for Valsalva studies. On a normal testing day, when the examiner has obtained at least 2 complete Valsalva studies, ANS testing for the patient is complete.

At the conclusion of Valsalva testing, tubing assembly for the Valsalva apparatus is disconnected from the manometer, the single use mouthpiece discarded and the tubing assembly is disinfected prior to subsequent subject tests (Appendix D).

#### **20.5.3 Valsalva Maneuver in Patients with PDR**

**All patients who are known to have PDR are excused from the Valsalva portion of ANS testing. This is not a local option.**

#### **20.5.4 Recording, Documentation and Mailing**

EDIC form 55 is used to document subject eligibility or preparedness for ANS testing, as well as the outcome of each test component. The form also provides space for recording problems or errors that may have been encountered during the course of testing. Examiners are encouraged to record all protocol deviations, problems or other significant events that occur during testing as this information will aid the reading center when analyzing the data. Each ANS study must be accompanied by form 55.

Form 55 must also be completed when submitting normal control studies and for certification studies. (Normal control studies are done on healthy, non-diabetics in order to establish normative reference values. Certification studies are done for practice and for proof of competency of new technicians.) If the study is a normal control or certification study, the subject ID field of form 55 is not completed, but “NORMAL” or “CERTIFICATION” is written next to the ID line.

ANS studies are recorded electronically, and transmitted to the ANS reading center via secure FTP server, or mailed to the reading center as a data CD. Files are to be named using the following convention; Clinic ID(space) Subject ID(space) Test Date (mmddyyyy).mdb. For example, subject 99510 tested at clinic 42 on March 14, 2006 would have the file names 42 99510 03142006.mdb.

Clinics need to make sure that an electronic copy of each ANS study is maintained locally.

Transmission to the reading center via FTP server is preferred. Once a file is placed in the FTP server, the site must fax form 55 and appropriate mailing list to the reading center, and also send an email to the reading center to alert them to the presence of the file. Sites that cannot access the FTP server may submit studies via CD. Form 55 and the mailing list must accompany all studies recorded on a data CD and submitted to the reading center by surface mail. CD's must be labeled with the clinic number, subject ID number, subject initials and date of the study.

Copies of all forms are retained at the clinic, and a separate copy submitted to the data coordinating center in the monthly forms mailing.

At the time of writing, documentation of ANS mailings and Nerve Conduction Study mailings are recorded on form 59. In the future, other methods of recording or tracking studies mailed to reading centers may be put into place.

## **20.6 Quantitative Sensory Testing - Vibration Perception Testing (VPT)**

### **20.6.1 Patient Preparation**

There is no advance preparation required for this test. Explain to the subject that the test is being done to evaluate his or her ability to detect different levels of sensation (in this case, vibration) on one index finger and one great toe. The patient will remove his or her shoe and sock from the foot to be tested. The subject's hand and foot on the dominant side is tested, unless the extremity is not available (for example, due to amputation, injury, etc). Tests are performed unilaterally, on the subject's dominant side. If either extremity on the dominant side is not available, the non-dominant side may be tested and this must be indicated on the testing form (EDIC form 054).

Give the subject a brief period (1-2 minutes) to become comfortable and familiar with the stimulus. Subjects are instructed to press the digit being tested (index finger, then great toe) lightly against each rod in the sequence (A then B) for about 1 second. Tell the subject that only one rod will be vibrating during each trial, and they may only touch each rod once. Tell the subject that the task will become increasingly difficult and that they should make their best “guess” if s/he is not certain. Make sure that the subject knows how to touch the post with the toe – with the fleshy part of the toe and with sufficient pressure to cause the nail to blanch

slightly. Only the digit being tested should touch the rod; no part of the foot should contact the box.

### **20.6.2 Equipment**

The Vibratron II device will be used. The vibration control device is placed on a firm surface, plugged in, and turned on. It should be positioned so that the subject cannot see the control readout or position switches. The vibration units (labeled A and B) are placed on a solid, non-mobile table (for testing the finger) or floor (when testing the toe). Vibration damper pads provided with the device are placed under each vibration unit.

### **20.6.3 Test Algorithm for VPT**

Set the stimulus to either rod A or B using the stimulus grid in EDIC form 054. A separate grid is provided for testing the finger and the great toe. Index finger testing is started at 7.0 stimulus units and great toe testing at 9.6 stimulus units. These levels should give most subjects an opportunity to correctly identify the stimulus in the first 6 to 8 trials. If the subject correctly identifies the stimulus, circle the corresponding letter on the grid. If the subject's choice is incorrect, slash through the corresponding letter. Testing proceeds by moving down one row following each correct response, and diagonally up and to the right after each incorrect response. Testing continues in this manner for a minimum of 18 trials. If the subject incorrectly identifies 5 stimuli in the course of the first 18 trials, the test of that digit is complete. Otherwise, continue until the subject makes a total of 5 errors. If the subject reaches the maximum vibration intensity of 20 prior to completing 18 trials, continue testing at the maximum vibration until 18 trials have been administered. Trials at  $\leq 1.0$  vibration units should be repeated regardless of the response (correct or incorrect). To repeat a trial at  $\leq 1.0$  vibration units, move horizontally to the right (Figure 3 – example of grid marking and scoring).

Persons administering the test are cautioned to not give any visual or verbal clues to the subject. Subjects are reminded that if they are not certain about which rod is vibrating, they should guess. They are not to place their digit on either rod more than one time per trial.

### **20.6.4 Recording Results**

Once the subject has completed the minimum of 18 trials and has incorrectly identified 5 vibration stimuli, the test is complete. Record the vibration units corresponding to the first five errors in the appropriate column on page one of form 054. Record the five lowest correct vibration units in the appropriate column on page one of form 054. The form is submitted for scoring, with a copy retained in the clinic files. Scoring of vibration perception threshold is done by omitting the highest and lowest value of all 10 values recorded (the 5 errors and the 5 lowest correct), and then calculating the mean of the remaining 8 values.

## **20.7 NeuroQOL and Autonomic Symptom Profile Questionnaires**

The NeuroQOL (EDIC form 058) is given to the subject to complete **with the Peripheral Nervous System Tests (Table 1)**. The Autonomic Symptom Profile (ASP, EDIC form 057) is **to be completed with the Autonomic Nervous System Tests (Table 1)**. Once completed, the forms are mailed to the DCC in the clinic monthly mailing. A copy of each questionnaire is retained in the clinic file.

## 20.8 Clustering of Peripheral and Autonomic Nervous System Tests

While it is ideal to complete all neurological procedures at one annual visit, this may not be possible. If subjects must spread the examinations out across two consecutive annual visits, the tests should be clustered so that peripheral nerve measures are kept together, and autonomic nerve measures are kept together (Table 1).

<u>Peripheral Nervous System Tests</u>	<u>Autonomic Nervous System Tests</u>
Neurological History and Examination	Autonomic Nervous System Testing
Nerve Conduction Studies	R-R
Vibration Perception Threshold Testing	Postural Study
NeuroQOL	Valsalva
	Autonomic Symptom Profile

## 20.9 Guidelines for Peripheral and Autonomic Assessments in Pregnant EDIC Subjects

There are no foreseeable risks to either pregnant women or to their unborn children from either the autonomic testing, or peripheral nerve conduction studies performed during in the EDIC study.

However, pregnancy, beyond the first trimester has significant potential effects on standing blood pressure as well as other [autonomic] indices. Therefore, ANS testing should not be performed on pregnant subjects after the first 4 months.

Furthermore, pregnancy is associated with an increased incidence of carpal tunnel syndrome. Since the median nerve latency (sensory or motor) constitutes 1 of the 2 abnormalities required to diagnosis sub-clinical or confirmed neuropathy, the nerve conduction studies should be deferred until post-partum, to reduce the likelihood of introducing a confounding finding.

## 20.10 The Michigan Neuropathy Program

### 20.10.1 The Michigan Neuropathy Screening Instrument (MNSI)

The Michigan Neuropathy Screening Instrument (MNSI) is the initial component of the Michigan Neuropathy Program. It is a simple 2-step screening and staging program to diagnose and grade the severity of diabetic neuropathy (Diabetes Care, submitted). The Michigan Neuropathy Screening Instrument (MNSI) is designed to screen patients in an office setting by general practitioners or physician extenders for the presence of diabetic neuropathy. The first part of the screening instrument consists of 15 self-administered "yes or no" questions on foot sensation including pain, numbness and temperature sensitivity. The questions were chosen from among those in the Neuropathy Screening Profile of Peter Dyck that showed the highest degree of specificity and sensitivity for diabetic neuropathy among normal subjects and those with a variety of neuromuscular disorders (Neurology, 36:1300-1308, 1986). The second part of the MNSI is a brief physical examination involving 1) inspection of the feet for deformities, dry skin, hair or nail abnormalities, callus or infection, 2) semi-quantitative assessment of vibration sensation at the dorsum of the great toe and 3) grading of ankle reflexes. Patients screening

positive on the clinical portion of the MNSI (greater than 2 points on an 8 point scale) are considered neuropathic.

The MNSI will be administered yearly to track neuropathic symptoms, identification of foot problems, and assessment of sensory function. This is consistent with existing clinical guidelines for the management of diabetic patients. Patients screening positive on the MNSI during EDIC may undergo the full Michigan Neuropathy Program (consisting of a quantitative neurological examination and nerve conduction studies), which will confirm, stage, and grade the severity of the neuropathy.

### **20.10.2      Administration of the MNSI**

#### Questionnaire:

The questionnaire is self-administered by the patient.

#### The Michigan Neuropathy Screening Instrument (MNSI):

For all assessments, the foot should be warm (> 30°C).

Foot Inspection: The feet are inspected for evidence of excessively dry skin, callus formation, fissures, frank ulceration, or deformities. Deformities include flat feet, hammertoes, overlapping toes, halux valgus, joint subluxation, prominent metatarsal heads, medial convexity (Charcot foot), and amputation.

Vibration sensation: Vibration sensation should be performed with the great toe unsupported. Vibration sensation will be tested bilaterally using a 128 Hz tuning fork placed over the dorsum of the great toe on the bony prominence of the DIP joint. Patients, whose eyes are closed, will be asked to indicate when they can no longer sense the vibration from the vibrating tuning fork.

In general, the examiner should be able to feel vibration from the hand held tuning fork for 5 seconds longer on his distal forefinger than a normal subject can at the great toe (e.g., examiner's DIP joint of the first finger versus the patient's toe). If the examiner feels vibration for 10 or more seconds on his or her finger, then vibration is considered decreased. A trial should be given when the tuning fork is not vibrating to be certain that the patient is responding to vibration and not pressure or some other clue. Vibration is scored as 1) present if the examiner senses the vibration on his or her finger for < 10 seconds, 2) reduced, if sensed for > 10 or 3) absent (no vibration detection).

Muscle stretch reflexes: The ankle reflexes will be examined using an appropriate reflex hammer (e.g., Tromner or Queen square). The ankle reflexes should be elicited in the sitting position, with the foot dependent and the patient relaxed. For the reflex, the foot should be passively positioned and the foot dorsiflexed slightly to obtain optimal stretch of the muscle. The Achilles tendon should be percussed directly. If the reflex is obtained, it is graded as present. If the reflex is absent, the patient is asked to perform the Jendrassic maneuver (i.e., hooking the fingers together and pulling). Reflexes elicited with the Jendrassic maneuver alone are designated "present with reinforcement". If the reflex is absent, even in the face of the Jendrassic maneuver, the reflex is considered absent.

10 Gram Filament: For this examination, it is important that the patient's foot be supported (i.e., allow the sole of the foot to rest on a flat, warm surface). The filament should initially be prestressed (4-6 perpendicular applications to the dorsum of the examiner's first finger). The filament is then applied to the dorsum of the great toe midway between the nail fold and the DIP joint. Do not hold the toe directly. The filament is applied perpendicularly and briefly (< 1 second) with an even pressure. When the filament bends, the force of 10 grams has been applied. The patient, whose eyes are closed, is asked to respond yes if he or she feels the filament. Eight correct responses out of ten applications is considered normal; one to seven correct responses indicates reduced sensation and no correct answers translates into absent sensation.

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<sup>2</sup> Feldman EL, Stevens MJ, Russell JW, Greene DA. Diabetic neuropathy. In: Principles and Practice of Endocrinology and Metabolism, 3rd edition, Becker KL, ed., Lippincott Williams & Wilkins, pp. 1391-1399, 2001

<sup>3</sup> Hilsted J and PA Low. Diabetic Autonomic Neuropathy. In: Clinical Autonomic Disorders, 2nd ed. Ed. P.A. Low. 1997. Lippincott-Raven Publishers, Philadelphia, p. 487-507.

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<sup>6</sup> The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Retinopathy and Nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. N Engl J Med 1993;342:381-389.

<sup>7</sup> The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Effect of intensive therapy on microvascular complications of type 1 diabetes mellitus. Journal of the American Medical Association 2002; 287: 2563-2569.

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<sup>9</sup> Martin CL, Albers JW, Herman WH, Cleary P, Waberski B, Greene DA, Stevens MJ, Feldman EL, The Diabetes Control And Complications Trial/Epidemiology Of Diabetes Interventions And Complications (DCCT/EDIC) Study Group. Neuropathy among the Diabetes Control and Complications Trial cohort eight years after trial completion. Diabetes Care. 2006; 29, 340-344.

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- <sup>11</sup> American Diabetes Association. Report and recommendations of the San Antonio Conference on diabetic neuropathy. *Muscle Nerve* 1988;11:661-667.
- <sup>12</sup> Boulton AJ, Vileikyte L. The diabetic foot: the scope of the problem. *J Fam Pract* 2000;49:S3-S8.
- <sup>13</sup> Korner PI, Tonkin AM, Uther JB: Reflex and mechanical circulatory effects of graded Valsalva maneuvers in normal man. *J Appl Physiol* 1976; 40: 434-440.
- <sup>14</sup> The Diabetes Control and Complications Trial Research Group. Effect of intensive diabetes treatment on nerve conduction in the Diabetes Control and Complications Trial. *Annals of Neurology* 1995; 38(6):869-880.
- <sup>15</sup> Franssen H, Notermans NC, Wieneke GH. The influence of temperature on nerve conduction in patients with chronic axonal polyneuropathy. *Clin Neurophysiol* 1999;110:933-940.

Figure 1. Overview of Data Verification Process for Vibration Perception Threshold Testing

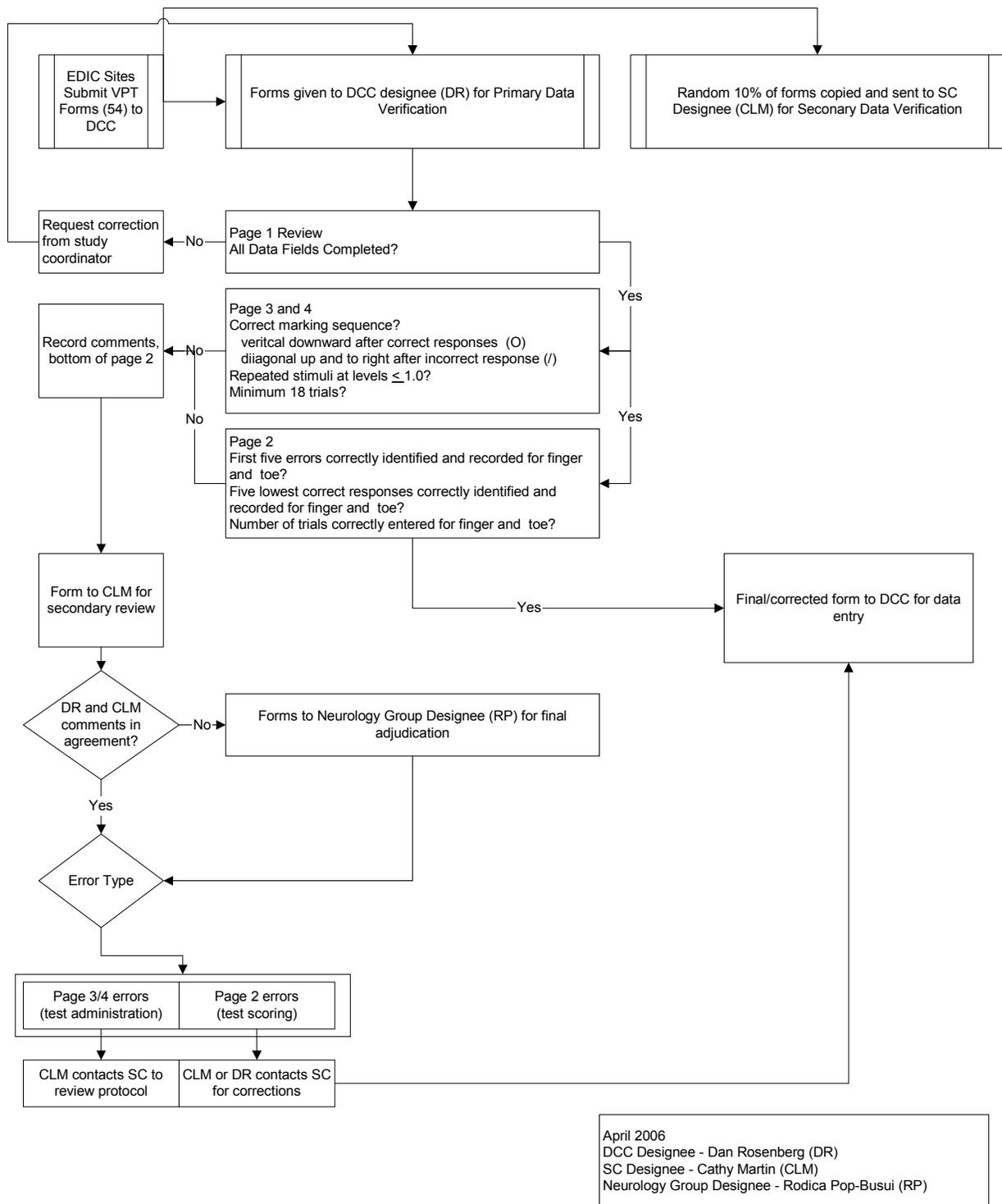


Figure 2. Overview of ANS Eligibility and Test Sequence

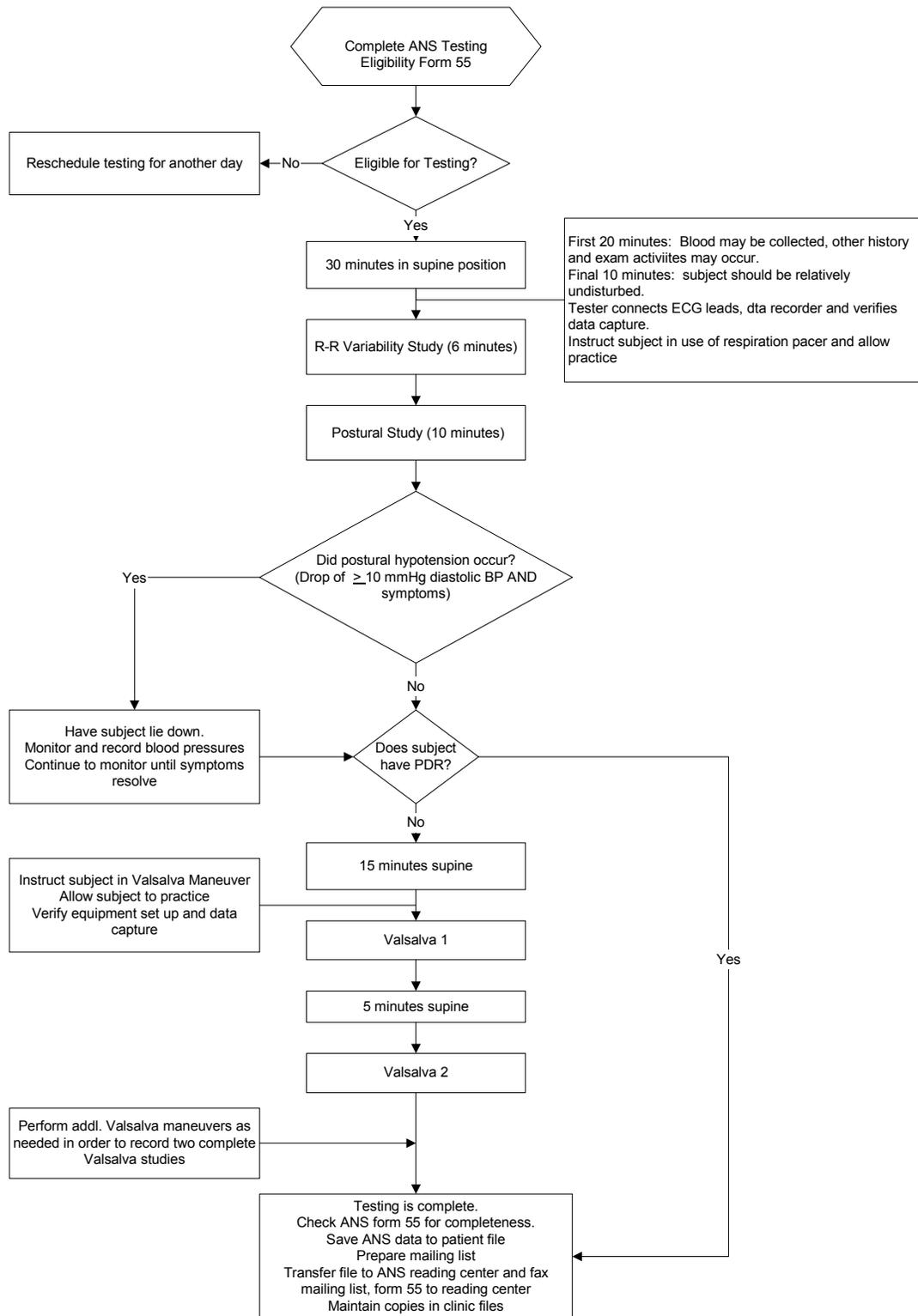


Figure 3: Example of Marking and Scoring the VPT Grid

After each correct response (O), the examiner moves vertically down the column. After each incorrect response (I), the examiner moves diagonally upwards and to the right. In this sample test of the dominant index finger, the minimum of 18 consecutive trials are administered. The **first five errors** occur at vibration intensities of 2.0, 1.3, 0.9, 0.8, and 0.8. The **five lowest correct** vibration intensities are at 0.8, 0.9, 0.9, 0.9, and 0.9. Note that stimuli at or below 1.0 vibration units are repeated (a horizontal move to the right) and the second response determines whether subsequent moves are to lower (following correct response) or higher (after incorrect response) vibration units. These responses are recorded on page 2 of EDIC form 58 as shown below the sample grid:

11.0	B	A	A	B	B	A	A	B	B	A	A	A	B	B	A	B	B	A	B	A	B
10.6	B	A	A	B	B	A	A	B	B	A	A	A	A	A	B	A	A	A	A	A	B
9.6	A	B	A	B	A	A	A	A	B	A	B	A	B	B	A	A	A	A	A	A	A
8.6	B	B	B	B	A	A	A	A	B	B	B	A	B	B	B	B	A	A	A	A	A
7.7	A	A	B	A	A	A	B	A	B	A	B	A	A	B	B	B	B	B	A	A	A
7.0 (start)	<u>A</u>	B	A	B	B	B	B	A	B	A	B	A	A	A	B	A	A	A	A	A	B
6.3	<u>A</u>	A	A	A	A	B	A	A	B	B	B	A	A	B	B	A	A	B	B	A	A
5.6	<u>A</u>	A	A	B	A	A	B	B	B	A	B	B	B	A	A	B	A	A	A	A	B
5.1	<u>B</u>	A	A	B	A	B	A	A	A	A	B	B	A	A	A	B	A	A	A	A	B
4.6	<u>A</u>	A	B	B	A	B	B	B	B	A	B	B	B	A	A	A	A	A	B	A	A
4.1	<u>A</u>	A	A	A	A	A	A	A	A	B	B	A	A	B	A	A	A	A	B	B	A
3.7	<u>B</u>	B	B	A	A	B	A	A	A	B	A	A	A	B	A	A	A	A	B	B	B
3.3	<u>A</u>	A	A	B	A	A	B	B	A	B	A	B	A	A	B	B	A	B	A	A	A
3.0	<u>B</u>	B	B	B	B	A	B	B	B	A	B	A	A	B	B	A	A	B	A	A	A
2.7	<u>A</u>	A	B	A	A	A	B	A	A	A	A	B	B	A	A	A	A	A	B	A	A
2.4	<u>B</u>	B	B	B	A	A	B	B	A	A	A	A	A	A	A	A	A	A	B	B	A
2.2	<u>A</u>	<u>A</u>	A	B	A	A	B	B	B	B	A	A	A	B	B	A	B	B	B	B	B
2.0	<del>B</del>	<u>A</u>	A	B	B	A	B	A	A	A	A	B	A	A	A	A	A	A	A	B	B
1.8	A	<u>B</u>	A	A	A	A	B	A	A	B	A	A	A	A	A	A	B	A	A	A	A
1.6	A	<u>B</u>	B	A	B	A	A	B	A	A	B	B	B	B	B	B	A	A	A	B	B
1.4	A	<u>B</u>	<u>B</u>	A	A	B	A	B	A	A	A	B	A	A	A	A	B	A	A	A	A
1.3	B	<del>B</del>	<u>B</u>	B	A	B	B	A	B	A	B	A	B	A	A	A	A	B	A	A	A
1.2	A	B	<u>A</u>	B	A	B	B	B	A	A	B	A	A	B	B	B	A	B	A	B	A
1.1	B	A	<u>B</u>	A	A	A	A	A	B	A	A	B	B	A	B	A	B	B	B	B	A
1.0	B	A	<u>B</u>	<u>A</u>	A	<u>B</u>	<u>A</u>	<u>B</u>	A	A	A	A	B	B	B	B	B	A	A	A	B
0.9	B	B	B	<u>B</u>	<del>B</del>	B	<u>B</u>	<u>B</u>	B	<u>B</u>	<u>A</u>	B	B	B	B	B	B	A	A	A	A
0.8	A	B	B	A	B	A	A	<u>A</u>	<del>B</del>	A	<del>B</del>	B	B	B	B	B	A	A	A	A	A
0.7	B	B	B	B	B	A	B	A	B	B	B	B	A	A	A	B	A	B	B	B	B
0.6	A	B	B	A	B	B	A	A	A	A	A	A	B	A	A	B	B	A	B	A	A

Form 54, Page 2

Index Finger

- |     |                     |    |                         |
|-----|---------------------|----|-------------------------|
| 3a. | Number of trials:   | 18 |                         |
|     | First 5 Errors      |    | Lowest Correct          |
|     | (Vibration Units)   |    | (Vibration Units)       |
| 4a. | <u>0</u> <u>2.0</u> |    | 4b. <u>0</u> <u>0.8</u> |
| 5a. | <u>0</u> <u>1.3</u> |    | 5b. <u>0</u> <u>0.9</u> |
| 6a. | <u>0</u> <u>0.9</u> |    | 6b. <u>0</u> <u>0.9</u> |
| 7a. | <u>0</u> <u>0.8</u> |    | 7b. <u>0</u> <u>0.9</u> |
| 8a. | <u>0</u> <u>0.8</u> |    | 8b. <u>0</u> <u>0.9</u> |

## Appendix A

### Reference Values for Vibration Perception Threshold (VPT) Testing.

The following is taken directly from the booklet “Quantitative Sensory Testing of Vibration Threshold Vibratron II Rationale and Methods” Prepared by J.C. Arezzo, Albert Einstein College of Medicine, Bronx, New York, for Physitemp Instruments, Inc. 154 Huron Avenue, Clifton, New Jersey. The booklet was included with each Vibratron II Instrument sent to EDIC sites. The EDIC study is using a Two Alternative Forced Choice testing method.

#### 5.0 Normal Values

*The data presented below are valid for the Two Alternative Forced Choice testing procedures only. Normal values for the Method of Limits will differ slightly and generally will be higher (less sensitive). The mean vibration threshold for the index finger in the normal population between 18 and 65 years of age is 0.76 vibration units with a standard deviation of 0.43 vibration units. The mean vibration threshold for the great toe in the same population is 1.28 vibration units, with a standard deviation of 0.55 vibration units. Values at 2.5, 4.5, and 6.5 standard deviation units above normal means for several age windows are presented in Tables 1 and 2. Categories are as follows:*

*Within Normal Limits – less than 2.5 S.D.U.*

*Mild Dysfunction – between 2.5 and 4.5 S.D.U.*

*Moderate Dysfunction – between 4.5 and 6.5 S.D.U.*

*Severe Dysfunction – greater than 6.5 S.D.U.*

TABLE 1 – Vibration Thresholds – Index Finger			
Age	2.5 S.D.U.	4.5 S.D.U.	6.5 S.D.U.
< 35	1.58 vu	2.30 vu	3.02 vu
36-50	1.82 vu	2.68 vu	3.54 vu
51-65	2.10 vu	3.12 vu	4.14 vu
>65	2.45 vu	3.69 vu	4.93 vu

TABLE 2 – Vibration Thresholds – Great Toe			
Age	2.5 S.D.U.	4.5 S.D.U.	6.5 S.D.U.
< 35	2.39 vu	3.35 vu	4.31 vu
36-50	2.56 vu	3.60 vu	4.64 vu
51-65	2.89 vu	4.07 vu	5.25 vu
>65	3.43 vu	4.87 vu	6.31 vu

## Appendix B

### ANS Eligibility Deviations

This document has been prepared to provide guidance to EDIC Study Coordinators who must decide whether or not to proceed with a scheduled ANS test when all ANS testing eligibility requirements have not been met.

The three principle reasons for the ANS eligibility and preparation instructions detailed in the EDIC Manual of Operations are 1. to reduce the number of variables that affect autonomic function, 2. to standardize test procedures allowing for comparison of results among subjects and 3. to replicate the DCCT protocol, allowing for comparison of ANS tests done in EDIC to ANS tests done during DCCT. **For these reasons, study coordinators are to encourage all subjects to adhere to the preparation guidelines outlined in the manual of operations and listed on the ANS testing eligibility form (EDIC form 55).** Subjects who do not meet the eligibility requirements for ANS testing should be re-scheduled for testing on a different day.

Recognizing that situations arise in which subjects do not, cannot or will not meet all the eligibility requirements for ANS testing, that participants are older and have more concurrent illnesses now than in the DCCT (and as a result are taking more medications), and that changes in the frequency of subject visits from DCCT (at least every three months) to EDIC (one visit annually) complicates rescheduling of subjects, the following guidelines have been developed to assist study coordinators in deciding whether or not to proceed with ANS testing. **The ANS reading center will review all tests submitted on subjects who did not meet test eligibility requirements and will determine on a case by case basis whether the test is acceptable or not. The decision will be based on the nature of the protocol deviation, the rationale for proceeding despite the deviation, and quality of testing. If the study is judged unacceptable, the ANS reading center will notify the study coordinator that the test should be repeated.**

1. In general, if the study coordinator believes that a subject is unlikely to return for a visit within the study window, and/or would be unlikely to meet ANS eligibility requirements at a rescheduled visit, (for example, a subject who refuses to abstain from smoking prior to testing) then testing may proceed. Carefully document on the form 55 all deviations from the eligibility requirements specified by the protocol, and the rationale for proceeding with testing despite the deviations.
2. Hypoglycemia and concurrent acute illness are reasons to reschedule, rather than proceed.
3. Hyperglycemia. The DCCT protocol did not specify an upper limit for blood glucose and so no upper limit of blood glucose is included in the EDIC ANS protocol. However, coordinators should consider re-scheduling subjects who present with marked hyperglycemia (blood glucose exceeding 400 mg/dl), especially if the subject is experiencing symptoms of hyperglycemia (excessive urination, shortness of breath, nausea, etc.).
4. Insulin to correct hyperglycemia prior to ANS testing. Correcting hyperglycemia with supplementary doses of short-or rapid -acting insulin, even while fasting, is common practice among EDIC subjects. However, insulin produces vasodilating effects that can affect autonomic testing. If a subject has taken a correction bolus of insulin prior to ANS testing, is not hypoglycemic, and is otherwise prepared for testing, then testing may proceed after at least one hour has elapsed after the dose if insulin was taken. The patient should be observed closely for

symptoms of hypoglycemia throughout the test. Subjects who wish to take a corrective bolus should be advised to use caution to avoid “over-correcting” and inducing hypoglycemia.

5. Medications (including basal insulin) on the morning of the test. Subjects should be encouraged to hold all routine morning medications until testing is completed. However, if a subject expresses unwillingness to comply with this, he or she should be allowed to take those medications that they feel should not be deferred. This applies also to medications that are extremely time-dependant. Proceeding with testing under these circumstances is generally preferable to not testing the subject. Record all medications taken prior to testing on the form 55.

Documenting protocol deviations and missed or incomplete ANS tests. Coordinators are reminded to document on form 55 all protocol deviations and rationale for proceeding with testing despite those deviations. If a test is judged unacceptable by the ANS reading center (either because of poor technical quality or because the protocol violation significantly confounds the measurement of autonomic function, as would be the case with some medications), then the coordinator should try to reschedule the test within the subject’s visit window. If the test cannot or will not be repeated within the visit window, then a form 141 – missed visit form, should be completed and submitted to the Data Coordinating Center.

A form 141 may also be used if a specific portion of an ANS test is found to be unacceptable but the subject cannot or will not return for repeat testing. For example, if the Stand portion of an ANS test is judged technically unacceptable, but Valsalva’s and HRV portions are fine, the ANS reading center may request that just the Stand portion of the test be repeated. If the site cannot arrange for the subject to repeat that portion of the test, complete and submit a missed visit form (form 141) to indicate that.

Finally, study coordinators are encouraged to contact the ANS reading center for assistance with and questions about ANS test preparation and subject eligibility. Contact information for the ANS reading center is available on the EDIC web site.

## Appendix C

### Clarification of Valsalva Maneuver – Definition of “Complete” Valsalva

The following clarification is to help study coordinators determine whether or not a subject has completed a satisfactory Valsalva maneuver. Please remember that the goal is to record 2 Valsalva maneuvers on all eligible subjects, each with a blow duration of 20 seconds and a pressure of 40 mmHg. Recognizing that some subjects may not be able to blow for 20 seconds and /or reach and sustain 40 mmHg, a Valsalva maneuver may be considered complete **if the subject blew for at least 10 seconds at a pressure of at least 20 mmHg.**

Subjects should still be encouraged to do the best they can to meet the intensity (40mmHg) and duration (20 sec) of blow specified by the protocol. The guidelines listed above for minimum intensity and minimum blow duration have been adopted to accommodate subjects who may have physical limitations that prevent them from blowing at the intensity and duration specified in the protocol.

Remember to record the number of Valsalvas attempted, and the number of Valsalvas completed (again, completed as defined above) on form 55. Use the third page of form 55 to document any deviations from the protocol.

Example of Comments Related to Valsalva Maneuver on Form 3, Page 55.

#### *Comments*

*Valsalva 1 – Blow duration about 17 seconds @ 35 mm Hg*

*Valsalva 2 – Blow duration about 12 seconds @ 30 mm Hg*

*Valsalva 3 – Blow duration about 18 seconds @ 25 mm Hg*

*No additional attempts due to subject fatigue.*

**Appendix D**

## Guidelines for Disinfection of Valsalva Apparatus

The following guidelines have been developed in consultation with Infection Control Liaisons at the University of Michigan Health System.

A new, disposable mouthpiece must be used for each EDIC subject.

After each subject test, discard the mouthpiece and disconnect the tubing assembly from the manometer. The tubing assembly consists of a length of black rubber tubing, a rubber stopper and a small nylon connector (that connects the tubing to the stopper). These individual parts do not need to be separated and they are not single use items. Place the tubing assembly in a container (e.g. an emesis basin or specimen collection cup) of alcohol (70% isopropyl) and swish the tubing assembly around such that the alcohol contacts the inner lumen of the tubing assembly. Drain the tubing and let it air dry. Discard the alcohol.

**Standard Operating Procedure for EDIC ANS Reading Center  
Mayo Clinic  
Rochester, Minnesota**

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**I. Standard Operating Procedure for Study Coordinator Training (See ANS step by step 1 10 2006.ppt on EDIC website.) This section contributed by Catherine Martin, EDIC Study Coordinator.**

**A. ANS 2000 System Requirements; in brief**

1. Refer to manual for full operating instructions and system requirements
2. IBM Compatible PC running Windows 98® or a newer Windows® operating system.
3. The computer must have an available communication port (COM) to connect to the ANS 2000 (software default to Com 1)
4. The program requires about 20 megabytes of hard disk space. A hard drive with 1000 megabytes of blank storage space is recommended.

**B. Loading the software to a PC.**

1. Insert the ANS Software installation CD into your computer's D drive.
2. From the start menu, select RUN.
3. Type D:\setup and press enter
4. Follow the onscreen instruction to complete the set-up.
5. To create a shortcut on your desktop to the software file, highlight the ANS 2000 icon, right click the mouse, select create shortcut and click on the desktop (or other location that you want your shortcut to appear).

**C. The ECG Monitor / Respiration Pacer**

1. Install one 9-volt alkaline battery to the back of the monitor
2. Connect the male-end of the supplied serial cable to the base of the monitor.
3. Connect the female-end of the supplied serial cable to the appropriate port on the PC.
4. Note: It may be possible to connect the monitor to your PC via USB port. An appropriate serial -to - USB cable would be required to do this.

**D. Starting the ANS 2000 Data Acquisition Software**

1. Make sure that the subject leads are correctly placed
2. Double click the ANS 2000 ICON or short cut icon on your PC.
3. BATTERY SAVER: The acquisition software automatically turns off whenever there has been no user input for 8 minutes. You may restart by selecting Reset/Restart Instrument from the Patient drop-down menu, or you may disable the automatic shut off feature through the Options drop-down menu. When using Reset/Restart Instrument , make sure you allow time for the ECG tracing to appear on the screen before starting any tests.
4. The Data Acquisition Screen should appear when you open the program. If the main screen appears when you open the program, (instead of the data acquisition screen), select "Record Data" to take you to the data acquisition screen.
5. A message "Please Apply Patient Leads" will appear on the screen.
6. If you already have connected the subject, click OK. Otherwise, connect the leads, then click "OK".
7. You are now ready to begin ANS testing.

**E. Key Areas of the Data Acquisition Screen.**

1. The drop down menus on the upper left of the data acquisition screen let you enter subject demographics, start, restart or stop the various tests, and copy patient tests to a separate file (CD or other electronic storage).
2. The Options Drop Down Menu can be used to customize your program to your clinic. Select "Modify Site Recording Info" to enter your site number and name. This will then automatically be entered into the demographics screen each time you perform a test on a subject.

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3. Test Protocol Selection Buttons on the lower left hand portion of the screen are used to select the test to perform.
  - a. Use the mouse to select the desired test.
  - b. You may also use the Protocols drop-down menu to select the desired test.
4. Test Status Box. The messages that appear in this box will prompt you to enter demographics, start a test, or alert you that recording is in progress.
5. Test Timers. During each test, a timer will appear in the lower right hand corner of the screen. Both remaining time and elapsed time will appear.

**F. Event Markers.**

1. Event markers are placed using the spacebar on your computer keyboard.
2. Event markers are placed:
  - a. during the postural study, within the first minute of recording and as soon as the patient begins to stand up
  - b. during the Valsalva Test to indicate both the start and cessation of blowing
3. The timer and status boxes will change appropriately after using the space bar.
4. Note: The postural study timer runs for the first minute after the space bar has been hit to indicate the start of patient standing. You will need a separate timing device (watch, clock, stopwatch, for the postural testing)!

**G. Lead Placement.**

1. Prepare the skin surface for the adhesive electrodes either with an alcohol prep, or mildly abrasive skin preparation (e.g., Duraprep).
2. Attach the leads to the electrodes.
3. Attach the electrodes to the subject:
  - a. Black on the left upper chest - on the mid-clavicular line, just below the clavicle;
  - b. White on the right upper chest – on the mid-clavicular line, just below the right clavicle;
  - c. Red on the left lower abdomen.

**H. Starting ANS Testing – Entering Demographics.**

1. Once the patient's leads are in place, click "OK"
2. A message will appear asking for your Tech ID Code.
3. Enter your EDIC certification number (for example, 41-04) and select "OK"
4. On future tests, your certification number will appear automatically. Verify that the number is correct (or change if more than one person is certified at your site) and select "OK".
5. The Demographics Screen will then open.
6. If the Demographics Page does not open automatically (or if you need to change something before completing testing) use the Patient Drop Down Menu. Select "Enter Demographics".
7. The Demographics screen appears.
8. Areas highlighted in orange must be filled in.
9. Areas highlighted in blue are automatically entered by the software.
10. White areas, Recording Site, Comments, Tech Code and Gender must also be completed.
11. All other fields are left blank.
12. Your EDIC clinic ID (Recording Site) can be filled in automatically.
  - a. To do this, click on "Options" from the drop down menu and select "Modify Recording Site Info". Enter your clinic ID in the text box and click "OK". This will then autofill for each patient.

**I. Starting the 6 minute R-R test (HRV).**

1. Make sure the patient has been supine for 30 minutes.

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2. Verify correct placement of ECG leads. An ECG wave form should appear on the monitor.
3. Make sure the patient is breathing in conjunction with the lights on the ANS ECG Monitor/Respiration Pacer (inhale as lights ascend, exhale as lights descend).
4. Monitor and record supine blood pressure on form 55.
5. Click on “Paced Breathing (HRV)” below the Test Protocol Icon on the lower left portion of the screen.
6. From the Patient Drop Down menu select “Record Another Test” (or, hit F3 on your keyboard).
7. Recording begins automatically and the timer, showing elapsed and remaining time, appears on the lower right portion of the screen
8. The status bar will change to show that recording is in progress.

**J. R-R Testing.**

1. Observe the subject and the monitor to ensure that (s)he is breathing in conjunction with the pacer.
2. The respiration tracing (center panel - green line) ascends and descends in sync with the respiration pacer.
3. The heart rate variability monitor (lower panel) calculates the beats per minute throughout the test. Generally, peak heart rate will coincide with the peaks of the respiration monitor.
4. You should monitor both lines to ensure that the subject is breathing in sync with the respiration pacer.
5. Keep an eye on the test timer on the lower right of the screen.
6. Recording stops automatically after 6 minutes. Test timers will vanish and the message “Test Complete” will appear on the center of the screen.
7. The patient may breathe ad lib once the 6 minute recording period has stopped.

**K. Starting the 10 Minute Postural Test.**

1. Measure supine blood pressure after completing the R-R recording.
2. Record the blood pressure on form 055.
3. Click on 30:15 Stand from the Test Protocol Menu
4. Make sure that the area where the patient will stand is clear of obstacles and that EKG and computer cords will not be in the way.
5. From the Patient Drop Down menu select “Record Another Test”, (or hit F3 on keyboard). A message appears on the screen asking if you want to proceed with the currently entered demographics. Click “OK”.

**L. Postural Testing.**

1. Follow the screen prompts to begin recording.
2. When the test timer appears on the lower right hand portion of the screen, ask the patient to stand-up. The patient must begin standing within one minute of the start timing.
3. Press the space bar on your computer keyboard as soon as (s)he begins standing.
4. Have the patient stand for 10 minutes.
5. Recording will stop after the patient has stood for about 1 minute. Record the 1 minute blood pressure at this time.
6. You will need a separate timer to record blood pressures at 2,3,4,5 and 10 minutes from the time of standing.
7. Record blood pressures on form 55.
8. Use the EDIC centrally supplied blood pressure cuff for blood pressures
9. Measure blood pressures on the right arm unless contraindicated.
10. The patient may hold his or her arm at the side (versus supported at heart level).

**M. Postural Hypotension.**

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1. A drop of 10 mm Hg or more PLUS symptoms of orthostasis (dizziness, lightheadedness, etc.)
2. If Postural Hypotension occurs, return the patient to the supine position until symptoms resolve.
3. Continue to record blood pressures.
4. Note the event on form 055.

**N. Valsalva Test.**

1. The Valsalva Apparatus is a sphygmomanometer gauge with bulb (used for holding the device), length of black tubing with a black rubber stopper. A red switch is on the back of the apparatus. This switch controls the force of blowing by the subject.
2. A fresh, disposable, single use mouth piece must be used for each subject. Place the mouthpiece securely on the black rubber stopper.
3. No cleaning of the apparatus is required between subjects, but remind subjects only to blow into the Valsalva device, not to inhale through it. And make sure to use a fresh disposable mouthpiece for each subject.
4. There is a red switch on the back of the sphygmomanometer.
5. The red switch must be in the “down” position. When properly positioned, you will hear a small amount of air escaping from the device.

**O. Starting the Valsalva Test**

1. After the postural test, the patient rests in the supine position for 15 minutes
2. Select “Valsalva” from the Test Protocol Menu
3. Make sure that 20 sec is selected on the icon to the right of the test protocol box
4. Select “Start Test” from the “Patient” drop down menu, (or F3 on keyboard) then click OK on the screen prompt
5. The timer on the lower right of the screen will begin a 1 minute countdown. The patient is to breathe ad libitum for this minute.

**P. Valsalva Test.**

1. The timer on the lower right of the screen will begin a 1 minute countdown and “Ready for Blow” appears in the center of the screen. The patient is to breathe ad libitum for this 1 minute.
2. When about 2 to 3 seconds are shown on the “Remaining Time” indicator, have the patient take a deep breath and prepare to blow into the Valsalva apparatus
3. Hit the space bar once to indicate the start of blowing
4. The timer will reset to 20 seconds and “Blowing Phase” will appear in the center of the screen.
5. Encourage the subject to blow at 40 mm Hg for 20 seconds The timer will count down the 20 second blowing period.
6. Use the space bar to mark the cessation of blowing even if the subject could not blow for the duration (20 sec) and intensity (40 mm Hg) indicated in the protocol. Indicate any deviations from the protocol on form 055.
7. Pressing the spacebar at the cessation of blowing resets the timer to 1 minute. “Post (Ad lib) Phase” appears in the center of the screen.
8. During this final minute of recording, the patient remains supine and breathes ad lib.
9. Recording stops automatically after 1 minute.
10. Reasonable efforts should be made to record at least 2 good Valsalva efforts (“good” defined as blowing at or near 40 mm Hg for 20 seconds).
11. Five minutes of rest are needed between Valsalva attempts.
12. Subjects are encouraged to blow consistently at 40 mm Hg, but must keep the pressure at least at 30 mm Hg for a valid test.
13. Clinical judgment dictates how many efforts (beyond two) should be made.

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14. Comments about subject performance during the Valsalva may be recorded on form 055.

**Q. Stopping/Restarting Tests.**

1. If you have to stop and restart a test, do so using the commands under the “Patient” drop down menu. If you do restart, or, if no recording has occurred for 8 or more minutes, the unit will need time to reset. Restart in Progress will appear. Do not begin recording until that message has disappeared and HR tracing is visible.

**R. Marking Tests for Data Transfer.**

1. From the Patient Drop Down menu select “Open Database of Recordings”.
2. A list of all tests performed and stored in the data files will appear.
3. Click on the box next to “Enable Export” located on the upper left of the screen.
4. Identify the tests you wish to submit to the reading center by clicking on in the “select” column (first left column) to change the status from “no” to “yes” for each test for a given subject.
5. Once you have selected all the files you wish to transfer, click on “Export Selected Recordings” (located just to the right of the “Enable Export” button).
6. A dialog box will pop up and ask you to designate where you want the files to be placed and what name you would like to use.
7. Select the file on your computer where you will store your recordings for transfer to the reading center, and then proceed to name the file.
8. The “File Name” field will show the following “\*.MDB”. You are going to overwrite this with a subject-specific file name.
9. Name the file according to the following convention:
  - a. EDIC ID (space) EDIC Initials (space) DATE (ddmmyyyy)\*
  - b. (e.g. 41000 clm 10272005) (Do not use placeholders (/ or -) in the date field.)
10. You do not need to add “.mdb” after you complete the file name. This will automatically be filled in for you.
11. Hit Enter. This will send the patient-specific file to the folder on your computer that you have designated. You can later retrieve the file for transfer to the Reading Center.

**S. Transferring Files to the Reading Center.**

1. Files are sent to the ANS Reading Center via secure FTP web site following the instructions provided by the reading center. The URL is ftp://ftp.mayo.edu). If you are unable to configure your computer for FTP file transfer, you may send a CD to the reading center with the files. More than one subject’s studies may be sent on one CD.
2. When you send files to the reading center, send an email message to the reading center at edicstudy@mayo.edu. Also, fax the form 55 to the reading center at 507-266-6754. (If you are sending files via CD rather than via FTP, include form 55 with the CD, instead of faxing).
3. Always make sure a copy of the file is available at the clinic until the data has been analyzed and recorded at the DCC. You may back up files either on your computer, or to a separate CD.
4. Use the Neuropathy Studies Mailing list (form number TBD) to record studies sent to the reading center. The mailing list is to be sent to the DCC monthly.

**T. ANS Study Coordinator Competency/ Checklist can be found in Appendix D.**

**II. Standard Operating Procedure for Database Management by ANS Reading Center at Mayo Clinic (Reading Center)** Set up of flow and organization of data received and reported by the Reading Center.

**A. FTP site for incoming files from testing sites.**

1. Request Mayo Clinic Department of Information Technology to provide a secure FTP site.
2. Sites will use Internet Explorer to access URL: ftp://ftp.mayo.edu using “edic” as username and “read-c33” as password.
3. Reading Center will provide ftp instructions to the EDIC website for reference. (Appendix F)

**B. FTP site for outgoing files to the Biostatistics Center at George Washington University.**

1. FTP must be over a SSL (Secure Socket Layer) secure channel. Download and install a FTP client that supports FTP-S.
  - a. Core FTP LE (Free) <http://www.coreftp.com/>
  - b. FileZilla FTP (Free) <http://sourceforge.net/projects/filezilla/>
2. Use Help to determine correct setup of client. In the case of Core FTP LE:
  - a. Click on File > Connect to open the Site Manager window.
  - b. Enter a name into Site Name: GWU Biostatistics Center
  - c. Enter the URL into Host/IP/URL: ftp.bsc.gwu.edu
  - d. Enter the Username provided by the Biostatistics Center: edicmayo
  - e. Enter the Password provided by the Biostatistics Center: 4afh6w3
  - f. Enter a check mark next to PASV due to Mayo’s firewall.
  - g. Enter a check mark next to AUTH SSL to enable SSL Listings, SSL transfers and OpenSSL.
3. Set the drive for the files to be transferred.
  - a. In the case of Core FTP LE, click on the Drives/Folders button located just right of the magnifying glass on the left hand side of the window.
  - b. Browse for the desired folder, click OK.
  - c. Select the files/folders to be transferred and click on the ⇨ button to make the transfer.
4. To exit, Select File > Disconnect, then close with the X in the upper right corner.

**C. Database design.**

1. Types of data that will be received by the Reading Center.
  - a. Request for Certification Form 127.1 received via fax.
    - i. Information received on this form is listed in Appendix A1a.
    - ii. None of this information will be entered into the database.
    - iii. Reading Center must approve 1<sup>st</sup> test before a 2<sup>nd</sup> test may be sent from trained technician.
    - iv. Reading Center Certification Results Form will be sent to site technician either approving 1<sup>st</sup> certification test and okaying 2<sup>nd</sup> to be performed OR requesting 1<sup>st</sup> or 2<sup>nd</sup> certification test to be repeated and citing problems encountered (most common listed in Appendix C).
    - v. Final signed Form 127.1 will be faxed to the trained technician certifying that the technician is approved to perform ANS testing on EDIC subjects.
    - vi. All Reading Center Certification Results Forms and all Forms 127.1, including final signed form will be kept on file by Site Number in Certified Technician section at the Reading Center.
  - b. ANS Testing Eligibility Form 55.1 received via fax.
    - i. Information received on this form is listed in Appendix A2a.
    - ii. During Technician Certification none of this information will be entered into the database.
    - iii. Relevant data from this form that will be entered into the database from testing on EDIC subjects are listed in Appendix A2b.



**III. Standard Operating Procedure for Technician Certification by ANS Reading Center**

- A. Reading Center receives email from the site(s) in the EDIC mailbox (edicstudy@mayo.edu) stating that a test has been sent to the ftp Server and Forms 55.1 (ANS Testing Eligibility) and 127.1 (Certification Request—only sent if Certification Test is sent) have been faxed.**
1. Print email.
  2. Fax comes to Reading Center on a dedicated Fax machine. This machine is located in a secure area at the Reading Center, under the direct supervision of Dr. Phillip Low (PAL).
  3. Test is sent to the Mayo ftp Server (ftp://ftp.mayo.edu)
- B. File is transferred from the ftp Server to the “to be Analyzed folder” located on the L Drive.**
1. Open ftp (Located on Internet Explorer)
    - a. Type ftp://ftp.mayo.edu in address bar or click on bookmark ftp.mayo.edu
    - b. Login in using User Name: edic (using lower case)
    - c. Password: read-c33
    - d. Click on Login
  2. Open the “to be Analyzed” folder located on the L Drive
    - a. Location: L/AnsCtr/EDICDB/tobeAnalyzed
    - b. Position each open file so they are both visible
  3. Click on file to be transferred/ Drag folder to be transferred to the “tobeAnalyzed” folder/release/file has been transferred (check to make sure file is listed in folder)
  4. Close Internet Explorer and “to be Analyzed” folder
- C. Send return email to site letting them know file and fax have been received**
1. Set up delivery receipt
    - a. Click on Tools/Options/Under Preferences click on email options/Tracking Options/Make sure delivery receipt option is checked/Okay to all
  2. Print return email
  3. Print delivery receipt
- D. Check to make sure Technician performing the test has been approved**
1. See list of Technicians (Location: L/Ansctr/EDICDB/Documentation/WorkingFilesforCobbie/Controls Completed & Technician List)
  2. If Technician is not on list--notify site (by fax or email---if contacted by phone, follow up with an email for documentation that site has been notified) that they need to send the RC documentation indicating the new Technician has been trained by someone at the site that has already been certified. Request that they fill out the New Technician Authorization Form and submit it to the Reading Center as soon as the new Technician has been trained.
- E. Enter Technician/Test Information on Excel spreadsheet (L/AnsCtr/EDICDB/Documentation/WorkingFilesforCobbie/EDIC Controls)(Verify that Form 55.1 and 127.1 have been properly filled out, with no missing information)**
- F. Open (double click) ANS Reader on desktop (c:\Program Files\ANS\_Reader.exe)**
1. Click on Edit/Review
  2. Click on “To Import ECG Recordings from Another File. Click Here” (upper right hand corner)
  3. Select file to be imported (read)/Double Click/Table (Importable Recordings) will pop up with tests selected to be imported (there should be 1 HRV, 1 Stand and 2 Valsalva---check heading “Test” for number of tests performed and “Protocol” for which tests were performed).
    - a. Test 1 is HRV

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- b. Test 2 is Stand
- c. Test 3 is Valsalva
- d. Test 4 is Valsalva
- 4. Options to choose from are:
  - a. Top left---“Select All” (notice “no” in first column “Select ? has changed to “yes”
  - b. “Select None”---use if incorrect test was selected to be imported
  - c. Individually---select by clicking on “no” or “yes” until arrow appears in that field---click arrow to select option (yes or no)
- 5. Once selections are made click on “Import” button (upper left hand corner)
- 6. “For Your Information” box will appear indication the number of recordings that you are importing
  - a. Click ok to exit window
  - b. If incorrect files were imported  enable delete (upper left hand corner/Highlight test to be deleted/click delete selected recording under “list of Recordings” table. Once all desired test have been deleted repeat steps 6b through 6f
- 7. Close table
- 8. Imported recordings will appear in table “List of Recordings” as Status “unread” which appears when previous table “Importable Recordings” is closed
- 9. Verify Tech number matches Technician submitting Certification Test and forms 55.1 and 127.1
- 10. Make sure Technician has completed 1 HRV, 1 Stand and 2 Valsalva
- 11. Check “Rec.Date” column for date and time tests were performed (times are important for determining if protocol was followed).

**G. Review Test for the following:**

**1. Heart Rate Variability (HRV)**

- a. Highlight HRV portion of test/Double Click (opens recording)/Click “ok” for create a new edit series/Enter Reading Center Tech (Person reading test) in Tech ID required box (only required for 1<sup>st</sup> edit session)/Click okay/Verify the test was 6 minutes using scroll bar below test to view entire test
- b. Click on Report/Analyze & Review/Paced Breathing (HRV) Report pops up/Make sure there are 5 breathes per minute (6 seconds inspiration/6 second expiration)
- c. Click on Patient (upper left hand corner)/select print
- d. Close report/Close recording (located below recording on the left)

**2. Postural Study**

- a. Highlight Stand row/Check time---should be 6 minutes after HRV began/Double Click (opens recording) )/Click “ok” for create a new edit series/Enter Reading Center Tech (Person reading test) in Tech ID required box (only required for 1<sup>st</sup> edit session)/Click okay
- b. Use scroll bar below recording to see entire test/Check for: Event marker at Start of Study (appears as red boxes—1 above and 1 below recording/Recording only shows a maximum of 2 minutes of recording.
- c. Click on Report (upper left hand corner)/Analyze & Review 30:15 Stand Report will open
- d. Click on Patient (upper left hand corner)/select print
- e. Close report/Close recording (located below recording on the left)
- f. Verify Blood Pressures were taken @ 1, 2, 3, 4, 5 & 10 minutes (reported on 2<sup>nd</sup> page of Form 55.1 (ANS Testing Eligibility)

**3. Make sure there is 25 minutes between start of Postural Study and 1<sup>st</sup> Valsalva (1 minute of ad libitum breathing before 1<sup>st</sup> Valsalva begins**

**4. Valsalva #1**

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- a. Highlight Valsalva (Test #3)/Check start time (should be 25 minutes after start of Postural Study)/Double click (Opens recording) )/Click “ok” for create a new edit series/Enter Reading Center Tech (Person reading test) in Tech ID required box (only required for 1<sup>st</sup> edit session)/Click okay
  - b. Use scroll bar below test to see entire test/Check to make sure Event Markers (appear as red boxes--located at the top and bottom of the recording) are at the start (E1 in red box) and end (E2 in red box) of test/Maximum pressure achieved (40 mm HG for 20 seconds)
  - c. Click on Report (upper left hand corner)/Analyze & Review/Verify there is a Pre/Blow/Post period indicated on the report/If any of these are missing---test is incomplete and entire test will need to be repeated
  - d. Click on Patient (upper left hand corner)/Select print
  - e. Close Valsalva Report/Close recording (located below recording on the left)
5. **5 minutes between start of 1<sup>st</sup> and start of 2<sup>nd</sup> Valsalva**
6. **Valsalva #2**
- a. Highlight Valsalva (Test #4)/Check start time (should be 5 minutes after start of 1<sup>st</sup> Valsalva)/Double click (Opens recording) )/Click “ok” for create a new edit series/Enter Reading Center Tech (Person reading test) in Tech ID required box (only required for 1<sup>st</sup> edit session)/Click okay
  - b. Use scroll bar below test to see entire test/Check to make sure Event Markers (appear as red boxes--located at the top and bottom of the recording) are at the start (E1 in red box) and end (E2 in red box) of test/Maximum pressure achieved (40 mm HG for 20 seconds)
  - c. Click on Report (upper left hand corner)/Analyze & Review/Verify there is a Pre/Blow/Post period indicated on the report/If any of these are missing---test is incomplete and entire test will need to be repeated
  - d. Click on Patient (upper left hand corner)/Select print
  - e. Close Valsalva Report/Close recording (located below recording on the left)
7. **Close/Exit ANS Reader**
- H. Enter results of test on Excel spreadsheet (L/AnsCtr/EDIC WorkingFilesforCobbie/EDIC Controls & EDIC Controls Completed &Tech List)**
- I. Provided the forms have been properly filled out and test is satisfactory, notify (fax) technician that their 1<sup>st</sup> control has been successfully completed (using Certification Results Form) and they may proceed to their 2<sup>nd</sup> control (following the same procedure as their 1<sup>st</sup> Control)**
- J. If the 1<sup>st</sup> control was not satisfactory notify (fax) the technician. ANS Reading Center will fill out the Certification Results Form which will indicate what was not satisfactory and request that they repeat the Control.**
- K. Once both Controls have been completed satisfactorily, Form 127.1 (Request for Certification of Autonomic Nervous System Tester) should be completed (see Section B. ANS Certification) by circling #1. Dr. Low will sign and date the form. Once the form has been completed, fax to the Site. This form will serve as notification that this technician may begin testing patients.**
- L. File both completed controls and any correspondence related to the controls in the appropriate Site file.**

**IV. Standard Operating Procedure for EDIC Subject Reading by ANS Reading Center.**

The following procedures have been incorporated and will comprise SOP, as in place on 2/15/2006. The Mayo Autonomic Disorders Center (hereafter referred to as Reading Center) will provide Quality Control, of the Heart Rate Variability (HRV) Test, Postural Study and Valsalva Maneuver. The following procedures will be followed:

- A. Reading Center receives email from the site(s) in the EDIC mailbox (edicstudy@mayo.edu) stating that a test has been sent to the ftp server and Form 55.1 (ANS Testing Eligibility) has been faxed.**
1. Print email.
  2. Fax comes to Reading Center on a dedicated Fax machine. This machine is located in a secure area at the Reading Center, under the direct supervision of Dr. Phillip Low (PAL).
  3. Test is sent to the Mayo ftp Server (<ftp://ftp.mayo.edu>)
- B. File is transferred from the ftp Server to the “to be Analyzed folder” located on the L Drive.**
1. Open ftp (Located on Internet Explorer)
    - a. Type <ftp://ftp.mayo.edu> in address bar or click on bookmark [ftp.mayo.edu](ftp://ftp.mayo.edu)
    - b. Login in using User Name: edic (using lower case)
    - c. Password: read-c33
    - d. Click on Login
  2. Open the “to be Analyzed” folder located on the L Drive in Windows Explorer.
    - a. Location: L/AnsCtr/EDIC DB/ToBeAnalyzed
    - b. Position both the Internet Explorer window with ftp site and the Windows Explorer window with ToBeAnalyzed folder so they are both visible.
  3. Click and hold on file to be transferred/ Drag file to be transferred to the “tobeAnalyzed” folder/release/file has been transferred (check to make sure file is listed in folder).
- C. Receive fax---ANS Testing Eligibility Form (55.1)**
1. Verify that all fields have been completed.
    - a. If there are any blank fields, contact the site either by fax, email or phone (follow-up phone call with email for documentation purposes) and verify that the response is correct. If response was incorrect request that the site correct the ANS Testing Eligibility Form (55.1)/Initial and date any changes, then resubmit corrected form.
- D. Send return email** to site letting them know that fax and ftp file have been received.
- E. Check to make sure Technician performing the test has been approved and has completed the Certification process.**
1. Technician List may be found @ L/AnsCtr/EDIC DB/Documentation/EDICWorkingFileForCobbie /EDIC Controls Completed & Tech List
- F. If Technician has not been certified contact the site, either by fax, email or phone (follow-up phone call with email for documentation purposes) to let them know the technician has not been certified.**
1. The technician will need to be trained to perform ANS Testing by a certified technician.
  2. Once training has been completed they will need to send in the completed New Technician Authorization Form to the Reading Center.
  3. The Reading Center will then notify the new Technician that they may proceed with performing their controls (must have 2 approved controls before they are certified)
  4. When both controls have been satisfactorily completed, the Reading Center will notify the new Technician (on Form 127.1) that he/she may begin testing Patients.

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**G. Record receipt of Form 55.1 and ftp file containing ANS recordings on EDIC Data Tracking System**

1. Open Paradox and set Working Directory to L:\AnsCtr\EDIC DB\ParadoxEDICDB.
2. Open form OpeningMenu.fsl.
3. Click on Open Patient Log.
4. In upper table record site, Technician, Cert#, Patient ID#, Patient Initials, Date Test Received, Form 55.1 received (yes, no), name of ANS file, comments.
5. Close Paradox.

**H. Check ANS Testing Eligibility Form to see if Patient is eligible for testing**

1. If the Patient has answered “yes” to any of the eligibility fields, check to make sure there is documentation on the form explaining the “yes” answers. When there is no documentation supporting the “yes” reply, contact the site, either by fax, email or phone (follow-up phone call with email for documentation purposes) requesting that they supply written documentation supporting the “yes” reply and an explanation of why the test was performed even though the patient was not eligible for testing. Make sure written documentation is signed and dated.

**I. Enter Analysis (from form 55.1) information in Paradox**

1. Open Paradox and set Working Directory to L:\AnsCtr\EDIC DB\ParadoxEDICDB.
2. Open form OpeningMenu.fsl.
3. Click on OpenFax Form 55.1
  - a. Check to see if patient information exists.
  - b. Enter 5-digit Patient ID Number in upper left corner labeled “Enter Patient ID# press Enter:”, then press enter to move to that record.
4. **VERY IMPORTANT: Create a Mayo Tracking Number. This is a unique ID for each test received.**
  - a. This is located BELOW the yellow heading labeled in large red letters Mayo Tracking Number:.
  - b. The first time a record is filled for an existing subject, the default Mayo Tracking Number is the 5-digit Patient ID Number followed by a hyphen, 4 zeros, hyphen, 2 zeros. Change the 4 zeros to the present year and the 2 zeros to the visit number for the year.  
EXAMPLE: 06500-0000-00 change to 06500-2006-01
  - c. When additional tests are received a new record will need to be created.
    - i. Locate the first record for this subject as above.
    - ii. Click on the arrow on the task bar to move through records until the last record is found for this subject.
    - iii. Note the last Mayo Tracking Number used, particularly if it is within the same year.
    - iv. Click on the far right end of the yellow heading labeled: “Click HERE to insert a new record for this Patient ID#”.
    - v. Enter a new Mayo Tracking Number in the format of 5-digit Patient ID Number, hyphen, 4-digit present year, hyphen, 2-digit visit number. If a record already exist for the present year, be sure to increment the 2-digit visit number.
5. Enter data from Form 55.1; not all information is entered into Paradox; see Appendix A2b.

**J. Review test (check procedure)**

1. Open (double click) ANS Reader on desktop (c:\Program Files\ANS\_Reader.exe)
2. Click on Edit/Review
3. Click on “To Import ECG Recordings from Another File. Click Here” (upper right hand corner)

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4. Select file to be imported (read)/Double Click/Table (Importable Recordings) will pop up with tests selected to be imported (there should be 1 HRV, 1 Stand and 2 Valsalva---check heading “Test” for number of tests performed and “Protocol” for which tests were performed).
  - a. Test 1 is HRV
  - b. Test 2 is Stand
  - c. Test 3 is Valsalva
  - d. Test 4 is Valsalva
5. Options to choose from are:
  - a. Top left---“Select All” (notice “no” in first column “Select ? has changed to “yes”
  - b. “Select None”---use if incorrect test was selected to be imported
  - c. Individually---select by clicking on “no” or “yes” until arrow appears in that field---click arrow to select option (yes or no)
6. Once selections are made click on “Import” button (upper left hand corner)
7. “For Your Information” box will appear indication the number of recordings that you are importing
  - a. Click ok to exit window
  - b. If incorrect files were imported  enable delete (upper left hand corner/Highlight test to be deleted/click delete selected recording under “list of Recordings” table. Once all desired test have been deleted repeat steps 6b through 6f
8. Close table
9. Imported recordings will appear in table “List of Recordings” as Status “unread” which appears when previous table “Importable Recordings” is closed
10. Verify Tech number matches Technician submitting Certification Test and forms 55.1 and 127.1
11. Make sure Technician has completed 1 HRV, 1 Stand and 2 Valsalva
12. Check “Rec.Date” column for date and time tests were performed (times are important for determining if protocol was followed).

**K. Review Test for the following:**

**1. Heart Rate Variability (HRV)**

- a. Highlight HRV portion of test/Double Click (opens recording)/Click “ok” for create a new edit series/Enter Reading Center Tech (Person reading test) in Tech ID required box (only required for 1<sup>st</sup> edit session)/Click okay/Verify the test was 6 minutes using scroll bar below test to view entire test
- b. Click on Report/Analyze & Review/Paced Breathing (HRV) Report pops up/Make sure there are 5 breathes per minute (6 seconds inspiration/6 second expiration)
- c. Click on Patient (upper left hand corner)/select print
- d. Close report/Close recording (located below recording on the left)

**2. Postural Study**

- a. Highlight Stand row/Check time---should be 6 minutes after HRV began/Double Click (opens recording) )/Click “ok” for create a new edit series/Enter Reading Center Tech (Person reading test) in Tech ID required box (only required for 1<sup>st</sup> edit session)/Click okay
- b. Use scroll bar below recording to see entire test/Check for: Event marker at Start of Study (appears as red boxes—1 above and 1 below recording/Recording only shows a maximum of 2 minutes of recording.
- c. Click on Report (upper left hand corner)/Analyze & Review 30:15 Stand Report will open
- d. Click on Patient (upper left hand corner)/select print
- e. Close report/Close recording (located below recording on the left)





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- vi. You can either make additional corrections by repeating steps f. i, f. ii or f. iii or you may close out the edit session by clicking on the “close” button located below the test on the left side.
- h. The steps under “f” and “g” will be used to edit all tests (HRV, Stand and both Valsalva)
- i. If you would like to review or re-edit a test that you have already edited
  - i. Access the edit session by highlighting the desired test (under “List of Recordings”)
  - ii. Check the lower table for your edit session
  - iii. Double click on desired edit session
  - iv. Test will appear on screen. Make any additional changes by following the steps under “f.” and review changes by following steps under “g.”
  - v. Or you may create a new edit session by following the steps under “e.” and then repeating the procedure for f. Editing a test and g. Reviewing Analysis (under “g.”)
- j. Once you have completed your edit sessions close all open windows by pressing “Esc” and then “Exit” out of Hokanson 2000 ANS Reader/Select “no” for “Do you wish to archive database?”
- k. Log off computer

**M. 2<sup>nd</sup> Reader reviews analyzed test**

- 1. See above Reader Instructions

**N. Compare results of 1<sup>st</sup> and 2<sup>nd</sup> Reader**

- 1. **Modify test as requested by Reader if necessary (add additional instructions)**

**O. Print final Analysis Report**

- 1. **Insert instructions**

**P. Enter Analysis information in Paradox**

- 1. Open Paradox and set Working Directory to L:\AnsCtr\EDIC DB\ParadoxEDICDB.
- 2. Open form OpeningMenu.fsl.
- 3. Click on Open Form for ANS 2000 data.
  - a. Check to see if patient information exists.
  - b. Enter Mayo Tracking Number, created in Section I above, in upper right corner labeled “Enter Mayo Tracking Number Press Enter:”, then press enter to move to that record.
  - c. If record does not exist, go to Section I above and enter information from Form 55.1.
- 4. Enter all fields as listed in Paradox and in Appendix 3.
- 5. Close Paradox.

**Q. If test is not acceptable contact the site either by fax, email or phone (follow-up phone call with email for documentation purposes) letting them know they need to repeat the test and the reason why (ANS Feedback Form)**

**R. Transfer test results to the Biostatistics Center at George Washington University using FTP-S.**

- 1. **Insert Procedure for how often.**
- 2. FTP must be over a SSL (Secure Socket Layer) secure channel. Download and install a FTP client that supports FTP-S.
  - a. Core FTP LE (Free) <http://www.coreftp.com/>
  - b. FileZilla FTP (Free) <http://sourceforge.net/projects/filezilla/>
- 3. Use Help to determine correct setup of client. In the case of Core FTP LE:
  - a. Click on File > Connect to open the Site Manager window.
  - b. Enter a name into Site Name: GWU Biostatistics Center
  - c. Enter the URL into Host/IP/URL: ftp.bsc.gwu.edu
  - d. Enter the Username provided by the Biostatistics Center: edicmayo
  - e. Enter the Password provided by the Biostatistics Center: 4afh6w3

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- f.* Enter a check mark next to PASV due to Mayo's firewall.
- g.* Enter a check mark next to AUTH SSL to enable SSL Listings, SSL transfers and OpenSSL.
- 4. Set the drive for the files to be transferred.
  - a.* In the case of Core FTP LE, click on the Drives/Folders button located just right of the magnifying glass on the left hand side of the window.
  - b.* Browse for the desired folder, click OK.
  - c.* Select the files/folders to be transferred and click on the ⇨ button to make the transfer.
- 5. To exit, Select File > Disconnect, then close with the X in the upper right corner.

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**V. Appendix**

**A. Types of data received by Reading Center.**

1. Data fields from Request for Certification Form 127.1

a. All fields that exist from Request for Certification Form 127.1t.

- 127.1A1Clinic Number
- 127.1A2Date of request
- 127.1A3Person initiating request
- 127.1A4Name and credentials of person to be certified
- 127.1A5Type of request (initial certification or repeat request)
- 127.1B1Acknowledgement of 2 good subject test
- 127.1B2aAcknowledgement of repeated tests need to be done
- 127.1B2bNumber of requested repeated tests
- 127.1B2cProblems identified
- 127.1Signature of Certification
- 127.1Date of Certification

b. Fields that will be stored in Paradox database from Request for Certification Form 127.1.  
None

2. Data fields from ANS Testing Eligibility Form 55.1

a. All fields that exist from ANS Testing Eligibility Form 55.1.

55-1A1Clinic ID	55-1B11Hypoglycemic	55-1D2diStdg4SBP
55-1A2PID	55-1B12aFastingBloodSugar	55-1D2eiiStdg5DBP
55-1A3Pat Initials	55-1B12bBelow50	55-1D2eiStdg5SBP
55-1A4DateFormCmpltd	55-1C1Height	55-1D2fiiStdg10DBP
55-1A5EDICFollow-upYear	55-1C2Weight	55-1D2fiStdg10SBP
55-1A6Normal Control	55-1C3Medications	55-1D3Hypotension
55-1A7ANS Certification	55-1D1AiiRR-VarPreDBP	55-1D4If yes-minutes
55-1B1Food	55-1D1aiRR-VarPreSBP	55-1E1aWasRRcmltd
55-1B2Liquids	55-1D1biiRR-VarPostDBP	55-1E1bIfNoRR-why
55-1B3Caffeine	55-1D1biiRR-VarPostSBP	55-1E2aWasPstrlCmpltd
55-1B4Rx	55-1D2aiiStdg1DBP	55-1E2bIfNoPosNoHypo
55-1B5OTC	55-1D2aiStdg1SBP	55-1E3#VMsAttempted
55-1B6Alcohol	55-1D2biiStdg2DBP	55-1E4VMsCmpltd
55-1B7Tobacco	55-1D2biStdg2SBP	55-1E5WhyVMLessThan2
55-1B8Exercise	55-1D2ciiStdg3DBP	55-1PersonCmpltgForm55-1
55-1B9Emotional	55-1D2ciStdg3SBP	55-1PersoncmlptgFormCert#
55-1B10Illness	55-1D2diiStdg4DBP	

b. Fields that will be stored in Paradox database from ANS Testing Eligibility Form 55.1.

55-1A1Clinic ID	55-1D1biRR-VarPostSBP	55-1D2diiStdg4DBP
55-1A2PID	55-1D2aiiStdg1DBP	55-1D2diStdg4SBP
55-1A3Pat Initials	55-1D2aiStdg1SBP	55-1D2eiiStdg5DBP
55-1A5EDICFollow-upYear	55-1D2biiStdg2DBP	55-1D2eiStdg5SBP
55-1D1AiiRR-VarPreDBP	55-1D2biStdg2SBP	55-1D2fiiStdg10DBP
55-1D1aiRR-VarPreSBP	55-1D2ciiStdg3DBP	55-1D2fiStdg10SBP
55-1D1biiRR-VarPostDBP	55-1D2ciStdg3SBP	

3. Data fields to be stored in Paradox database and reported to DCC from Hokanson report.

Clinic ID	Supine0SBP	VMDateEval
PID	Stdg1SBP	VMRepeatEval
Pat Initials	Stdg2SBP	VM1PreMeanRRItvl
DateFormCmpltd	Stdg3SBP	VM1PreSD
EDICFollow-upYear	Stdg4SBP	VM1SmallestRRItvl
SixMinAvail	Stdg5SBP	VM1LgstPostRRItvl
RR-VarStudyDate	Stdg10SBP	VM1Ratio
RR-VarDateRecd	Supine-6DBP	VM1Time

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RR-VarDateEval	Supine0DBP	VM2PreMeanRRItvl
RR-VarRepeatEval	Stdg1DBP	VM2PreSD
RR-VarMeanRRItvl	Stdg2DBP	VM2SmallestRRItvl
RR-VarSD	Stdg3DBP	VM2LgstPostRRItvl
RR-Var	Stdg4DBP	VM2Ratio
PstrlStudyDate	Stdg5DBP	VM2Time
PstrlDateRecd	Stdg10DBP	Quality
PstrlDateEval	WasVMCmplt	SubjectPreparedness
PstrlRepeatEval	VMStudyDate	PersoncmpltgFormCert#
Supine-6SBP	VMDateRecd	

**B. Data reported to EDIC correlated with DCCT fields.**

DCCT SAS Var.	Type	Len	DCCT Description	Reading Center Description
PATIENT	Num	4	PATIENT ID NUMBER	55-1.A2 and Report Cover "Patient ID"
INITIALS	Char	3	PATIENT'S INITIALS	55-1.A3
FORMDATE	Char	6	DATE OF STUDIES	Report Cover "Exam Date"
CLINIC	Num	2	DCCT CLINIC NUMBER	55-1.A1 and Hokanson Demographics
BHMEANRR	Num	4	MEAN RR INTERVAL (MSEC)	???
BHSDRR	Num	4	STD DEV OF RR INTERVAL	???
BHRR1	Num	4	MEAN RR INTERVAL, STUDY I	Pre Event Mean Test 3
BHRR2	Num	4	MEAN RR INTERVAL STUDY II	Pre Event Mean Test 4
BHRRSD1	Num	4	SD OF RR INTERVAL, STUDY I	Pre Event SD Test 3
BHRRSD2	Num	4	SD OF RR INTERVAL, STUDY II	Pre Event SD Test 4
BHRRMNI	Num	4	SMALLEST INTERVAL, STUDY I	Blow Event Min Test 3
BHRRMNI2	Num	4	SMALLEST INTERVAL, STUDY II	Blow Event Min Test 4
BHRRMX1	Num	4	LARGEST INTERVAL, STUDY I	Post Phase Max Test 3
BHRRMX2	Num	4	LARGEST INTERVAL, STUDY II	Post Phase Max Test 4
CERTIF	Num	4	CERTIFICATION NUMBER-FORM 28.5	From Hokanson Demographics
BHTAPDAT	Char	6	DATE TAPE RECEIVED	Logged by Reading Center
FORMDAT1	Char	6	DATE OF EVALUATIONS	Report Cover "Exam Date"
BHRRSTDT	Char	6	RR-STUDY DATE	Report Cover "Exam Date"
BHRRECDT	Char	6	RR-RECEIVE DATE	Logged by Reading Center
BHRREVDT	Char	6	RR-EVALUATION DATE	Report Cover "Most Recent Edit Date"
BHPSTDT	Char	6	POSTURAL STUDIES-STUDY DATE	Report Cover "Exam Date"
BHPSREDT	Char	6	POSTURAL STUDIES-RECEIVE DATE	Logged by Reading Center
BHPSEVDT	Char	6	POSTURAL STUDIES-EVALUATION DATE	Report Cover "Most Recent Edit Date"
BHVSTDT	Char	6	VALSALVA-STUDY DATE	Report Cover "Exam Date"
BHVRECDT	Char	6	VALSALVA-RECEIVE DATE	Logged by Reading Center
BHVEVDT	Char	6	VALSALVA-EVALUATION DATE	Report Cover "Most Recent Edit Date"
BHRRVAR	Num	8	RR VARIATION X 1000	???
BHRATI	Num	8	VALSALVA RATIO, STUDY I	Summary Valsalva Ratio Test 3
BHVALTMI	Num	8	TIME OF VALSALVA, STUDY I	???
BHRATI2	Num	8	VALSALVA RATIO, STUDY II	Summary Valsalva Ratio Test 4
BHVLTMI2	Num	8	TIME OF VALSALVA, STUDY II	???
BHVSITNO	Num	2	VISIT NUMBER(O-BASELINE,4-1 YR,8-2 YRS)	55-1A5EDICFollow-upYear
BHSIXMIN	Num	2	6 MIN. RECORD. AVAILABLE-(1-OK,2-NOT OK)	Reading Center checks HRV Test1
BHRRRPT	Num	2	RR REPEAT FLAG(1-NOT, 2-IS REPEAT)	Reading Center checks if test exists?
BHPSRPT	Num	2	POSTURAL REPEAT FLAG(1-NOT, 2-REPEAT)	Reading Center checks if test exists?
BHSYS6	Num	2	SYSTOLIC BP -6	55-1.DSupine-6SBP
BHDIAS6	Num	2	DIASTOLIC BP -6	55-1.DSupine-6DBP
BHSYS0	Num	2	SYSTOLIC BP 0	55-1.DSupine0SBP
BHDIAS0	Num	2	DIASTOLIC BP 0	55-1.DSupine0DBP
BHSYS1	Num	2	SYSTOLIC BP 1	55-1.DStdg1SBP
BHDIAS1	Num	2	DIASTOLIC BP 1	55-1.DStdg1DBP
BHSYS2	Num	2	SYSTOLIC BP 2 2	55-1.DStdg2SBP
BHDIAS2	Num	2	DIASTOLIC BP 2	55-1.DStdg2DBP
BHSYS3	Num	2	SYSTOLIC BP 3	55-1.DStdg3SBP
BHDIAS3	Num	2	SYSTOLIC BP 3	55-1.DStdg3DBP
BHSYS4	Num	2	SYSTOLIC BP 4	55-1.DStdg4SBP
BHDIAS4	Num	2	DIASTOLIC BP 4	55-1.DStdg4DBP
BHSYS5	Num	2	SYSTOLIC BP 5	55-1.DStdg5SBP
BHDIAS5	Num	2	DIASTOLIC BP 5	55-1.DStdg5DBP
BHSYS10	Num	2	SYSTOLIC BP 10	55-1.DStdg10SBP
BHDIAS10	Num	2	DIASTOLIC BP 10	55-1.DStdg10DBP
BHVALMAN	Num	2	VAL.COMP(1-NEITHER,2-BOTH,3-VAL1,4-VAL2)	Reading Center verifies
BHVRPT	Num	2	VALSALVA-REPEAT EVALUATION	Reading Center checks if test exists?
BHQUALIT	Num	2	QUALIT(1-NO,2-BAD,3-FAIR,4-GOOD,5-EXCEL)	Reading Center evaluates quality of tape?
BHPREP	Num	2	PREPAREDNESS (1-NOT,2-SOMEWHAT,3-WELL)	???

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C. Common reasons for test is being returned.

1. Person Submitting the test has not been trained or authorized to submit controls for certification.
2. Form 127.1 (Request for Certification of ANS Tester) not included.
3. ANS Testing Eligibility Form (55.1) not submitted with study.
4. Required subject and site information not entered into test program (patient demographics).
5. HRV Testing
  - a. < 6 minutes of HRV Testing
  - b. Patient is not following pacer (6 seconds inspiration/6 seconds expiration)
6. Postural Study (Stand)
  - a. Event marker not inserted at start of Postural Study(indicates when Patient stands)
  - b. BP not recorded at 1, 2, 3, 4, 5 & 10 minutes
7. Valsalva #1
  - a. < 15 minutes between Postural Study and 1st Valsalva.
  - b. 1 minute of resting HR not recorded before start of blowing period.
  - c. Event Marker not inserted at start of blowing period.
  - d. Patient has not maintained required blowing pressure and duration (40 mm HG for 20 seconds) and no explanation given on form 55.
  - e. Event Marker not inserted at end of blowing period.
  - f. 1 minute of resting HR not recorded after end of blowing period.
8. Valsalva #2
  - a. < 5 minutes between Valsalva 1 and Valsalva 2
  - a. 1 minute of resting HR not recorded before start of blowing period.
  - b. Event Marker not inserted at start of blowing period.
  - c. Patient has not maintained required blowing pressure and duration (40 mm HG for 20 seconds) and no explanation given on form 55.
  - d. Event Marker not inserted at end of blowing period.
  - e. 1 minute of resting HR not recorded after end of blowing period.

D. ANS Study Coordinator Competency/ Checklist.

Activity/Critical Behavior	Resource/Reference
1. Reviews eligibility criteria and confirms subject eligibility	EDIC Form 55 EDIC Manual of Operations, Chapter 20
2. Connects computer cables to Hokanson Respiration Pacer and to PC.	Hokanson ANS 2000 Manual EDIC Manual of Operations, Chapter 20
3. Connects disposable ECG electrodes to Respiration Pacer's color-coded ECG leads and attaches to subject: - <b>Black</b> on the left upper chest - on the mid-clavicular line, just below the clavicle; - <b>White</b> on the right upper chest – on the mid-clavicular line, just below the right clavicle; - <b>Red</b> on the left lower abdomen.	
4. Positions patient in supine position and positions EDIC-supplied blood pressure cuff on right arm (unless BP measurements on right are contraindicated).	
5. Activates ANS acquisition software (ANS 2000), and verifies ECG and respiration pacer tracings on computer screen.	
6. Enters required subject demographics into ANS acquisition software fields:	Patient ID = EDIC 5-digit ID number Last Name = EDIC Initials Recording Site = EDIC 2-digit site number Comments = EDIC 2-digit year Tech Code = EDIC Certification Number Date of Birth = Subject DOB as mm/dd/yyyy Gender = M or F
7. Reviews R-R protocol with subject -Use of respiration pacer – inhale as lights ascend – exhale as lights descend -Testing will last for 6 minutes. -Subject will be told when time is up and can then breathe ad lib. -Subject will be asked to stand for 10 minutes shortly after conclusion of 6 minute breathing	EDIC Manual of Operations, Chapter 20 EDIC Form 55 Hokanson ANS 2000 Manual
8. Allows subject to practice breathing with respiration pacer.	

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9. Verifies that subject has been supine for at least 30 minutes	
10. Begin 6 minute R-R test: -Measures and record baseline blood pressure -Selects HRV test from software menu and start test. -Observes subject throughout to ensure he or she is breathing in conjunction with pacer and encourage compliance with paced breathing throughout six minute test period -Observes computer monitor for ECG signal throughout	
11. Concludes 6 minute R-R test. -Observes test timer to verify test completion -Measures and records blood pressure	
12. Begins 10 minute postural study. -Reminds subject to breathe ad lib (not in conjunction with pacer). -Makes sure area is clear for subject to stand (cables are not positioned so as to pose trip hazard) -Selects 30:15 Stand Test from test protocol menu and starts test. -Asks subject to carefully stand <b>-Hits computer space bar as soon as subject starts to stand.</b> -Monitors and records blood pressures at 1,2,3,4,5 and 10 minutes	
13. Defines and can respond appropriately to orthostatic hypotension <sup>1</sup> -Records any occurrence of orthostatic hypotension -Places subject supine and monitor condition/status of blood pressure until orthostatic episode is resolved	EDIC Manual of Operations, Chapter 20 EDIC Form 55
14. Returns subject to supine position at completion of 10 minutes of standing. Subject remains supine for 15 minutes	EDIC Manual of Operations, Chapter 20
15. Prepares subject for Valsalva testing -Verifies eligibility for Valsalva testing -Explains test procedure -Places new, disposable mouthpiece on Valsalva Apparatus -Verifies that Valsalva Apparatus switch is in "down" position. -Offers subject opportunity to practice with Valsalva apparatus.	
16. Begins first Valsalva study by selecting "Valsalva" and "20 sec" from test protocol menu and starts test	
17. Records resting HR for one minute -Observes timer on computer screen	
18. Begins 20 second blowing period -Instructs subject to take a deep breath and begin to blow into Valsalva Apparatus <b>-Hits spacebar on computer AS SOON AS SUBJECT STARTS TO BLOW</b> -Observes manometer to verify that pressure is at or near 40 mm/Hg -Encourages subject to continue blowing for 20 seconds -Observes timer for elapsed time -Tells subject to stop blowing once 20 seconds has elapsed	EDIC Manual of Operations, Chapter 20 Hokanson ANS 2000 Manual NeuroEDIC FAQ Document (Nov, 2005) (EDIC Web Site – Home>Projects>Neurology)
19. <b>HITS SPACEBAR</b> to mark cessation of blowing (even if subject stopped prior to 20 seconds)	
20. Records resting HR for 1 minute after blowing has stopped. -Observes timer for 1 minute elapsed time after blowing.	
21. Maintains subject in supine position for at least 5 minutes	
22. Repeats Valsalva test	
23. Records at least 2 acceptable Valsalva efforts (if possible)	
24. Documents Valsalva performance	EDIC Form 55
25. Reviews all documentation for completeness	
26. Selects subject test files for transfer and saves as MDB file	Hokanson ANS 2000 Manual ANS Step by Step Powerpoint file (EDIC Web Site – Home>Projects>Neurology)
27. Transfers electronic test file to Mayo ANS Reading Center and notifies reading center via email	Mayo ANS Reading Center FTP Transfer Protocol (EDIC Web Site – Home>Projects>Neurology) NeuroUpdate Memo to Study Coordinators (EDIC Web Site – Home>Groups>Study Coordinators>Miscellaneous)
28. Faxes EDIC Form 55 to ANS Reading Center	

<sup>1</sup> Drop of 10 mm/Hg in diastolic blood pressure **PLUS** symptoms of hypotension

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E. Reader Quick Reference

1. Reader analyzes test and makes necessary modifications
  - a. Open (double click) ANS Reader on desktop/May also be accessed @ (c:\Program Files\ANS\_Reader.exe)
  - b. Click on Edit/Review
  - c. There are 4 (four) sections to each test: Each Test will need to be analyzed and the following steps will used to modify the tests.
    - i. Test 1 – HRV (see column “Test” for test number)
    - ii. Test 2 – Stand
    - iii. Test 3 – Valsalva
    - iv. Test 4 – Valsalva
  - d. Click on Test desired (this will highlight the test)
    - i. Check lower table (Existing Edit Sessions) to see if you have already analyzed highlight test. If test has already been analyzed by you, your edit session will appear in this table. Otherwise, you will not have an entry in this table.
  - e. If selected test has not been analyzed or if you would like to create another edit session---
    - i. Right click on the highlighted test
    - ii. Click on “Create a New Edit Session”
    - iii. Ok
    - iv. Enter your name in the box
    - v. Ok
    - vi. Test desired will appear on the screen
  - f. Editing the test:
    - i. To set the threshold at the desired height—
      1. Click on Options (upper left hand corner)
      2. Click on “Enable R-Wave Threshold Redefinition
      3. To adjust the Threshold—Click on the scroll bar located to the left of the recording—holding down the left mouse button you can raise or lower the threshold (indicated by a thin blue line). Any points selected below the line will be deleted.
      4. Release mouse button once desired threshold has been selected
      5. “Re-Calculate R Waves Crossings” will appear on screen (select “ok” if you are satisfied with your selection or “cancel” if you would like to readjust the threshold). If you click on “ok” the test will be adjusted according to where you set your threshold.
    - ii. To delete points---
      1. Click on “x” (upper left hand corner---just above the test)
      2. Go to the point you wish to remove (narrow red line) place cross over the red line
      3. Click on point to be deleted
      4. Box appears on screen (ok to delete selected R-Wave?)
      5. Click ok
      6. Above steps may be repeated as many times as necessary
    - iii. To insert points
      1. Click on key (upper left hand corner---just above test)
      2. Go to the point that you would like to insert a point/Place up arrow over point you would like to include in analysis.
      3. Click on point (thin red line will appear where selection was made)
      4. Box appears on screen (ok to insert selected R-Wave?)

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5. Click ok
6. Above steps may be repeated as many times as necessary  
The above steps may be repeated as many times as necessary until the desired results are achieved.
- g. Reviewing Analysis---Once the test has been modified the analysis for the selected test may be viewed by:
  - i. Click on Report (upper left hand corner)
  - ii. Select Analyze and Review
  - iii. Click on either "ok" if finished with editing the test or "cancel" if additional changes are needed
  - iv. If "ok" is selected Analysis for edited test will appear on the screen
  - v. Once reviewed close window (click on x in upper right hand corner)
  - vi. You can either make additional corrections by repeating steps f. i, f. ii or f. iii or you may close out the edit session by clicking on the "close" button located below the test on the left side.
- h. The steps under "f" and "g" will be used to edit all tests (HRV, Stand and both Valsalva)
- i. If you would like to review or re-edit a test that you have already edited
  - i. Access the edit session by highlighting the desired test (under "List of Recordings")
  - ii. Check the lower table for your edit session
  - iii. Double click on desired edit session
  - iv. Test will appear on screen. Make any additional changes by following the steps under "f." and review changes by following steps under "g."
  - v. Or you may create a new edit session by following the steps under "e." and then repeating the procedure for f. Editing a test and g. Reviewing Analysis (under "g.")
- j. Once you have completed your edit sessions close all open windows by pressing "Esc" and then "Exit" out of Hokanson 2000 ANS Reader/Select "no" for "Do you wish to archive database?"
- k. Log off computer

# EPIDEMIOLOGY OF DIABETES INTERVENTION AND COMPLICATIONS

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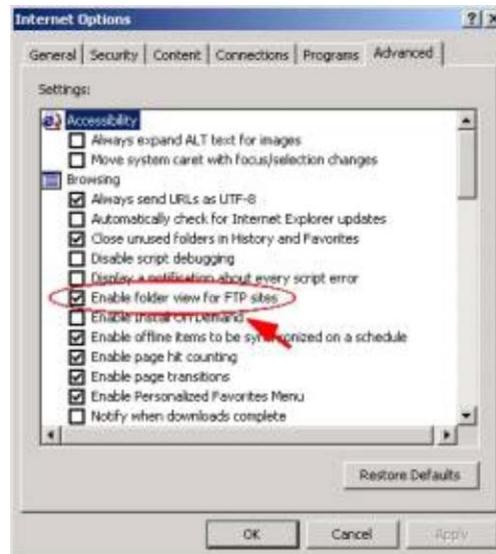
### F. Ftp instructions.

How to FTP (File Transfer Protocol) to Mayo Clinic Reading Center

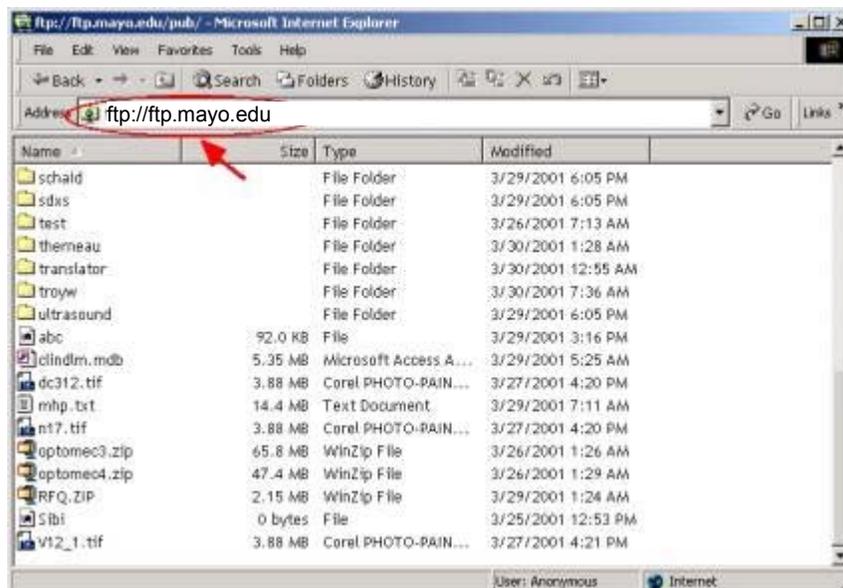
Updated 12/16/2005

#### A. Transferring files using Internet Explorer

- For data security reasons, all files should be uploaded between 8:00 A.M. – 1:00 P.M., Monday - Friday, Central Standard Time, to ensure same-day retrieval.
- Launch Microsoft Internet Explorer.
- To verify that your browser has been FTP enabled select *Internet Options* from the *Tools* menu.
- Select the *Advanced* tab and verify that *Enable Folder View for FTP sites* has been checked and click the *OK* button.



- Enter the URL *ftp://ftp.mayo.edu* in the *Address* window.



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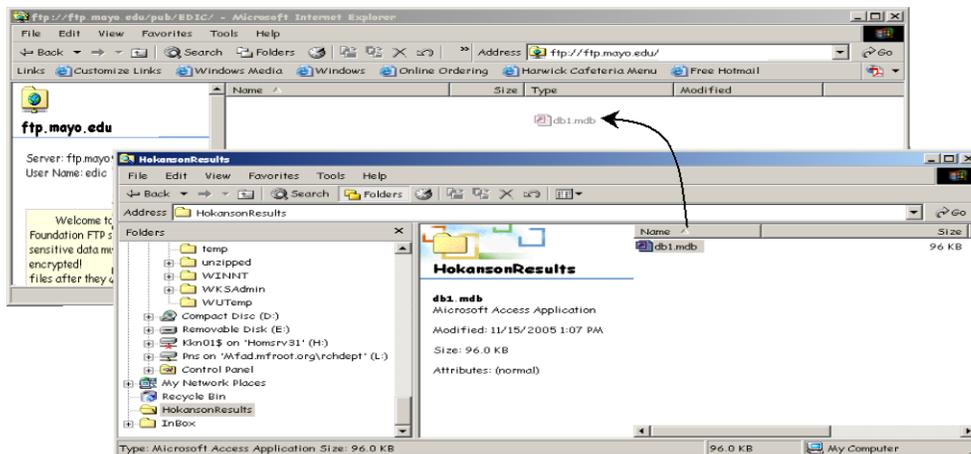
- The first time you enter, the following window will appear:



- Change the User Name to “edic” and the password to “read-c33”. You may save your password if you wish and add the site to Favorites for future file transfers.



- To put a file/folder on Mayo’s FTP server drag the file/folder from wherever you have the file stored in Windows Explorer (Right-click Start Button > Explore) into the Microsoft Internet Explorer window.



- Once you have put the files on the FTP server, send an email including the file/folder name(s) to [edicstudy@mayo.edu](mailto:edicstudy@mayo.edu). Files are automatically deleted after 5 days so it is important to inform the Mayo Clinic Reading Center that the file has been uploaded.
- Close the Internet Explorer window, you have successfully FTP’d the file/folder(s).
- Fax the ANS Patient Eligibility Form (55.1) to the Mayo Clinic Reading Center at 507-266-6754. Call the Reading Center at 507-284-4103 if fax machine is not answering.

## FAQ Page

- Q. I selected "EDIC" from the drop down box, why doesn't it open??**
- A. "edic" should be entered by typing with lower case letters, do not select from drop down box if it is in upper case.**

## 21. PSYCHOLOGICAL PROCEDURES

### 21.1 Quality of Life Questionnaire

#### 21.1.1 Introduction

The Quality of Life Questionnaire (EDIC Form 060) is a questionnaire designed to assess subjectively the impact of diabetes upon the individual and his/her total living situation. It therefore includes questions that focus on life satisfaction, frequency of activities, and worries. The questionnaire takes about 10 minutes to complete.

Some parts of the form apply to all subjects; others to only some groups such as adolescents or students, but all subjects complete the same form.

Ideally, all self-administered forms should be given to the participant and completed during the annual EDIC visit. Experience over time indicates that forms that are not completed during the in-person study visit experience lower completion rates compared to forms completed during the visit.

#### 21.1.2 Procedures

1. Administer the Quality of Life Questionnaire every 2 years beginning with year one. Many ancillary studies include this questionnaire in the protocol design and data collection. This may result in the need to complete this questionnaire during the year the ancillary study is completed, which may result in more frequent administration.
2. To introduce the questionnaire to the participant explain that we want to assess the impact that diabetes has on their total living situation. We are therefore asking questions that focus on life satisfaction, frequency of activities and worries. You may also explain that it will take approximately 10 minutes to complete.
3. The first time the Quality of Life Assessment is given, the individual administering it should read the instructions to the patient. Patients should be reassured that there are no correct answers to these questions, but individual opinions only. These forms or ones like them have been widely used in many other studies. They should feel free to approximate a best answer if they are not sure how to choose between specific alternatives.
4. When the Questionnaire is finished, the coordinator should review it to make sure all items have been filled out. If patient has not given an answer to any or all parts of the questionnaire, check with them if there is a reason something has been missed. In most cases they will have simply missed completing an answer. If not, try encouraging them by discussing their reason(s) for not wanting to complete an answer. If they still refuse, do not push further. Please return the forms with any explanation and notify the Principal Investigator at your site, as refusal may be part of an overall negative reaction to the study. Outright refusal will be very rare.
5. When complete, return this form in the monthly forms mailing to the Data Coordinating Center for scoring

6. The data from the scored instrument, when stored on the patient's data file, will include total scores, as well as individual item scores.

7. Data from the Quality of Life Assessment will be analyzed to assess the impact of the study on individual patients. This data may be useful for understanding differential rates of specific problems in individual centers.

## **21.2 Health Status Questionnaire**

### **21.2.1 Introduction**

The Health Status Questionnaire 2.0 (EDIC Form 061) is a questionnaire designed to assess a patient's feelings about his/her general health and the limitations or changes made in the patient's life as a result of his/her physical health. The Health Status Questionnaire 2.0 takes about 10 minutes to complete. In order to achieve the breadth necessary to measure generic health, the HSQ measures three major health attributes and eight health concepts (1):

- I. Functional Status
  - Physical Functioning
  - Social Functioning
  - Role Limitations attributed to:
    - Physical Problems
    - Emotional Problems
- II. Well-Being
  - Mental Health
  - Energy/Fatigue
  - Pain
- III. Overall Evaluation of Health
  - General Health Perception

### **21.2.2 Procedures**

1. The Health Status Questionnaire 2.0 is given every 2 years, beginning with year one. Many ancillary studies include this questionnaire in the protocol design and data collection. This may result in the need to complete this questionnaire during the year the ancillary study is completed, which may result in more frequent administration.

2. The first time the Health Status Questionnaire 2.0 is given, the individual administering it should read the instructions to the patient. Patients should be reassured that there are no correct answers to these questions, but individual responses only. They should feel free to approximate a best answer if they are not sure how to choose between specific alternatives

3. When the Questionnaire is finished, the coordinator should review it to make sure all items have been filled out. The coordinator is encouraged to review the responses to question 37-39, regarding depression and seek input from the Principal Investigator if patient safety is a concern. If patient has not given an answer to any or all parts of the questionnaire, check with

them if there is a reason something has been missed. In most cases they will have simply missed completing an answer. If not, try encouraging them by discussing their reason(s) for not wanting to complete an answer. If they still refuse, do not push further. Please return the forms with any explanation and notify the Principal Investigator at your site, as refusal may be part of an overall negative reaction to the study. Outright refusal will be very rare.

4. When complete, this form should be returned in the monthly forms mailing to the Data Coordinating Center for scoring.

### **21.3 Completion of Forms 60 and 61**

The Quality of Life Questionnaire and the Health Status Questionnaire should both be completed on the same visit.

### **21.4 Quality of Well-Being Scale, Self-Administered QWB-SA, V1.04**

#### **21.4.1 Introduction**

The Quality of Well-Being Scale, Self-Administered QWB-SA, V1.04 (EDIC Form 062) is a comprehensive measure of health-related quality of life. It covers six domains that include:

- Acute and chronic symptoms,
- Self care,
- Mobility,
- Physical activity,
- Usual activity, and
- General health

#### **21.4.2 Procedures**

1. The Quality of Well-Being Scale, Self-Administered is given once in either EDIC Years 13 or 14. It is self administered by the participant.

2. Instructions for one-time completion of the Quality of Well-Being Scale, Self-Administered should be reviewed with the patient. These forms or ones like them have been widely used in many other studies. All questions are in reference to health problems that the participant may have experienced in the last 3 days only. Patients should be reassured that there are no correct answers to these questions, but individual responses only. They should feel free to approximate a best answer if they are not sure how to choose between specific alternatives.

3. When the Questionnaire is finished, the coordinator should review it to make sure all items have been filled out. If the patient has not given an answer to any or all parts of the questionnaire, check with them if there is a reason something has been missed. In most cases they will have simply missed completing an answer. If not, try encouraging them by discussing their reason(s) for not wanting to complete an answer. If they still refuse, do not ask for further explanations. Please return the forms with any explanation and notify the Principal Investigator at your site, as refusal may be part of an overall negative reaction to the study. Outright refusal will be very rare.

4. When complete, this form should be returned in the monthly forms mailing to the Data Coordinating Center for scoring.

#### References

1. User Guide, Health Status Questionnaire (HSQ) 2.0, TyPE Specification, Health Outcomes Institute, 1993.
2. Sieber WJ, Groessl EJ, David KM, Ganiats TG, Kaplan RM. Quality of Well-Being Self-Administered (QWB-SA) Scale User's Manual, 2004.

## 22. LISTING OF EDIC FORMS COMPLETION AND MAILING OF FORMS

The EDIC forms were constructed to serve the following functions:

1. To provide the data required for a thorough statistical evaluation of the outcomes;
2. To allow the followup and monitoring of an EDIC patient in a thorough format that is standard for all clinical centers;
3. To document that certain study procedures have been followed either by the clinic staff or by the patient;
4. To request certification of new clinic staff;

This chapter will describe the various types of study forms, how to complete them, and how to distribute them to their proper destination.

### 22.1 The Various Types of Forms

Although there are a large number of forms (Table 22.1), many of these are designed for a special purpose and may be completed by the clinic staff, the participant or a central reading or laboratory. The forms used by the Central Units for reporting results to the Data Coordinating Center are not used in the clinic. There are a number of forms of this type (Table 22.2).

The forms used to inventory specimens or other materials mailed to the Central Units are also used to create an audit trail for the Data Coordinating Center for tracking any missing material. These administrative forms are listed in Table 22.3. The instructions on the form indicate the use of each of the copies.

Another special type of form is that which is used by a clinical center to request that the certification process be initiated for a new clinic staff member (Table 22.4). Chapter 24 of this Manual describes certification procedures.

There are also a number of special-purpose forms (Table 22.5). These are used on an as-required basis to notify the Data Coordinating Center of events affecting patient health, missed follow-up visits, transfer of a patient to another clinical center, and so on.

Table 22.6 lists forms that are used during followup of an enrolled patient.

### 22.2 Forms Supplies

The Data Coordinating Center posts the EDIC forms on the secure study website (see Chapter 30). The clinic is responsible for making copies of these forms for use in their clinic and insuring that the most updated version of the form are used, as accessed from the EDIC web site. In addition, whenever a form is completed, the clinical center should make the appropriate number of copies. The Data Coordinating Center also posts a prototype of the Informed Consent form (EDIC Form 001) on the secure study website. Utilize locally informed consent forms and additions to the informed consent documents approved for clinic use to reflect any changes requested by that institution's IRB.

## 22.3 Form, Patient, and Visit Identifying Information

### 22.3.1 Form Number and Version Number

The EDIC forms are numbered according to what category or group they represent. For example, all cardiovascular forms are numbered from 10 to 19, the renal forms are numbered from 20 to 29, and the ophthalmologic forms are numbered from 30 to 39. Mailing lists are numbered beginning with 100. See Table 22.1 for the listing of forms and their corresponding form numbers.

The number for each form consists of an integer and a decimal. The integer indicates the form number and the decimal indicates the version of the form. For example, from Table 22.1, EDIC Form 002.2 indicates that this is the form entitled "Annual Medical History and Physical Examination" and that it is the second version. The date on the upper right corner of the form indicates the date this version was adopted.

### 22.3.2 Identifying Information

Before a patient arrives for a scheduled visit, assemble all forms required for that visit with that patient's folder and the I.D. section filled out in advance. On all forms, the following identifying information will be employed.

1. Clinic Number
2. Patient ID Number
3. Patient's Initials
4. Date of Visit

### 22.3.3 Collaborating Clinic Number

Each of the 28 EDIC clinical centers is assigned a Clinical Number that is used on every study form. These Clinic Numbers are:

01 Case Western Reserve University	15 University of Texas
02 Children's Hospital of Philadelphia	16 University of Toronto
03 Cornell University	17 University of Washington
04 Henry Ford Hospital	18 University of Western Ontario
41 University of Michigan	19 Vanderbilt University
05 Joslin Diabetes Center, Inc.	20 Washington University
06 Massachusetts General Hospital	21 Yale University
07 Mayo Foundation	22 Albert Einstein College of Medicine
08 Medical University of South Carolina	23 Northwestern University
09 International Diabetes Center	24 University of California, San Diego
10 University of Iowa	25 University of Maryland
11 University of Minnesota	26 University of New Mexico
12 University of Missouri at Columbia	27 University of South Florida
13 University of Pittsburgh	41 University of Michigan
14 University of Tennessee	

#### **22.3.4 Patient Identification Number**

Each patient was assigned a permanent 5-digit identification number (ID No.) in the DCCT. The first two digits of the patient identification number refer to the clinical center in which the patient was first screened for eligibility and the last three digits are a code to identify the patient. The identification numbers that were assigned to each patient during the DCCT will continue as the patient's identification number in the EDIC.

#### **22.3.5 Patient's Initials**

The patient's initials—comprising the patient's first, middle, and last initials—constitute a second patient identifier. If the patient has no middle name or initial, an "X" is used as the middle initial. The initials that are entered onto the first EDIC Annual Medical History and Physical Form (Form 002) are the initials used for the duration of the EDIC. (The initials identifier was determined for the EDIC and it will never change, even if the patient's name changes during the course of the EDIC. There was a one-time allowance to change initials at the beginning of EDIC to reflect change in name.)

#### **22.3.6 Examination Date or Date of Visit**

The examination date is the date an examination / visit is conducted. A number of procedures may be associated with each examination. An examination is not regarded as complete until all procedures are complete or a Missed Visit Form (141) has been completed documenting procedures that were not completed.

#### **22.3.7 Follow-up Visit Number**

The follow-up visit number is sequentially numbered starting at 1 for the first annual. There is one scheduled follow-up visit per patient per year.

#### **22.3.8 Patient Schedules**

The Data Coordinating Center will generate a schedule of target dates for all regularly scheduled follow-up visits for each patient. The schedules will specify which procedures need to be performed for each patient at each visit. Initially, two versions of the schedules were distributed. The first laid out the patient's entire follow-up assessment schedule for EDIC through year 10. (Figure 22.1). The second schedule has continued annually, providing the clinics with one year only and will be sequentially ordered by month and patient (Figure 22.2). This list is useful for scheduling patients and is sent to the clinics in fall of the year preceding the next EDIC year. Figure 22.3 is the mailing schedule for each clinic's monthly mailing (see section 22.5). A list of the Study Week Numbers that identifies the week of follow-up during which a form is completed and mailed (Figure 22.4) is on the EDIC secure website.

### **22.4 Completing Forms**

Each form was prepared such that all instructions required for properly completing the form are self-contained. Some forms are questionnaires completed by participants but some forms are intended to be completed by EDIC staff as an interview, and are not given to participants. Carefully fill out forms using a ballpoint pen with black ink. (Black ink is preferred because experience has shown that it is clearest on microfiche and scanned copies.) Make changes carefully and neatly. Do not make extra notations if there is no space designated for

them. If you find that there are inadequacies in a form, please notify the Data Coordinating Center so that revisions can be considered.

Sometimes an item on a form requires a written response rather than a simple check of a box or an entry of a number. In these cases, the clinic staff should print the answer clearly, avoiding the use of abbreviations, especially abbreviations of medical terms.

Before the patient leaves the clinic, at the conclusion of the visit, the Study Coordinator should review each of the required forms for accuracy and completeness. The Study Coordinator should also ensure that all tests and procedures required for that visit have been conducted and the appropriate forms completed (see Chapter 5).

Each form should bear the printed name of the individual who completed the form, or the person with primary responsibility, if more than one person completed it. Self-completed forms by participants should not include their name. Any self-completed form with a signature line should be left blank as no identifiers are ever sent outside of the local EDIC clinic.

## **22.5 Batching and Mailing**

Mail forms to the Data Coordinating Center once a month on the Thursday of the week designated to your clinic. See Figure 22.3 for the clinic mailing schedule. A monthly batch of forms, therefore, will comprise all forms completed since the last mailing.

### **22.5.1 Copying and Inventorying Forms**

Collect all forms completed during the preceding month and sort them by Form Number and by Patient I.D. Number within Form Number. Complete a copy of the Clinic Forms Inventory (EDIC Form 100), which requires specification of the Form Number, date, and Patient ID number. Then photocopy the batch of forms and compare the copies against the just completed Forms Inventory. The clinic's copies of the forms may then be re-sorted by Patient ID number and filed in the clinic's medical record for each patient.

Organize forms and the Clinic Forms Inventory by Form Number in order to facilitate processing at the Data Coordinating Center, where the forms must be batched and keyed by Form Number.

When photocopying forms for the DCC, be sure to use one-sided copying only. The data entry procedures used by the DCC require one-sided copies.

### **22.5.2 Batching Forms**

Batch the form originals for mailing to the Data Coordinating Center. The Data Coordinating Center's copies are always the originals. Include a copy of the Clinic Forms Inventory (EDIC Form 100) and the Forms Mailing List (EDIC Form 101) with the batch. During follow-up, first sort all forms by number within a monthly batch, i.e., all forms of a given type should be together in the batch. The Study Coordinator will then inventory the batch of forms by completing the Forms Mailing List (EDIC Form 101). On this form, list the number of each type of form in the batch. The entries on the mailing list should correspond to the total number of entries on the Clinic Forms Inventory.

### **22.5.3 Mailing Forms**

Then, place the forms in one or more envelopes and mail them to this address:

EDIC Data Coordinating Center--Forms  
The Biostatistics Center  
6110 Executive Boulevard, Suite 750  
Rockville, MD 20852

When more than one envelope is required to mail a batch, write the date of mailing on each envelope, and then number each at the bottom as 1 of x, 2 of x, etc., where x is the total number of envelopes included in that mailing.

Then, place another copy of the Forms Mailing List in a separate envelope for mailing to the Data Coordinating Center. This is done as a security measure; it helps insure that the Data Coordinating Center will become aware of a missing batch of forms. Next, mail the batch of forms, Clinic Forms Inventory, and Forms Mailing List with first-class postage on Thursday afternoon so that the forms will arrive at the Data Coordinating Center the following Monday.

Send copies of the specific mailing lists (Table 22.3) to the Data Coordinating Center and central laboratories or reading units with specimens, photographs, etc.

There may be some months in which no forms are completed. In this event, the clinic should complete the Forms Mailing List (Form 101) and check the box indicating that no forms are being sent. This form alone should then be mailed to the Data Coordinating Center.

### **22.6 Receipt of Forms**

When forms arrive at the Data Coordinating Center, the Data Control Clerk will open the mail and reassemble the batch if multiple mailing envelopes were used. Forms should arrive at the Data Coordinating Center by the Monday following the Thursday mailing. If a complete batch is not received by the next Thursday, a trace will be initiated. The clinical center will also be contacted so that copies of any missing forms may be mailed with the next month's batch.

When the batch is reassembled, the Clerk will count the number of forms received and compare the counts with those given on the Mailing List and the Inventory. If there are any discrepancies noted, the clinical center is called immediately.

### **22.7 Editing Data on Forms**

Each form is edited by a separate edit program that searches for missing data, inconsistencies, and values that are out of range. An edit notice is printed which lists all the errors detected for a given form. An example of an edit notice printing from the EDIC is presented in Figure 22.5. These notices are returned to the originating clinic for recording the correct information. The error notice is a "turn-around" document on which the corrections to the error notices are written and the document returned to the Data Coordinating Center.

An edit message should be returned to the Data Coordinating Center in the next month's mailing, even if the data in question are correct.

An edit message consists of a table showing the form number, the Clinic Number, the Patient ID and initials, the date the form was completed and the study week it was mailed, and the certification number of the clinic staff member who completed the form. Below this information is listed one or more error notices. Each error notice lists the form Item Number and an abbreviated description of the item. The Variable Name for the datum in question (as used in the Data Coordinating Center's edit and analysis programs) is printed next to the value of the variable. A message describing the reason for questioning the value is printed. A line labeled "new value" is provided for entering a response to the message. The possible responses include:

1. entering a new value;
2. entering the word "missing" if the correct datum cannot be retrieved;
3. entering the word "okay" if the original value is correct;
4. entering another explanation.

The edit program also prints a table of control totals for forms edited in that batch to compare with the data entry control totals. In addition, tables containing the number of forms edited and the number of errors per form are printed by form type and clinic. These edit summary tables can be used to monitor clinic performance.

There will be occasions when the clinic staff will realize they have made an error in completing a form, yet the nature of the error may be such that an edit program may not detect it. To make an unsolicited correction to a form, the clinic should:

1. make a copy of page 1 of the form and the page(s) to be updated;
2. write "correction" in red ink on page 1;
3. indicate all needed changes in red ink;
4. send the pages to the Data Coordinating Center. Corrections may be sent with the regular monthly mailing but should be clearly separate from it and from any edit messages generated by the Data Coordinating Center's edit programs.

## Table 22.1

## Listing of EDIC Forms (May 18, 2012)

All EDIC forms are listed below. **However, not all forms are used annually.**

Please refer to the EDIC secure website for the listing of CURRENT and HISTORIC forms.

EDITING WEBPAGE **EDIC CURRENT FORMS**  **CURRENT GENERAL**   001.5 - Informed Consent For Participation-CONTINUING FOLLOW-UP (11/09/05)   002.7 - Annual Medical History and Physical Examination (05/30/12)    004.6 - Current Medications (05/30/12)    **CURRENT MAILING LISTS**    100.2 - Clinic Forms Inventory (03/29/94)   101.6 - Forms Mailing List (01/07/2010)    102.2 - Special Forms Inventory (03/29/94)    103.2 - Resting Electrocardiogram Mailing List (03/28/94)    105.3 - Lipid, Serum Creatinine, Serum Cystatin and Saved Specimen Mailing List (05/30/12)    107.6 - Fundus Photograph Mailing List (05/30/12)    108.2 - Hemoglobin A1c Specimen Mailing List (05/30/12)    110.3 - HbA1c Quality Control Mailing List (10/04/95)    111.1 - Renal Quality Control Mailing List (10/04/95)    113.1 - Lipid Quality Control Mailing List (10/04/95)    115.1 - Renal Studies Specimen Mailing List (05/30/12)    **CURRENT RETINOPATHY**    030.3 - Ophthalmic Examination & visual Acuity (05/30/12)   031.4 - Fundus Photography Quality Review (05/30/12)    033.1 - National Eye Institute Visual Functioning Questionnaire - 25 (VFQ-25) Version 2...    034.1 - CORU Digital Color System Certification Request Form (04/04/12)    035.1 - CORU Photographer Certification Request Form for Digital Images (04/04/12)    **CURRENT GLYCEMIA**    042.3 - Notification and Further Details of Severe Hypoglycemia (06/04/99)   **CURRENT NEUROPATHY**    050.3 - Michigan Neuropathy Screening Instrument and 10-gram Filament Exam (11/22/05)   **CURRENT PSYCHOLOGICAL**    060.2 - Quality of Life Questionnaire (05/30/12)   061.2 - Health Status Questionnaire 2.0 (05/30/12)    **CURRENT HEALTH CARE DELIVERY**    070.5 - Health Care Delivery Questionnaire (07/25/97)   **CURRENT VERIFICATION**    090.6 - Verification of Cardiovascular Disease (05/02/06)   091.5 - Verification of Cerebrovascular Event (05/25/11)    

- 092.4 - Verification of Peripheral Vascular Event (05/27/99) 📌📌📌📌
- 093.4 - Verification of DKA Event (06/04/99) 📌📌📌📌
- 094.4 - Verification of Psychiatric Disease Requiring Treatment (06/04/99) 📌📌📌📌
- 095.4 - Verification of Major Accident (06/04/99) 📌📌📌📌
- 096.1 - Verification of Renal Failure Event (Dialysis or Kidney Transplant) (07/17/08) 📌📌📌📌

### CURRENT CERTIFICATION ! 📌📌📌

- 120.2 - Certification of ECG Technician (03/28/94) 📌📌📌📌
- 121.4 - Certification of Carotid Sonographer (11/19/98) 📌📌📌📌
- 122.2 - Certification of Visual Acuity Examiner (03/28/94) 📌📌📌📌
- 123.3 - Certification of Study Coordinator or Principal Investigator (03/28/94) 📌📌📌📌

### CURRENT PATIENT STATUS NOTIFICATION ! 📌📌📌

- 140.2 - Notification of Death (03/24/94) 📌📌📌📌
- 141.4 - Notification of Missed Clinic Visit or Modification of Follow-up Schedule 📌📌📌📌
- 142.3 - Notification of Patient Transfer or Move (09/05/06) 📌📌📌📌
- 143.8 - Notification of Update to Personal Locator Form (05/30/12) 📌📌📌📌
- 144.3 - Notification of Transfer to Inactive Status (10/04/94) 📌📌📌📌
- 145.2 - Checklist for Tracking Inactive or Recalcitrant Patient (03/24/94) 📌📌📌📌

### CURRENT M & M ! 📌📌📌

- 151.9 - Morbidity & Mortality Review Form: Myocardial Infarction(MI) & other Cardiovasc... 📌📌📌📌
- 152.4 - Mortality Review Form (05/05/06) 📌📌📌📌
- 153.4 - Mortality & Morbidity Transmittal Form (04/23/08) 📌📌📌📌
- 154.4 - Mortality & Morbidity Status Form (07/18/08) 📌📌📌📌
- 154.5 - Mortality & Morbidity Status Form (03/09/12) 📌📌📌📌

### CURRENT URO-EDIC II ! 📌📌📌

- 162.1 - Urologic Complications Questionnaire for Women Follow-up (06/14/10) 📌📌📌📌
- 163.1 - Urologic Complications Questionnaire for Men Follow-up (06/14/10) 📌📌📌📌

### CURRENT CHEIROARTHROPATHY ! 📌📌📌

- 300.2 - Past Medical History and Exam (06/07/11) 📌📌📌📌
- 301.1 - DASH Cover.pdf (04/08/11) 📌📌📌📌
- 302.1 - Certification (02/17/11) 📌📌📌📌
- DASH - Questionnaire 📌📌📌📌

### Current C-Peptide ! 📌📌📌

- 400.2 - 4-Hour Mixed Tolerance Test (MMTT) Specimen Transmittal 📌📌📌📌

Table 22.2

## Forms Used by Central Units Only

CENTRAL OPHTHALMOLOGIC READING UNIT:

032 Fundus Photograph Detailed Color Grading Form

CENTRAL BIOCHEMISTRY LABORATORY:

012 Lipid Reporting Log

020 GFR Reporting Log

021 Renal Reporting Log

040 Hemoglobin A1c Reporting Log

041 Hemoglobin A1c Performance Characteristics

CENTRAL ELECTROCARDIOGRAM READING UNIT

010 Resting Electrocardiogram Grading Form

CENTRAL CAROTID ULTRASOUND READING UNIT

011 Carotid Ultrasonography Grading Form

Table 22.3

## EDIC Mailing Lists

- 100 Clinic Forms Inventory
- 101 Forms Mailing List
- 103 Resting Electrocardiogram Mailing List
- 104 Carotid Ultrasound Mailing List ??
- 105 Lipid, Serum Creatinine, Serum Cystatin, and Saved Specimen Mailing List
- 106
- 107 Fundus Photograph Mailing List
- 108 Hemoglobin A1c Specimen Mailing List
- 109 110 HbA1c Quality Control Mailing List
- 111 Renal Quality Control Mailing List
- 112
- 113 Lipid Quality Control Mailing List
- 114 115 Renal Studies Specimen Mailing List
- 116
- 118 119
- 400 C-Peptide Mailing list

Table 22.4

## Forms Used to Request Certification of a Clinic Staff Member

- 120 Certification of ECG Technician
- 121 Certification of Carotid Sonographer
- 122 Certification of Visual Acuity Examiner
- 123 Certification of Study Coordinator or Principal Investigator
- 124 EDIC Certification/Site Visitor Checklist
- 125 Certification of Neurobehavioral Technician
- 126 Request for Certification of Vibration Perception Threshold Tester
- 127 Request for Certification of Autonomic Nervous System Tester
- 128 Request for Certification of Neurological Examiner
- 129 Request for Certification of Electromyographers

Table 22.5

## Special-Purpose Forms

PATIENT STATUS FORMS

- 042 Notification and Further Details of Severe Hypoglycemia
- 140 Notification of Death
- 141 Notification of Missed Clinic Visit
- 142 Notification of Patient Transfer or Move
- 143 Notification of Update to Personal Locator Form
- 144 Notification of Transfer to Inactive Status
- 145 Checklist for Tracking Inactive or Recalcitrant Patient
- 146 Checklist for Tracking Vital Status of All DCCT/EDIC Participants

VERIFICATION FORMS

- 090 Verification of Cardiovascular Disease
- 091 Verification of Cerebrovascular Disease
- 092 Verification of Peripheral Vascular Disease or Lower Extremity Ulcer
- 093 Verification of DKA
- 094 Verification of Psychiatric Disease Requiring Treatment
- 095 Verification of Major Accident

Table 22.6

## Forms Used by Clinic During Patient Follow-up

COMPLETED ANNUALLY:

- 002 Annual Medical History and Physical Examination
- 004 Current Medications
- 050 Michigan Neuropathy Screening Instrument and 10 gm Filament Exam
- 070 Health Care Delivery Questionnaire

COMPLETED BIENNIALLY:

- 060 Quality of Life Questionnaire
- 061 Health Status Questionnaire

COMPLETED AS A FUNCTION OF RANDOMIZATION DATE:

- 030 Ophthalmic and Visual Acuity Examination
- 031 Fundus Photography
- 033 National Eye Institute Visual Functioning Questionnaire – 25  
(VFQ-25) Version 2000

COMPLETED ONCE:

- 005 Ethnicity Questionnaire
- 051 Neurological History and Examinations
- 052 Nerve Conduction Studies
- 054 Vibration Perception Threshold
- 057 Autonomic Symptom Profile
- 058 Neuropathy Specific Quality of Life Questionnaire
- 062 Quality of Well-Being Scale, Self Administered, QWB-SA, V1.04
- 146 Checklist for Tracking Vital Status of All DCCT/EDIC Participants
- 300 Cheiroarthropathy
- 301 DASH

## HISTORIC FORMS

Forms that are no longer in use are can be found on the EDIC secure website of the FORMS page under Historic Forms.

Figure 22.1

Patient's Entire EDIC Schedule of Examinations and Procedures to Complete

(Replace with hard copy)

Figure 22.2

Patient's One Year EDIC Schedule of Examinations and Procedures to Complete

(Replace with Hard Copy)

Figure 22.3

## EDIC Mailing Schedule of Forms

<u>Clinic Number</u>	<u>Week of Month</u>
1-7	1st Week
8-14	2nd Week
15-21	3rd Week
22-27,41	4th Week

Figure 22.4

## Listing of EDIC Study Week Numbers

List #	Week Date	EDIC Week Number	List #	Week Date	EDIC Week Number	List #	Week Date	EDIC Week Number
594	04/14/06	1200	638	02/16/07	1244	682	12/21/07	1288
595	04/21/06	1201	639	02/23/07	1245	683	12/28/07	1289
596	04/28/06	1202	640	03/02/07	1246	684	01/04/08	1290
597	05/05/06	1203	641	03/09/07	1247	685	01/11/08	1291
598	05/12/06	1204	642	03/16/07	1248	686	01/18/08	1292
599	05/19/06	1205	643	03/23/07	1249	687	01/25/08	1293
600	05/26/06	1206	644	03/30/07	1250	688	02/01/08	1294
601	06/02/06	1207	645	04/06/07	1251	689	02/08/08	1295
602	06/09/06	1208	646	04/13/07	1252	690	02/15/08	1296
603	06/16/06	1209	647	04/20/07	1253	691	02/22/08	1297
604	06/23/06	1210	648	04/27/07	1254	692	02/29/08	1298
605	06/30/06	1211	649	05/04/07	1255	693	03/07/08	1299
606	07/07/06	1212	650	05/11/07	1256	694	03/14/08	1300
607	07/14/06	1213	651	05/18/07	1257	695	03/21/08	1301
608	07/21/06	1214	652	05/25/07	1258	696	03/28/08	1302
609	07/28/06	1215	653	06/01/07	1259	697	04/04/08	1303
610	08/04/06	1216	654	06/08/07	1260	698	04/11/08	1304
611	08/11/06	1217	655	06/15/07	1261	699	04/18/08	1305
612	08/18/06	1218	656	06/22/07	1262	700	04/25/08	1306
613	08/25/06	1219	657	06/29/07	1263	701	05/02/08	1307
614	09/01/06	1220	658	07/06/07	1264	702	05/09/08	1308
615	09/08/06	1221	659	07/13/07	1265	703	05/16/08	1309
616	09/15/06	1222	660	07/20/07	1266	704	05/23/08	1310
617	09/22/06	1223	661	07/27/07	1267	705	05/30/08	1311
618	09/29/06	1224	662	08/03/07	1268	706	06/06/08	1312
619	10/06/06	1225	663	08/10/07	1269	707	06/13/08	1313
620	10/13/06	1226	664	08/17/07	1270	708	06/20/08	1314
621	10/20/06	1227	665	08/24/07	1271	709	06/27/08	1315
622	10/27/06	1228	666	08/31/07	1272	710	07/04/08	1316
623	11/03/06	1229	667	09/07/07	1273	711	07/11/08	1317
624	11/10/06	1230	668	09/14/07	1274	712	07/18/08	1318
625	11/17/06	1231	669	09/21/07	1275	713	07/25/08	1319
626	11/24/06	1232	670	09/28/07	1276	714	08/01/08	1320
627	12/01/06	1233	671	10/05/07	1277	715	08/08/08	1321
628	12/08/06	1234	672	10/12/07	1278	716	08/15/08	1322
629	12/15/06	1235	673	10/19/07	1279	717	08/22/08	1323
630	12/22/06	1236	674	10/26/07	1280	718	08/29/08	1324
631	12/29/06	1237	675	11/02/07	1281	719	09/05/08	1325
632	01/05/07	1238	676	11/09/07	1282	720	09/12/08	1326
633	01/12/07	1239	677	11/16/07	1283	721	09/19/08	1327
634	01/19/07	1240	678	11/23/07	1284	722	09/26/08	1328
635	01/26/07	1241	679	11/30/07	1285	723	10/03/08	1329
636	02/02/07	1242	680	12/07/07	1286	724	10/10/08	1330
637	02/09/07	1243	681	12/14/07	1287	725	10/17/08	1331

List #	Week Date	EDIC Week Number	List #	Week Date	EDIC Week Number	List #	Week Date	EDIC Week Number
726	10/24/08	1332	774	09/25/09	1380	822	08/27/10	1428
727	10/31/08	1333	775	10/02/09	1381	823	09/03/10	1429
728	11/07/08	1334	776	10/09/09	1382	824	09/10/10	1430
729	11/14/08	1335	777	10/16/09	1383	825	09/17/10	1431
730	11/21/08	1336	778	10/23/09	1384	826	09/24/10	1432
731	11/28/08	1337	779	10/30/09	1385	827	10/01/10	1433
732	12/05/08	1338	780	11/06/09	1386	828	10/08/10	1434
733	12/12/08	1339	781	11/13/09	1387	829	10/15/10	1435
734	12/19/08	1340	782	11/20/09	1388	830	10/22/10	1436
735	12/26/08	1341	783	11/27/09	1389	831	10/29/10	1437
736	01/02/09	1342	784	12/04/09	1390	832	11/05/10	1438
737	01/09/09	1343	785	12/11/09	1391	833	11/12/10	1439
738	01/16/09	1344	786	12/18/09	1392	834	11/19/10	1440
739	01/23/09	1345	787	12/25/09	1393	835	11/26/10	1441
740	01/30/09	1346	788	01/01/10	1394	836	12/03/10	1442
741	02/06/09	1347	789	01/08/10	1395	837	12/10/10	1443
742	02/13/09	1348	790	01/15/10	1396	838	12/17/10	1444
743	02/20/09	1349	791	01/22/10	1397	839	12/24/10	1445
744	02/27/09	1350	792	01/29/10	1398	840	12/31/10	1446
745	03/06/09	1351	793	02/05/10	1399	841	01/07/11	1447
746	03/13/09	1352	794	02/12/10	1400	842	01/14/11	1448
747	03/20/09	1353	795	02/19/10	1401	843	01/21/11	1449
748	03/27/09	1354	796	02/26/10	1402	844	01/28/11	1450
749	04/03/09	1355	797	03/05/10	1403	845	02/04/11	1451
750	04/10/09	1356	798	03/12/10	1404	846	02/11/11	1452
751	04/17/09	1357	799	03/19/10	1405	847	02/18/11	1453
752	04/24/09	1358	800	03/26/10	1406	848	02/25/11	1454
753	05/01/09	1359	801	04/02/10	1407	849	03/04/11	1455
754	05/08/09	1360	802	04/09/10	1408	850	03/11/11	1456
755	05/15/09	1361	803	04/16/10	1409	851	03/18/11	1457
756	05/22/09	1362	804	04/23/10	1410	852	03/25/11	1458
757	05/29/09	1363	805	04/30/10	1411	853	04/01/11	1459
758	06/05/09	1364	806	05/07/10	1412	854	04/08/11	1460
759	06/12/09	1365	807	05/14/10	1413	855	04/15/11	1461
760	06/19/09	1366	808	05/21/10	1414	856	04/22/11	1462
761	06/26/09	1367	809	05/28/10	1415	857	04/29/11	1463
762	07/03/09	1368	810	06/04/10	1416	858	05/06/11	1464
763	07/10/09	1369	811	06/11/10	1417	859	05/13/11	1465
764	07/17/09	1370	812	06/18/10	1418	860	05/20/11	1466
765	07/24/09	1371	813	06/25/10	1419	861	05/27/11	1467
766	07/31/09	1372	814	07/02/10	1420	862	06/03/11	1468
767	08/07/09	1373	815	07/09/10	1421	863	06/10/11	1469
768	08/14/09	1374	816	07/16/10	1422	864	06/17/11	1470
769	08/21/09	1375	817	07/23/10	1423	865	06/24/11	1471
770	08/28/09	1376	818	07/30/10	1424	866	07/01/11	1472
771	09/04/09	1377	819	08/06/10	1425	867	07/08/11	1473
772	09/11/09	1378	820	08/13/10	1426	868	07/15/11	1474
773	09/18/09	1379	821	08/20/10	1427	869	07/22/11	1475

List #	Week Date	EDIC Week Number	List #	Week Date	EDIC Week Number	List #	Week Date	EDIC Week Number
870	07/29/11	1476	918	06/29/12	1524	966	05/31/13	1572
871	08/05/11	1477	919	07/06/12	1525	967	06/07/13	1573
872	08/12/11	1478	920	07/13/12	1526	968	06/14/13	1574
873	08/19/11	1479	921	07/20/12	1527	969	06/21/13	1575
874	08/26/11	1480	922	07/27/12	1528	970	06/28/13	1576
875	09/02/11	1481	923	08/03/12	1529	971	07/05/13	1577
876	09/09/11	1482	924	08/10/12	1530	972	07/12/13	1578
877	09/16/11	1483	925	08/17/12	1531	973	07/19/13	1579
878	09/23/11	1484	926	08/24/12	1532	974	07/26/13	1580
879	09/30/11	1485	927	08/31/12	1533	975	08/02/13	1581
880	10/07/11	1486	928	09/07/12	1534	976	08/09/13	1582
881	10/14/11	1487	929	09/14/12	1535	977	08/16/13	1583
882	10/21/11	1488	930	09/21/12	1536	978	08/23/13	1584
883	10/28/11	1489	931	09/28/12	1537	979	08/30/13	1585
884	11/04/11	1490	932	10/05/12	1538	980	09/06/13	1586
885	11/11/11	1491	933	10/12/12	1539	981	09/13/13	1587
886	11/18/11	1492	934	10/19/12	1540	982	09/20/13	1588
887	11/25/11	1493	935	10/26/12	1541	983	09/27/13	1589
888	12/02/11	1494	936	11/02/12	1542	984	10/04/13	1590
889	12/09/11	1495	937	11/09/12	1543	985	10/11/13	1591
890	12/16/11	1496	938	11/16/12	1544	986	10/18/13	1592
891	12/23/11	1497	939	11/23/12	1545	987	10/25/13	1593
892	12/30/11	1498	940	11/30/12	1546	988	11/01/13	1594
893	01/06/12	1499	941	12/07/12	1547	989	11/08/13	1595
894	01/13/12	1500	942	12/14/12	1548	990	11/15/13	1596
895	01/20/12	1501	943	12/21/12	1549	991	11/22/13	1597
896	01/27/12	1502	944	12/28/12	1550	992	11/29/13	1598
897	02/03/12	1503	945	01/04/13	1551	993	12/06/13	1599
898	02/10/12	1504	946	01/11/13	1552	994	12/13/13	1600
899	02/17/12	1505	947	01/18/13	1553	995	12/20/13	1601
900	02/24/12	1506	948	01/25/13	1554	996	12/27/13	1602
901	03/02/12	1507	949	02/01/13	1555	997	01/03/14	1603
902	03/09/12	1508	950	02/08/13	1556	998	01/10/14	1604
903	03/16/12	1509	951	02/15/13	1557	999	01/17/14	1605
904	03/23/12	1510	952	02/22/13	1558	1000	01/24/14	1606
905	03/30/12	1511	953	03/01/13	1559	1001	01/31/14	1607
906	04/06/12	1512	954	03/08/13	1560	1002	02/07/14	1608
907	04/13/12	1513	955	03/15/13	1561	1003	02/14/14	1609
908	04/20/12	1514	956	03/22/13	1562	1004	02/21/14	1610
909	04/27/12	1515	957	03/29/13	1563	1005	02/28/14	1611
910	05/04/12	1516	958	04/05/13	1564	1006	03/07/14	1612
911	05/11/12	1517	959	04/12/13	1565	1007	03/14/14	1613
912	05/18/12	1518	960	04/19/13	1566	1008	03/21/14	1614
913	05/25/12	1519	961	04/26/13	1567	1009	03/28/14	1615
914	06/01/12	1520	962	05/03/13	1568	1010	04/04/14	1616
915	06/08/12	1521	963	05/10/13	1569	1011	04/11/14	1617
916	06/15/12	1522	964	05/17/13	1570	1012	04/18/14	1618
917	06/22/12	1523	965	05/24/13	1571	1013	04/25/14	1619

List #	Week Date	EDIC Week Number	List #	Week Date	EDIC Week Number	List #	Week Date	EDIC Week Number
1014	05/02/14	1620	1061	03/27/15	1667	1108	02/19/16	1714
1015	05/09/14	1621	1062	04/03/15	1668	1109	02/26/16	1715
1016	05/16/14	1622	1063	04/10/15	1669	1110	03/04/16	1716
1017	05/23/14	1623	1064	04/17/15	1670	1111	03/11/16	1717
1018	05/30/14	1624	1065	04/24/15	1671	1112	03/18/16	1718
1019	06/06/14	1625	1066	05/01/15	1672	1113	03/25/16	1719
1020	06/13/14	1626	1067	05/08/15	1673	1114	04/01/16	1720
1021	06/20/14	1627	1068	05/15/15	1674	1115	04/08/16	1721
1022	06/27/14	1628	1069	05/22/15	1675	1116	04/15/16	1722
1023	07/04/14	1629	1070	05/29/15	1676	1117	04/22/16	1723
1024	07/11/14	1630	1071	06/05/15	1677	1118	04/29/16	1724
1025	07/18/14	1631	1072	06/12/15	1678	1119	05/06/16	1725
1026	07/25/14	1632	1073	06/19/15	1679	1120	05/13/16	1726
1027	08/01/14	1633	1074	06/26/15	1680	1121	05/20/16	1727
1028	08/08/14	1634	1075	07/03/15	1681	1122	05/27/16	1728
1029	08/15/14	1635	1076	07/10/15	1682	1123	06/03/16	1729
1030	08/22/14	1636	1077	07/17/15	1683	1124	06/10/16	1730
1031	08/29/14	1637	1078	07/24/15	1684	1125	06/17/16	1731
1032	09/05/14	1638	1079	07/31/15	1685	1126	06/24/16	1732
1033	09/12/14	1639	1080	08/07/15	1686	1127	07/01/16	1733
1034	09/19/14	1640	1081	08/14/15	1687	1128	07/08/16	1734
1035	09/26/14	1641	1082	08/21/15	1688	1129	07/15/16	1735
1036	10/03/14	1642	1083	08/28/15	1689	1130	07/22/16	1736
1037	10/10/14	1643	1084	09/04/15	1690	1131	07/29/16	1737
1038	10/17/14	1644	1085	09/11/15	1691	1132	08/05/16	1738
1039	10/24/14	1645	1086	09/18/15	1692	1133	08/12/16	1739
1040	10/31/14	1646	1087	09/25/15	1693	1134	08/19/16	1740
1041	11/07/14	1647	1088	10/02/15	1694	1135	08/26/16	1741
1042	11/14/14	1648	1089	10/09/15	1695	1136	09/02/16	1742
1043	11/21/14	1649	1090	10/16/15	1696	1137	09/09/16	1743
1044	11/28/14	1650	1091	10/23/15	1697	1138	09/16/16	1744
1045	12/05/14	1651	1092	10/30/15	1698	1139	09/23/16	1745
1046	12/12/14	1652	1093	11/06/15	1699	1140	09/30/16	1746
1047	12/19/14	1653	1094	11/13/15	1700	1141	10/07/16	1747
1048	12/26/14	1654	1095	11/20/15	1701	1142	10/14/16	1748
1049	01/02/15	1655	1096	11/27/15	1702	1143	10/21/16	1749
1050	01/09/15	1656	1097	12/04/15	1703	1144	10/28/16	1750
1051	01/16/15	1657	1098	12/11/15	1704	1145	11/04/16	1751
1052	01/23/15	1658	1099	12/18/15	1705	1146	11/11/16	1752
1053	01/30/15	1659	1100	12/25/15	1706	1147	11/18/16	1753
1054	02/06/15	1660	1101	01/01/16	1707	1148	11/25/16	1754
1055	02/13/15	1661	1102	01/08/16	1708	1149	12/02/16	1755
1056	02/20/15	1662	1103	01/15/16	1709	1150	12/09/16	1756
1057	02/27/15	1663	1104	01/22/16	1710	1151	12/16/16	1757
1058	03/06/15	1664	1105	01/29/16	1711	1152	12/23/16	1758
1059	03/13/15	1665	1106	02/05/16	1712	1153	12/30/16	1759
1060	03/20/15	1666	1107	02/12/16	1713			

Figure 22.5

Example of an Edit Notice from the EDIC

## 23. FEEDBACK REPORTS

### 23.1 Purpose

The purpose of the Feedback Report is to provide the patient with the centrally determined results of his or her examinations each year.

### 23.2 Procedures

The Data Coordinating Center is responsible for generating the Feedback Reports. A report for each patient will be created every year shortly after the patient's annual visit data is on-line at the Data Coordinating Center. An example of the Feedback Report is in Figure 23.1. The Data Coordinating Center will send the reports to the EDIC clinic, which will keep a copy for the clinic's records and then forward the results to the patient and to the patient's medical care physician, if requested. The Study Coordinator or Principal Investigator may either discuss the results with the patient in person or over the telephone, or may decide to let the patient's own medical care physician discuss the results with the patient. As is the case for all laboratory results, if the value appears to be in error, the clinic should ask the CBL to repeat the measurement or redo the procedure.

### 23.3 Format

The results of the examinations performed for the EDIC will be added on to the patient's DCCT results that were sent to the patient as part of the DCCT Patient Debriefing Packet. For example, if a patient participated in the DCCT for six years, the first EDIC Feedback Reports that the patient receives will include exam results for a total of seven years (six years DCCT and one year EDIC).

The reports provide results for the following examinations:

HbA1c Measurement (%)  
 Retinopathy Level as measured with the ETDRS grading system  
 Visual Acuity (Snellen units)  
 Macular Edema Status  
 Intraocular Pressure (mmHg)  
 Glomerular Filtration Rate (Creatinine Clearance and GFR)  
 Serum Creatinine, Urine Albumin Excretion, Cystatin C  
 Lipids (Cholesterol, Triglycerides, HDL, LDL)

Test reports associated with ancillary studies or new projects are generated and either distributed by the DCC or posted on the clinic's Private Page, per the ancillary study protocol. Some examples of these include: Carotid Artery Grading Result, Neurology (ANS, neurologic exam, nerve conduction, vibration perception threshold), Cardiac MRI.

Consolidated reports of the following measures are posted periodically on the clinic's Private Page of the EDIC website:

- Blood pressure measurements / ABI
- Weight / height / BMI / waist-hip measures
- Creatinine / GFR

These reports include all participants at the clinic. These reports are accessible only to the individual clinic staff. Individual patient reports can be printed from these compiled documents and shared with participants, as requested or desire.

EDIC PATIENT FEEDBACK REPORT

Personal Data Presentation

EDIC Clinic Number:

EDIC Identification Number:

Birthdate:

Gender:

Month and Year of Initial Diagnosis of Diabetes:

Randomization Date:

Duration of Diabetes at Randomization:

Retinopathy Group at Baseline in DCCT:

Treatment Group in DCCT:

Primary

Experimental

Principal Investigator:

William Dahms, M.D.

Study Coordinator:

Betty Brown, R.N.

Patient ID

## DIABETES MANAGEMENT

Glycated Hemoglobin

Date of HbA1c Measurement: May 21, 1995

Study Time (Years)	Duration of Diabetes (Years, Months)	HbA1c (Percent)
DCCT Baseline	4, 0	10.5
1	5, 0	6.6
2	6, 0	6.1
3	7, 0	8.1
4	8, 0	7.6
5	9, 0	7.8
6	10, 0	7.6
7	10, 11	7.5
8	12, 0	7.3
9	13, 0	7.6
Close-Out	13, 0	7.2
EDIC 07/29/94	14, 6	8.5
05/21/95	15, 4	8.7

Patient ID \_\_\_\_\_

## KIDNEY FUNCTION

Date of Renal Exam: May 11, 1995

Study Time (Years)	Duration of Diabetes (Years, Months)	Serum Creatinine (mg/dl)	Urine Albumin Excretion (mg/24 hrs)
DCCT Baseline	9, 0	0.8	6
1	10, 1	0.8	7
2	11, 0	0.8	6
3	12, 1	0.8	4
4	13, 1	0.7	6
5	14, 1	0.8	6
6	15, 0	0.8	17
Close-Out	15, 6	0.8	12
EDIC 08/01/94	17, 1	0.9	NSPP*
05/11/95	17, 10	0.9	7

\*NSPP = Not Scheduled Per Protocol

Serum creatinine greater than or equal to 1.5mg/dl indicates decreased kidney function

Urine albumin excretion (AER) between 40mg/24hrs and 300mg/24hrs indicates an increased risk of development of decreased kidney function.

AER greater than 300mg/24hrs indicates kidney disease.

Patient ID

## Glomerular Filtration Rate

Date of Renal Exam: April 10, 1995

Study Time (Years)	Duration of Diabetes (Years, Months)	Creatinine Clearance (ml/min/1.73m <sup>2</sup> )	Iothalamate Clearance (ml/min/1.73m <sup>2</sup> )	Coefficient Of Variation
DCCT Baseline	2, 1	153	.	
1	3, 1	147	.	
2	4, 1	91	.	
3	5, 1	110	155	
4	6, 1	117	.	
5	7, 1	149	.	
6	8, 1	135	.	
7	9, 1	122	145	
Close-Out	9, 6	122	145	
EDIC 04/10/95	11, 8	125	132	13.2

A value less than 70 ml/min/1.73m<sup>2</sup> indicates decreased kidney function

Clinic 07

Patient ID \_\_\_\_\_

## Lipids

Date of Blood Collection: May 4, 1995

Study Time (Years)	Duration of Diabetes (Years, Months)	Cholesterol (mg/dl)	Triglycerides (mg/dl)	HDL Cholesterol (mg/dl)	LDL Cholesterol (mg/dl)
DCCT Baseline	1, 5	191	49	61	120
1	2, 5	205	75	66	124
2	3, 5	181	76	55	111
3	4, 5	168	73	56	97
4	5, 5	234	131	81	127
Close-Out	5, 4	234	131	81	127
EDIC 05/04/95	7, 6	154	36	65	82

The American Diabetes Association recommends that LDL cholesterol levels above 130 mg/dl be reduced by diet (and if still above 160 mg/dl by drug) therapy. The NCEP II Treatment Panel Report further suggests that aggressive lowering of LDL cholesterol (with a goal concentration below 100 mg/dl) can be applied to diabetic patients. Serum triglycerides greater than 500 mg/dl indicate hypertriglyceridemia and therefore LDL cannot be calculated.

## **24. PROCEDURES FOR CERTIFICATION**

### **24.1 Introduction**

It is essential that procedures be standardized within each center and among the participating clinical centers to assure that data from all centers are comparable and, therefore, can be pooled. Training sessions are one way to promote standardization of procedures. Individuals performing the procedures for acquiring the multiple outcome measurements need to be trained, tested, and certified as competent. Periodic retraining and certification are useful in long-term studies to reinforce consistency and train new personnel.

### **24.2 Certification of an EDIC Clinical Center**

The clinical staff who were involved in the DCCT / EDIC and are now a part of the EDIC Continuing Follow-Up have already completed the stringent certification process for the procedures that will be conducted. New personnel, however, will have to be certified before performing any tests (see Section 24.4).

### **24.3 Certification Procedures for the Various Examinations**

#### **1. Certification of the ECG Technician:**

If the ECG technician was certified for the DCCT, he/she does not need to be re-certified for the EDIC Continuing Follow-Up, regardless of whether a different ECG machine is being used or not.

If the ECG technician was not certified for the DCCT / EDIC, he/she must do the following to become certified. Technicians charged with responsibility for ECG recording in the EDIC clinics must submit three 12 standard lead electrocardiograms and a Request for Certification of ECG Technician form, EDIC Form 120 to the Data Coordinating Center. Technicians on staff of the cardiology laboratory and internists, however, need submit only one 12 standard lead ECG and EDIC Form 120. The ECGs should be sent to the Data Coordinating Center, which will forward them to the Central ECG Reading Unit (CERU) for review. All recommendations regarding certification will be returned to the Data Coordinating Center and forwarded to the clinic.

#### **2. Certification of Carotid Artery Sonographer:**

In order to obtain certification, the sonographer must:

- a) Understand ultrasound principles.
- b) Demonstrate ability to use Toshiba 270 duplex system (or other EDIC acceptable machine).
- c) Complete training program and successfully complete final exam.

- d) Perform studies on five non-EDIC patients and submit them to the Central Carotid Ultrasound Reading Unit.

The sonographer must also submit an EDIC Form 121, Request for Certification of Carotid Artery Sonographer to the Carotid Ultrasound Reading Unit with the five studies. A copy of the Form 121 should be sent to the Data Coordinating Center. The Data Coordinating Center will notify those clinics that are certified.

### 3. Certification of the Fundus Photographer:

As of May 8, 2012, all applications for certification for fundus photo equipment and new imaging technicians need to be done online via the Imaging Request and Information System (IRIS) of CORU (Central Ophthalmic Reading Unit). The URL is <https://iris.opth.wisc.edu>. This application is for CERTIFICATIONS only. Certifications for both the photographer and equipment may be made simultaneously. Subject visits should still be submitted in the manner currently used, be it through the Fundus Photograph Reading Center (FPRC) PORTAL or on CD via courier.

A username and password are required to log in to the system. If the applicant has worked on other studies and already has a username/password for the FPRC PORTAL, they will use the same credentials for IRIS. They would contact the FPRC at [irishelp@rc.opth.wisc.edu](mailto:irishelp@rc.opth.wisc.edu) or 608-410-0619 to request EDIC certification. If one does not have a username, they also need to contact the FPRC to start the certification process. Once a username is established, follow the instructions to set up a password. Please find attached documents regarding passwords.



Establishing  
Username Password i

Once the username and password have been established, follow these instructions for submitting the photo equipment and/or imaging technician request. Note: Java software is required to upload images. If Java is not currently installed on your computer, click on the link "Get Java" on IRIS's main page.



Submitting  
Certification Request:

The CORU will email the certification results to the Data Coordinating Center. The DCC will then email the individual EDIC center.

If the fundus photographer was certified for the DCCT/EDIC for standard photography, then he/she does not need to be re-certified for standard film photography in the EDIC Continuing Follow-Up, regardless of how long it has been since he/she has taken a photograph.

In June, 2009, the EDIC Core Followup study group approved the use of digital photography as the standard method of obtaining fundus imaging in EDIC. Certification is needed for all photographers obtaining digital images, even if they were certified previously for standard photography. Separate certifications numbers are given for standard photos and digital photography. Photographers and systems can be certified with the same group of images, provided that the images meet the certification criteria for both. The preferred order would be certification of the system then photographer but sites can apply in whatever order they choose. In either case they cannot study photography should not be undertaken take images until both certifications are approved.

Photographers taking photographs (or digital images: the terms will be used interchangeably in this procedure) for the EDIC Study must submit a CORU Photographer Certification Request Form 035.

Photographer certification is specific for EDIC and each photographer requesting certification must submit a signed EDIC Certification Request Form. Digital photography system certification requires a separate study-specific form for each system being used. (see previous section).

Certification consists of (1) review of study synopsis/protocol and imaging procedures and (2) demonstration of the ability to perform the imaging procedure(s) by submission of images of acceptable quality. The second requirement may be waived if the photographer has prior certification at the CORU using an identical procedure, and has been actively taking images, judged to be of good quality by the CORU, during the past 12 months. Photographers who are certified for a similar procedure also may be asked to submit sample photographs to become certified.

Photographers who are not eligible for certification on the basis of previous CORU certification should submit color images of four (4) eyes (two right eyes and two left eyes) taken according to the 7-Std-D procedure. The color images may be taken of patients with whom photography is being carried out for clinical purposes or of normal volunteers.

Photographers previously certified for this procedure on film (7Std-F) (7Std-D) must submit stereo color photographs of two (2) eyes (one right eye and one left eye) taken according to the 7-Std-D procedure. This allows the CORU to check image quality (stereo effect, color quality and image resolution) and to determine whether images can be opened and archived

For certification images, comply with HIPAA regulations by masking patient identifiers on the digital files. If sending images on CD/DVD and pre-printed labels are not available, hand-label using a permanent felt-tip marker. The CD/DVD label must indicate the fundus camera head serial number, patient identifier, photographer's name, date of photography and that the images are certification sets.

Photographers are encouraged to send complete submissions for each procedure for which he/she is requesting certification (i.e., if four eyes are required for certification, send all four eyes in one submission).

Photographers who meet certification criteria will receive confirmation of certification. Those who do not meet these criteria will receive feedback from the CORU imaging consultants and may be required to submit additional sets of images. A plan for improving image quality may be necessary after three complete unsuccessful certification submissions.

Certification for photographers must be done on-line by the photographer seeking certification, and not another clinic member as a proxy (e.g., study coordinator on their behalf).

#### **4. System Certification for Digital Imaging**

Any digital system to be used for the EDIC study must be certified for color capture capability before any EDIC participants undergo digital photography. A CORU Digital Color System Certification Request Form (34) must be completed and submitted to CORU to obtain certification along with photo images. If a digital system has been previously certified for digital color capture capability by the CORU for another study and no software or hardware changes have been made since the time of certification, it is only necessary to submit the EDIC form 034.

The preferred order of certifications would be system, and then photographer, but they can be accomplished at the same time (see #3 above).

Please refer to Appendix 18-C of Chapter 18 of the MOO for the details about the specific software requirements and contact information to certify the system if required. Only the standard methods existing in the capture software of the imaging system should be used to isolate images for submission. Specific image handling procedures are outlined by accessing the links listed in Appendix 18-D of Chapter 18 of the MOO.

The system certification process is complete for color capture capability after the CORU staff ensures that image quality is acceptable and that the files can be successfully viewed and analyzed.

The photography certification protocol is quite demanding and can be a time consuming process; therefore, it should be started as soon as possible. Contact the CORU if you have any questions regarding the protocol before you begin.

#### **5. Certification of the Visual Acuity Examiner:**

No training or special material or funding was available for non-ophthalmologists to be certified as visual acuity examiners. If, however, an ophthalmologist wants a non-

ophthalmologist to be certified, he/she is responsible for the training of that individual and for the examinations done by that person. The certification process for visual acuity is as follows:

- a) The visual acuity examiner who wants to be certified should complete the refraction and acuity sections of EDIC Form 030 on two non-EDIC patients, after careful review of Chapter 18 of the Manual of Operations.
- b) The designated certification examiner will complete Form 122, Certification of Visual Acuity Examiner to report certification status. Form 122 plus the two Form 030's are then submitted to the Data Coordinating Center. The Data Coordinating Center will notify the clinical center of certification.

6. Certification for Shipping Frozen Specimens to the CBL:

Frozen specimens are typically batched and shipped to the Central Biochemistry Laboratory (CBL) at the University of Minnesota on a monthly basis. For certification purposes only, the person seeking certification should fill five 5 ml. tubes (using 1 labeled "CrCy", 1 labeled "UCrA" and 3 "USav" tubes) with water and freeze them. Pack the frozen tubes of water along with EDIC Mailing List 115 (indicating "FOR CERTIFICATION" in the comments section) in an insulated shipping container packed with two and a half pounds of dry ice. Use the packing guidelines in Chapter 14 of the MOO under the "Shipment to the CBL" section.. Each clinic should attempt to ship by Federal Express using the CBL third party account for EDIC, This process is to ensure that clinics are abiding by the required shipping guidelines of the International Aviation Transportation Association. The Data Coordinating Center will notify those clinics that have fulfilled this requirement. There is no certification form specifically for frozen mailing certification.

7. Certification for Shipping HbA1c Specimens to the CBL:

HbA1c specimens (fresh whole blood) need to be shipped to the CBL within six days of collection. For certification purposes only, the person seeking certification should fill two 4.5 ml. tubes (labeled as "HA1c" from two different sets of barcode labels) with 1 mL water each. Pack the two tubes with liquid water plus EDIC Mailing List 108 (indicating "FOR CERTIFICATION" in the comments section) in an appropriate insulated container with a frozen gel pack. Use the packing guidelines in Chapter 14 of the MOO under the "Shipment to the CBL" section. Each clinic should ship by Federal Express using overnight delivery using the CBL third party account for EDIC. This process is to ensure that clinics are abiding by the required shipping guidelines of the International Aviation Transportation Association. The Data Coordinating Center will notify those clinics that have fulfilled this certification requirement. There is no certification form specifically for HbA1c mailings.

8. Certification of Study Coordinator or Principal Investigator as Forms Completer

The Study Coordinator and/or Principal Investigator must be certified if he/she will be completing any section of any form. In order to obtain certification, the Study Coordinator and/or PI must each complete the Annual Medical History and Physical Form (Form 002) on two non-EDIC patients with diabetes. The two Form 002s should be sent to the Data Coordinating Center along with the Request for Certification of Study Coordinator or Principal Investigator (Form 123). The Data Coordinating Center will notify those members of the staff who have correctly completed this process.

#### 9. Certification of Autonomic Nervous System Tester

The Study Coordinator and/or other clinic personnel must be certified if he/she will be conducting the Autonomic Nervous System testing. In order to obtain certification, the ANS tester must review the PowerPoint presentation “ANS Step By Step”, which can be found on the study website’s Projects page (<https://www.dcct-edic.org/EDIC/0SW9W6YX.PDF>).

Next, the ANS tester may do one or more of the following (all optional):

1. Request the CCC for travel funds to Mayo to be certified by the ANS Reading Center in person,
2. Request the CCC for travel funds to another clinic to receive further training from another certified coordinator, or
3. Arrange to receive further training from another certified coordinator at the next Study Coordinator meeting.

Prior to training, Form 127 should be submitted to the Autonomic Reading Center with the name of the individual to be certified. If training is to be completed by an already certified EDIC staff member (as opposed to training by the ANS reading center), include the name and certification status of the trainer on form 127. Once training has been completed, the person to be certified needs to submit one certification study along with Forms 127 and 55 to the Autonomic Reading Center, and when approved to do so, submit a second certification study (on any non-EDIC subject). Two complete and acceptable studies are required for certification.

ANS tests were done in Years 13/14 and repeated in Years 16/17 of the EDIC study. Because of the lapse in time since the Year 13/14 studies, each certified examiner was asked to submit one satisfactory study to the ANS reading center prior to testing subjects in Years 16/17. This will be the case with any further ANS testing.

#### 10. Certification of Vibration Perception Threshold Tester

The Study Coordinator and/or other clinic personnel wishing to be certified as a Vibration Perception Threshold tester may be trained in the procedure by any EDIC staff member already certified. The applicant should carefully review the procedures for vibration testing in the EDIC Manual of Operations, Chapter 20 and, complete two vibration tests using EDIC Form 54. The two vibration tests plus Form 126, Request for Vibration Perception Threshold Tester need to be submitted to Cathy Martin at EDIC

Clinic 41 (University of Michigan) at 734-936-6465 or [martinc@umich.edu](mailto:martinc@umich.edu). Questions about the procedure or certification may be directed to Ms. Martin.

#### 11. Certification of the Neurological Examiner

Certification of neurological examiners is done by Dr. James Albers at the University of Michigan. Physicians wishing to be certified to perform neurology assessments in EDIC should submit their Curriculum Vitae along with form 128, Request for Certification of Neurological Examiner to Dr. Albers. Neurological examiners must have the requisite training and board certification in order to be certified for EDIC. The candidate should then contact Dr. Albers, who will review the protocol in detail, and complete form 128. Dr. Albers can be reached at 734-936-8586 or [jwalbers@umich.edu](mailto:jwalbers@umich.edu). Contact Cathy Martin at the University of Michigan for additional information regarding EDIC Neurology Certification (734-936-6465 or [martinc@umich.edu](mailto:martinc@umich.edu)).

#### 12. Certification of the Electromyographer

Certification of the electromyographers is done by Dr. James Albers at the University of Michigan. Physicians wishing to be certified to perform EDIC nerve conduction studies should submit their Curriculum Vitae along with form 129, Request for Certification of Electromyographers to Dr. Albers. Electromyographers must have the requisite training and appropriate board certifications in order to be certified for Nerve Conduction Studies in EDIC. Once the CV and form 129 have been submitted, the candidate should contact Dr. Albers to review the protocol. The candidate must then complete two nerve conduction studies (form 52 plus the study tracings) following the EDIC protocol, and submit these to Dr. Albers for review and certification. Dr. Albers can be reached at 734-936-8586 or [jwalbers@umich.edu](mailto:jwalbers@umich.edu). Contact Cathy Martin at the University of Michigan for additional information regarding EDIC Electromyography Certification (734-936-6465 or [martinc@umich.edu](mailto:martinc@umich.edu)).

### **24.3 CERTIFICATION OF NEW PERSONNEL AT A CERTIFIED CLINICAL CENTER**

The EDIC is designed to last through the 2000's and into the 2010's. Certainly, new personnel will assume key positions in each and every clinic. Ideally, the training of new personnel should be performed by the individual who is being replaced. If the local training is not possible because of non-overlapping of staff, there are contingency plans for training at the central units, but the costs associated with such training will be from the clinical center and CCC budgets, funding permitting, not the Data Coordinating Center's budget. Any costs associated with review for certification will be paid by the Data Coordinating Center, however.

The new personnel should follow the appropriate procedures for certification described in the previous sections.

#### **24.4 Certification Numbers**

The Data Coordinating Center issues unique numbers to each of the clinical center staff. Those staff members who were a part of the DCCT already have been assigned certification numbers and will retain these same numbers for use in the EDIC Continuing Follow-Up. Any new staff will receive their certification numbers upon completion of the appropriate certification process. These numbers are a means of keeping track of turnover in clinic staff. We will wish to describe the stability of the clinics at the conclusion of the study. In the interim, on a random basis, the Data Coordinating Center will crosscheck the issued number with the name of the person completing the form. This process will provide some assurance that the certified individuals are collecting the appropriate data. (See Figure 24.1.)

A list of certification numbers is kept on the study website's Resources page.

Figure 24.1  
Certification Requirements

EDIC CLINICAL CENTERS	1	2	3	4	5	6	7	8	9	10	11	CERTIFICATION DATE

LEGEND:

- 1 = Certification of ECG Technician
- 2 = Certification of Carotid Artery Sonographer
- 3 = Certification of Fundus Photographer
- 4 = Certification of Visual Acuity Examiner
- 5 = Frozen specimens shipped to CBL
- 6 = HbA1c specimens shipped to CBL
- 7 = Certification of EDIC Data Forms Completer
- 8 = Certification of ANS Tester
- 9 = Certification of VPT Tester
- 10 = Certification of Neurological Examiner
- 11 = Certification of Electromyographer

## 25. POLICY AND GUIDELINES FOR PARTICIPANT TRANSFERS

### 25.1 Introduction

The ultimate goal of the policies and guidelines that follow is to keep subjects participating in the EDIC study. The prime considerations in transferring follow-up of participants are to maintain active participation and to continue complete and valid data collection. These guidelines are intended to establish uniform policies throughout the study group and to encourage open communication and a sense of teamwork among the clinical centers.

These policies and guidelines pertain to: (1) permanent and temporary relocations of EDIC participants to the geographic locale of another EDIC clinical center, and (2) permanent and temporary relocations of EDIC participants to a geographic area not served by an EDIC clinical center.

Participants who change residence during a long term multicenter study pose numerous potential problems. These include loss of follow-up, decreased adherence to the protocol, decreased interest in full participation, and increased costs and workload for the EDIC team in maintaining contact.

Each time an EDIC participant moves away from a clinical center the situation is unique and needs to be considered in a most sensitive manner. Taking the time to fully inform the participant of the various options for continuing EDIC participation promotes willingness to remain in the study. A collaborative, flexible relationship between the sending (initiating the transfer) and receiving (proposed clinic to receive the transfer participant) clinical centers promotes a smooth transition for the participant.

Participant transfers may be either permanent or temporary. A PERMANENT transfer is defined as a change of EDIC clinical center assignment due to the establishment of a permanent change of residence. A TEMPORARY transfer is defined as a change of EDIC clinical center assignment without the intention of establishing a permanent residence, e.g., when someone is assigned to work temporarily in a new area or is making an extended visit to an area closer to a different EDIC clinical center.

Participants who are considered “inactive” or difficult to follow are not to be transferred to another clinical center because of geographic proximity without the express agreement of the EDIC staff at the receiving center. See **Chapter 13 of the MOO** for a discussion of management of inactive participants. Instead, every effort should continue to be made by the assigned clinical center to maintain contact with the inactive participant unless he or she has withdrawn consent.

### 25.2 Participant Relocations Closer to Another EDIC Clinical Center

Being “close” to an EDIC clinical center means being within an area that is geographically close enough for a participant to visit the center without requiring undue time, trouble, hardship, or significant expense. This protocol does not mandate an automatic transfer of responsibility between clinical centers because of a move to an area geographically closer to another EDIC center. The participant and the study staff at the current clinical center should discuss plans for clinical center assignment based on the individual situation and with the goal of continued study participation.

### **25.2.1 Permanent Transfer**

A participant who makes a permanent move to a locale closer to another EDIC clinical center should ideally be officially transferred to the new center when possible, but only if the participant is amenable to that plan. In some cases, the participant may have such strong ties with the current clinical center staff that there may be some hesitation in transferring. In such a situation, using a “trial visit” (i.e. temporary transfer) may be an effective way of allowing the participant to meet staff and acclimate to the new clinical center.

It is expected that over the course of the study most clinical centers will both send and receive transfer participants. The five-digit subject identification number assigned to each participant upon entrance into the DCCT will remain with the participant for the duration of EDIC, regardless of subsequent transfers. The procedures outlined below should be followed:

#### **1. The Sending Clinical Center**

- a) The current EDIC study team initiates the transfer of an EDIC participant by discussing the transfer with the participant, confirming his or her agreement with the plan, and obtaining written consent for release of information to the receiving clinical center. Provide the participant with information about the receiving clinical center including names, addresses, and phone numbers of key team members. Discuss the potential for differences in EDIC clinical center modes of operation with the participant but give assurance that the study goals and overall methods are protocol-driven and remain the same wherever he or she may be seen.
- b) Contact the receiving clinical center’s study staff at the earliest possible opportunity about the need to transfer a participant.
- c) The sending clinical center’s Principal Investigator or Study Coordinator should write a summary of the participant’s EDIC history and send it to the receiving clinical center along with all pertinent contact information, schedule of upcoming assessments, eye photo labels, EDIC files and related medical records as soon as possible. However, these can be sent only after consent to release information has been obtained from the participant.
- d) The sending clinical center should complete the Notification of Transfer Form 142, and send it to the Data Coordinating Center in the next monthly mailing. A copy must also be sent to the receiving clinical center.

#### **2. Receiving Clinical Center**

- a) An EDIC clinical center is expected to accept the transfer participant from another EDIC center. The receiving clinical center should expect to be contacted by staff of the sending clinical center in sufficient time to allow opportunity for questions to be addressed and for planning well ahead of the time for the next annual visit. At some clinical centers it may be necessary to notify the Human Subjects Division of the transfer and increase in number of participants at the

time of transfer, rather than waiting for the time of the next annual institutional review.

b) As soon as possible, the receiving clinical center staff should complete a welcome letter and/or phone call to the participant including information about the staff, contact information, and directions to the center. If it is time to schedule the annual visit that can be done at the same time. If travel arrangements are necessary, see section 26.2.2 of the MOO to ensure that the participant's travel needs have been discussed and met.

c) If difficulties arise, contact the sending clinical center for consultation and advice.

### 3. Former Clinical Center's Role after the Transfer

a) The sending clinical center should relinquish the position of follow-up team and defer requests for advice to the receiving clinical center staff. Recognize and accept that operational styles may differ between clinical centers and that confusion will result if participants are given conflicting information from two different clinics. Criticism (either implied or specific) of the new clinical center or its methods must be avoided, as it only serves to undermine the participant's confidence in the study. Collaboration between the two clinical centers can ensure a smooth transition.

b) If the participant communicates concerns regarding the new clinical center, tactfully transmit this information to that center's staff and assist, as possible, in resolving the issues.

c) The sending clinical center may maintain social contact through greeting cards, local newsletters, etc., as appropriate, for such contact can serve to reassure the participant that s/he has not been abandoned.

#### **25.2.2 Temporary Transfer**

A relocation that is not permanent is one in which the assigned clinical center requests the temporary assistance of another center in the follow-up of an EDIC participant. This is most often done on a one-time only basis, but also can be for more than one visit in a row. The Data Coordinating Center needs to know (via Notification of Patient Transfer Form 142) which clinical center actually saw the participant, and will track if the move is temporary vs. permanent. More than one annual visit, asked of another clinical center on a temporary basis should trigger the discussion with the participant regarding a permanent transfer

#### 1. Assigned Clinical Center Responsibilities

a) As soon as the temporary need to visit another EDIC clinical center is made known by the participant, the sending Study Coordinator contacts the study staff of an identified receiving clinical center to discuss the need for assistance. A signed consent to release information is needed from the participant to allow transmission of information between institutions.

- b) After arrangements to accept the participant are made with the receiving clinical center, discuss a plan for follow-up with both the receiving center staff and the participant. Foster open communication between the participant and the receiving clinical center. The participant will need to discuss and sign all appropriate consent documents at the receiving clinical center, even for a temporary transfer.
  - c) The Principal Investigator and/or the Study Coordinator should prepare a written summary of the participant's pertinent medical history well in advance of the participant's visit to the receiving clinical center, and send it to that center along with any necessary materials. (e.g. consent to release information, history of EDIC labs, etc.)
  - d) With a temporary transfer, reimbursement for travel expenses to reach the receiving clinical center is the responsibility of the sending clinical center. See section 25.4 regarding travel expenses.
  - e) File the Notification of Patient Transfer Form 142, with the Data Coordinating Center in the next monthly forms mailing, and send a copy to the receiving clinical center as well.
2. Receiving Clinical Center's Role
- a) It is expected that the staff at each EDIC clinical center will provide all assistance required to maintain follow-up of EDIC participants who temporarily need to use a different clinical center.
  - b) The receiving clinical center will assume temporary responsibility for following the participant, obtaining and shipping blood samples, and performing follow-up exams as needed and as mutually arranged between clinical centers. Clinical centers do not reimburse one another for performance of procedures.
  - c) Provide feedback to the sending clinical center after each participant visit and whenever concerns arise. Ideally, until a permanent transfer is made, the study test results are sent to the assigned (sending) clinical center for transmission to the participant and his or her medical care team. However, due to the timing of database updates at the Data Coordinating Center it is possible that test results may go to either the sending or receiving clinical center. It is the responsibility of the Study Coordinator who actually performed the assessments to follow up, making sure that all test results are returned and passed on to the participant. Often this will be as simple as just confirming the Study Coordinator at the sending clinical center has already received the test results and notified the participant.
  - d) After the study procedures at the receiving clinical center and any follow up are completed, the receiving center staff should complete the Notification of Patient Transfer Form 142 to return the participant to the previous clinical center. Send the form to both the DCC in the monthly mailing and to the sending clinical center. NOTE that there may be times when a participant has more than one annual visit at the temporary location. If several visits to the temporary clinical center are planned, there should be discussion between the staff at both clinical

centers and with the participant about whether or not the transfer should be made permanent.

### **25.3 Participant Moves to Non-EDIC Area**

Any participant move can be disruptive to maintaining EDIC participation, additional challenges arise when a participant relocates to an area far from any existing EDIC clinical center. While immediate transfer of the participant to the closest EDIC clinical center might appear to be the simplest approach; this may not always be advisable. Long distance follow-up is challenging whether the participant is 300 miles or 3000 miles from an EDIC clinical center. The best chance for maintaining study participation may occur by having the “known” EDIC staff continue with the follow-up efforts. This is particularly important when a participant moves out of the country or to the Western USA or Canada where there are only three EDIC clinical centers to serve a very large geographic area

In these situations, responsibility for participant follow-up remains with the assigned clinical center unless the participant clearly agrees to a temporary or permanent transfer. When there is no transfer, the assigned clinical center must set up procedures for maintaining contact with the participant and for obtaining at least minimal outcome data. For example, arrangements might be made for yearly blood draws to be obtained locally and shipped by the sampling lab or the participant to the EDIC CBL. These arrangements, along with annual phone calls from the assigned clinical center staff may be combined with periodic follow-up visits at an EDIC clinical center.

While long-distance follow-up is less than ideal, in some cases it is the only option. It is possible to maintain study participation with routine phone contact and proper motivation and attitude on the part of the participant along with perseverance by the EDIC clinical center staff.

A participant who makes a permanent move to a non-EDIC area and who has not been officially transferred to another EDIC clinical center remains in the assigned clinical center’s census. Participants can remain active in the study by continuing to participate in any EDIC follow-up assessments, such as modified phone visits, mailed questionnaires, remote blood collection, etc. Reference Chapter 13 of the MOO, Changes in Follow-Up Schedule. Only data collected by certified EDIC staff, such as EKGs, height, weight, blood pressures, etc. are sent to the DCC. Blood samples must be sent to the EDIC CBL for analysis. Laboratory values measured at other labs are not allowed into the EDIC database. Many of the self-administered questionnaires can be completed by participants at home and then sent in pre-paid envelopes back to the clinical center for inclusion in the monthly mailings. Any data NOT obtained is accounted for by completion of Form 141, the missed visit form. Costs associated with follow-up of participants utilizing non-EDIC facilities, or with assistance in follow-up provided by another EDIC clinical center are the responsibility of the assigned center.

Participants starting EDIC visits at another clinical center, whether temporary or permanent, must discuss and sign all appropriate consent documents and release of information forms.

### **25.3.1 Use of Resources in a Non-EDIC Area**

Prior to 1996, when the Health Information Privacy and Accountability Act (HIPAA) the EDIC MOO recommended that former EDIC staff, such as fundus photographers or coordinators who now work in non-EDIC locations, might be an acceptable resource for completing assessments with participants who do not live close to any EDIC clinical center. With current HIPAA guidelines in place at all US EDIC clinical center, those suggestions have been removed from the MOO.

An alternative resource might be to use a participant's own local physician or a local clinical laboratory to obtain the blood samples from a participant for shipment to the CBL. Such collaboration has frequently been successful when arranged by the Study Coordinator or Primary Investigator. Each EDIC clinical center must first determine if this is allowed by its Institutional Review Board. It is possible the local Institutional Review Board may suggest revisions to the local consent documents or applications for "remote" collections of blood samples to be obtained.

#### **1. Annual Visits**

- a) As a general rule, it is highly desirable to see participants yearly at an EDIC clinical center for data collection by EDIC staff. Participants may choose to separate visits for their convenience. Reference Chapter 13 of the MOO if an alternative to an annual visit to an EDIC clinic is necessary. Some travel assistance has been made available; see below to be used on a discretionary basis.
- b) While responsibility for participant follow-up remains with the assigned clinical center, outcome assessments may need to be performed at a different EDIC center. The assigned Study Coordinator needs to consult with an identified assisting clinical center to discuss this and develop follow-up plans, to open lines of communication, and to foster a spirit of cooperation as described previously for assisting with temporary moves to another EDIC area. Permission to release information to assisting sites will need to be obtained in advance from the participant.
- c) A permanent transfer to the assisting clinic may occur if the participant requests it or agrees to such a transfer at the request of the assigned EDIC clinical center's staff.
- d) A transfer should be *considered* if it is believed that a participant has missed visits due to geographic distance and can more easily get to another EDIC clinical center. However, in no case should a participant be transferred to another clinical center without his or her knowledge or without collaboration with the receiving Study Coordinator just because of a move to a location closer to a different clinical center.
- e) Until such official transfer occurs, the follow-up responsibilities lie with the assigned clinical center.

## 2. Responsibility for Costs at Non-EDIC Facilities

Nominal reimbursement to practitioners for collection of specimens or performance of procedures specifically needed for EDIC (such as HbA1c or fundus photos) may be appropriate and should be considered if deemed essential to securing the cooperation of the non-EDIC practitioners. No special funds for this purpose are provided however, and clinical center staff must use their best judgment in allocating resources for this purpose.

### **25.4 Reimbursement for Participant Travel**

If it becomes known to the EDIC staff that to maintain continued participation in the study some reimbursement for participant travel is necessary, there are mechanisms to assist the participant with travel. An EDIC clinical center may provide reasonable funds for expenses associated with once yearly transportation to the center for outcome assessments. Some costs may be shared with the participant depending on his/her personal resources and circumstances. The EDIC Clinical Coordinating Center (CCC) has offered some reimbursement to clinics and participants for travel.

Participant travel expenses for EDIC annual visits are paid from two sources—either the local clinical center's supply budget or the Central Travel Fund. Travel that is < 100 miles one-way is reimbursed by the clinical center and is determined by local policy, including rates for any mileage reimbursement, rental cars, etc. Travel that is >100 miles one-way is reimbursed through the Central Travel Fund and determined by Case Western Reserve University policy regarding items such as mileage reimbursement and requirements for receipt submission. If the estimated cost of a trip that will be paid through the Central Travel Fund is >\$500, pre-approval from the Clinical Coordinating Center is required. Funding for travel in local supply budgets and in the Central Travel Fund is limited, so clinical centers are encouraged to use travel funds prudently.

The clinical center's decision to offer reimbursement and the extent of that reimbursement is dependent upon the individual's circumstances, need, and the availability of funds. In order to minimize travel costs, encourage participants to have follow-up exams completed at the clinical center accessible with the least cost.

### **25.5 Example of a Data Table to be Sent with Participant Transfer Documents** (A similar table is available on the EDIC Website in the Participant Test Report Booklet.)

### Figure 25-1 EPIDEMIOLOGY OF DIABETES INTERVENTIONS AND COMPLICATIONS ANNUAL EXAM REPORT

Date:

**Name** was seen for his/her EDIC visit on

The cumulative and most recent test results from the EDIC study are summarized below:

	Yr 1	Yr 2	Yr 3	Yr 4	Yr 5	Yr 6	Yr 7	Yr 8	Yr 9	Yr 10	Yr 11	Yr 12	Yr 13	Yr 14	Yr 15	Yr 16	Yr17	Yr18	Yr 19	Yr20	
Exam Date																					
Age																					
Duration of Diabetes																					
Blood Pressure																					
Weight in kg																					
HbA1c																					
Serum creatinine																					
Urine albumin																					
Creatinine																					
Cystatin - C																					
Iothalamate																					
Total cholesterol																					
Triglycerides -																					
HDL cholesterol -																					
LDL cholesterol -																					
Carotid																					
Cardiac CT																					
Eye photos (R,L)																					
Ankle/arm																					
EKG																					
Neurology exam																					

This report was prepared by:

D = Done - results are reported on a separate form. - = Not Done N=Normal A= Abnormal; Missing ankle reflexes  
 \* Minor Abnormality \*\* Ankle Reflexes Absent - Minor ECG Abnormality, A+=minor abnormality, normal sinus rhythm, left axis deviation,  
 baseline artifact, QS pattern V1-V2 without significant change from baseline ECG

REVIEWED BY: \_\_\_\_\_

## 26. ADHERENCE

### 26.1 General Principles of Adherence

#### 26.1.1 Definitions and Synonyms

Adherence suggests yielding to the wish, request, or command of another. Terms such as compliance, obedience, cooperation, collaboration, concordance, agreement, etc. have been used in lieu of adherence. Since there is no ideal term to describe these phenomena, adherence will be used to express the extent to which the participant's behavior (in terms of completing procedures, forms and surveys, and continuing to participate in exams and evaluations) coincides with the EDIC protocol. The EDIC goal is Adherence > 90% to completion of all endpoint assessments throughout the study period.

#### 26.1.2 Need to Monitor Adherence

During the performance of the DCCT, it was necessary to have procedures in place for monitoring and influencing **treatment protocol adherence**. **The EDIC study is an epidemiologic follow-up study and treatment adherence is no longer subject to modification or assessment by EDIC clinicians.**

A number of the factors that influence adherence, both in the setting of general medical care and in the specific context of clinical trials and long-term follow-up studies, have been identified. This knowledge can be used to improve the level of adherence. This Chapter will set out general guidelines to be used in addressing the issue of adherence, but it is anticipated that these guidelines will be developed and refined as experience in the application of the general principles of adherence to the Protocol of the EDIC is acquired.

#### 26.1.3 Determinants of Adherence

The many factors found to influence adherence can be divided into the following four general categories:

1. The protocol that the participant is being asked to follow.
2. The environment in which participation is provided.
3. The characteristics and behavior of the professional staff.
4. The characteristics of the participant as they affect his/her ability to follow the protocol.

The general relationship of each of these categories to adherence is outlined before considering its specific application to people with diabetes and the EDIC protocol.

##### 26.1.3.1 The Regimen

As noted above, the diabetes treatment regimen is no longer prescribed by the study group. Consequently, we are no longer in a position to evaluate adherence to a specific regimen; rather we evaluate the extent to which participants follow specific patterns of care and then compare these to recommendations made at study end. We can assess adherence with the tests described in the protocol.

### 26.1.3.2 The Environment

The nature of the physical surroundings in which follow-up is provided has an important bearing on the attitude of the participant towards the care and indirectly on his/her adherence to the protocol. If the participant finds the environment in which EDIC is implemented is congenial, he/she will be more likely to keep appointments. The general attractiveness and accessibility of the facility, including public transport, parking, and the provision of maps, signs, and directions will raise the probability that appointments are kept. The use of telephone and/or mailed appointment reminders may be a key factor in maximizing the number of appointments that are kept. Waiting times should be minimized and schedules should be flexible enough to allow appointments at times convenient for the participant. An appointment that is conducted in a timely, efficient and professional manner encourages adherence.

### 26.1.3.3 EDIC Staff

While it was necessary for the participant to see individuals of several disciplines at many visits (e.g., physician, nurse, and nutritionist) during the DCCT, the EDIC participant will have most contact with one or two staff members. Continuity of care is an important determinant of adherence in addition to the more obvious qualities of warmth, empathy, and interest of the provider(s). A smaller staff makes this easier, but it also means the burden of the EDIC protocol depends on the actions of an individual or small team. While the DCCT demanded extensive cross-disciplinary communication to carry out intensive treatment, the issues now involve communicating with fewer staff who have a smaller percent effort assigned to the study. The challenge of EDIC is to maintain DCCT standards of excellent communication among staff and with participants, with smaller percent effort.

The nature of EDIC also entails less frequency in communication with the participants. EDIC only requires annual visits, vs. the monthly visits or quarterly visits that were part of the DCCT. However, it is believed that the previous “bonding” to the DCCT/EDIC staff, trust in their assessments, referrals, and consultations will engender a continued commitment to EDIC. Staff should recognize annually, both verbally and with the EDIC annual gift, that the study thanks the participants continued commitment to the protocol. Staff should be prepared to provide understandable updates of the progress of EDIC as an introduction to each visit.

As staff changes are made, send letters from the departing staff to the participants, with the name of the contact during the transition, before the staff member's departure. Send a welcoming letter from the new Study Coordinator or Principal Investigator along with contact information. Attempts should be made to maintain a consistent phone number for EDIC contacts, despite staff changes. Upon staff departure, previous phone number(s) used by the EDIC participants should remain the same. The change in staff at the EDIC clinical centers can also offer an opportunity for a re-establishing enthusiasm among those participants that have had lagging participation. (For any changes in the personnel, reference the Staff Transition document (Appendix 26.1), or accessed on the EDIC web page under Administrative / Regulatory documents. <https://www.bsc.gwu.edu/edic/index.cgi>)

Participants often have educational questions about their diabetes – new treatments and educational questions. Study coordinators can be good listeners to participants' problems or concerns and provide education as necessary. Sometimes participants need suggestions for referrals to other health care providers or services as necessary.

#### 26.1.3.4 The Participant

Early research into adherence was based on the postulate that the "nonadherer" was a person with a particular set of personality characteristics that dictated his/her adherence behavior. However, it has become clear that there is no such set of personality characteristics or type, and that adherence is a function of the protocol itself, the behavior of the provider, and such participant-related characteristics as his/her knowledge of the protocol, social support, and skills in managing the protocol. This concept provides a much more optimistic view of adherence as a behavior that can, in principle, be developed under appropriate circumstances by all individuals who are appropriately educated to carry out the prescribed protocol. Additionally, competing demands on one's time and/or resources (i.e., job, family) may adversely impact adherence.

### 26.2 The EDIC Environment

The EDIC clinic itself should provide both the participant and the staff members with a positive experience. We know that environments do affect attitudes and behaviors. Crowded, noisy rooms with uncomfortable chairs and sterile walls to stare at are likely to make us irritable and uncomfortable—anxious to avoid that place. No participant should leave the study or have cause to develop negative attitudes toward the study because of environmental conditions that could have been avoided. Whether the EDIC visit is conducted in a Clinical Research Unit (CRU) clinic setting, or office setting, the accommodations need to be comfortable and conducive to all needs of the visit. This includes comfortable conditions to obtain evaluations like the Doppler blood pressures, 4-hour renal creatinine clearance collections, blood draws, meals or snacks availability, and rest rooms. Privacy for the visit should be assured.

#### 26.2.1 Clinic from the Participants Perspective

1. Accessibility—Because of the relatively large number of part-time clinical staff involved and because of the need for ancillary services such as fundus photography, it is likely that most EDIC clinics will be located in a large medical complex, even though the location of the complex within the city may not be optimal for transportation, parking, and safety. For these reasons, it is especially important to ensure that convenient parking (free, pre-paid or valet) is available, maps are provided, and that readily visible directional and identifying signs are posted on clinic days. Consideration should be given to assisting participants with transportation if they do not have their own transportation, are unable to afford transportation or are disabled for any reason.

2. Reception, waiting, and office facilities—The general atmosphere should be pleasant and relaxing with special attention to the following:

- a) Low noise levels or soft background music;
- b) Suitable light for reading without strong glare;
- c) Areas that are clean and orderly with attractive wall decorations;
- d) Current reading material, including newspapers and magazines, to appeal to participants of different ages and backgrounds;
- e) Attractively displayed information on diabetes or current health issues or institutional newsletters.
- f) A clinic bulletin board posting EDIC newsletters and synopsis of articles may be utilized if the location is EDIC specific;
- g) Comfortable furniture arranged for quiet reading and easy conversation;
- h) Offices providing privacy and comfort for the participants;

- i) The opportunity for suggestions to improve the clinic environment.

3. Scheduling system and waiting time—Minimize waiting time by efficient scheduling and clinical center promptness. The participant can be actively engaged in completing forms, questionnaires, or reviewing procedures with a member of the staff when waiting is unavoidable. Avoid an atmosphere of tension. Be willing to spend time with the participant who enjoys a leisurely visit. Movement from office to office should be well coordinated with suitable waiting areas, if necessary. The reason for any delay should be explained. If the participant must travel between departments, buildings, or institutions it is the responsibility of the Study Coordinator to ensure that the participant is escorted or is assisted with maps or directions, and a contact individual at the receiving destination is identified.

The scheduling system should be flexible. This may necessitate operating the clinic on weekends, in the early morning, and in the evening. If needed and/or requested, allow the participant to choose to split one annual visit into two shorter visits, ideally within the protocol window to complete all EDIC exams and evaluations. Visit completion, even outside of the protocol window, should be encouraged.

Most appointments are made via a telephone call from the Study Coordinator or designee well in advance of the target date of the 8-month window. Experience with a given participant usually dictates how much notice is needed to schedule an EDIC annual visit. Whomever is calling the participant to discuss the visit should know what is required at a given visit, how much time is needed to realistically complete all of the components, if the visit requires fasting circumstances, and if the availability of any of the EDIC or ancillary staff is in question. When scheduling, consider patient preference for date and time of the appointment and attempt to comply with requested date/time if feasible.

The participant should receive a written appointment reminder at least 2 weeks in advance of the scheduled annual visit. It should include the date, day, time, expected duration, clinic phone number, the name of the person to contact to change the appointment, and instructions for any necessary preparation such as fasting. An appointment reminder can also be made by phone or mail prior to the scheduled visit. For participants who tend to forget visits, it may be useful to make a telephone call on the day before or morning of a scheduled visit. Visit "schedules should be available to the individual making appointments, and these should be checked each week with the list of completed appointments. Participants who have missed a visit should be telephoned as soon as possible to reschedule the visit.

Tea, coffee, juice, and non-caloric drinks should be available. A snack or light breakfast or lunch should be provided in a suitable place after procedures that require fasting or an extended visit. It is important to ensure that the food available is consistent with healthy choices.

### **26.2.2 EDIC Participant Travel Expense Procedure**

Subject travel expenses for EDIC visits are paid from two sources—either the local clinical center's supply budget or the Central Travel Fund. Travel that is < 100 miles one-way is reimbursed by the clinical center and is determined by local policy, including rates for any mileage reimbursement, rental cars, etc. Travel that is >100 miles one-way is reimbursed through the Central Travel Fund and determined by Case Western Reserve University (CWRU) Clinical Coordinating Center (CCC) policy regarding items such as mileage reimbursement and requirements for receipt submission. If the estimated cost of a trip that will be paid through the

Central Travel Fund is >\$500, pre-approval by the CCC is required. Funding for travel in local supply budgets and in the Central Travel Fund is limited so centers are encouraged to use travel funds prudently.

The clinical center's decision to offer reimbursement and the extent of that reimbursement is dependent upon the individual's circumstances, need, and the availability of funds. In order to minimize travel costs, encourage participants to have follow-up exams completed at the clinical center accessible with the least cost. It is also acceptable to discuss and determine cost-sharing strategies with the participant for travel.

Since participant travel >100 miles one way is paid by CWRU from the master CCC funds, CWRU travel policies will need to be followed and CWRU travel forms completed and sent to the CCC. The CWRU check will be mailed directly to the participant, or to the clinic for appropriate charges paid by the clinic prior to the visit. The check should arrive 2 to 3 weeks after the CCC receives the completed documentation.

Receipts must be provided for all items, including taxis and parking. Original receipts must be submitted, with only two exceptions:

1. A copy of a canceled check is permitted, as long as both sides of the check are copied; and
2. Credit card statements (originals or copies) may be submitted.

26.2.2.1 Instructions for Completing the CWRU Travel Expense Statement:  
(Numbers refer to areas identified on attached sample form.)

1. Name and home address of the traveler.
2. Current date (date of trip appears elsewhere).
3. Department = Pediatrics
4. Bldg. = RB&C
5. Purpose of trip = EDIC annual visit
6. Begin and end date of trip.
7. List dates and corresponding travel expenses. The box marked "fare" does not include mileage, taxi, or limo service. Mileage reimbursement is periodically adjusted per CWRU guidelines and is automatically calculated when completing the reimbursement form, accessible from the EDIC website.
8. List dates and corresponding expenses. Total cost of all meals for the day should be shown under "Meals". When a receipt for a meal is not obtained, actual meal expenses up to the "maximum allowance for unreceipted" meals should be used. The maximum amount reimbursable is \$26 a day. The hotel receipt must show daily, itemized charges. There is no reimbursement for alcoholic beverages.
9. Total of all expenses.
10. Traveler's signature.
11. Signature of EDIC clinic personnel who reviewed expenses and prepared form, preferably the PI.

If your institution has already reimbursed the participant, CWRU will need the travel statement with backup as above, along with a copy of the institution voucher or the check from your institution to the participant. In this case, CWRU will issue the check to your institution rather than the individual. See the Appendix 26.1 for CWRU travel invoices, or access from the EDIC web site, Study Coordinator's page.

Rarely, some participants need travel funds prior to the visit to assist with travel costs. To insure that the local EDIC clinic has not utilized their own funds, CWRU, under a special arrangement with Dr. Saul Genuth and an Advance EDIC Travel fund, reimbursement can be applied for and sent prior to the visit. See Appendix 26.1 for a copy of those directions.

Questions and invoices should be directed to:

EDIC Clinical Coordinating Center  
Case Western Reserve University  
Wolstein Research Building  
Second Floor, room 2532  
10900 Euclid Avenue  
Cleveland, OH 44106-7287

Phone: 216-844-3661 Fax: 216-368-4832

Email: [rose.gubitosi-klug@uhhospitals.org](mailto:rose.gubitosi-klug@uhhospitals.org)

### **26.2.3 Clinic from the Staff's Perspective**

The environment should also be pleasant for the staff. Staff attitudes will be transmitted to the participants who will in turn be affected by their attitude towards and participation in the study. Comfortable office space should enhance the conduct of the job. In particular, appropriately private and soundproof rooms should be available for history taking and physical examinations.

The clinical center should be designed to maximize communication among staff members.

### **26.3 Role of EDIC Staff**

Address all participants by name. Make them feel that they are important and that their commitment to the study is a valuable and indispensable contribution. Provide positive comments, expression of appreciation, and praise for successful areas of participation as frequently as possible.

The organizational structure of the clinical center should be clearly delineated and understood by each staff member. Job tasks should be stimulating and rewarding to those performing them. Staff meetings should be held periodically and all staff members should be encouraged to participate in face-to-face discussion, including periodic review of staff working conditions.

Consistency is the key to successful communication with participants. All staff should convey the same information, instructions, and attitudes to all participants. The participant confronted with two opposing messages is unlikely to have much trust in the clinic staff. Supportive cohesive staff activities should be fostered and periodic recognition of the team effort in the conduct of the study should be made.

Over and above these general considerations, staff have the following five specific responsibilities toward participant adherence throughout the trial:

1. To educate all participants so that they are aware of exactly what is expected of them;
2. To intervene with participants who are having difficulties and bring them to their maximal level of adherence;
3. To maintain adherence in those areas where the participant is having success; and
4. To send results of tests/procedures to participants in a timely fashion.
5. To respect the participant's time and efforts, and encourage open dialogue regarding issues of concern.

### **26.3.1 Education and Adherence Efforts**

Most participants express interest in educational or "study update" programs. Educational programs can serve as motivating and reinforcing events for participants. In order to maintain interest and adherence, educational programs could include the following topics:

1. Periodic review of study progress;
2. Yearly reeducation of participants and staff about DCCT/EDIC study goals and protocol;
3. Periodic general programs on diabetes, its control and complications;
4. Routine skills assessment and retraining.

A variety of methods could be utilized for stimulating and maintaining adherence, including:

- Newsletters from the individual clinics, as well as the biannual EDIC Gazette, which can be mailed to the participant with a clinic cover letter.
- Educational materials on clinic bulletin boards;
- Relevant reading materials in waiting rooms;
- Periodic educational audio-visual programs in the clinic;
- Referral to Clinic/ADA/ CDA or other community sponsored diabetes programs; and
- Individual instruction and or/referrals.

### **26.3.2 Maintenance**

This program should provide continuous support and encouragement to each participant in all the areas in which s/he is adhering to the requirements of the study. The following procedures are recommended:

1. Tailor the appointment schedules to the participant's lifestyle and daily habits.
2. Maintain interim contacts with the participant and communicate with his/her family and social supports when appropriate. Consider sending seasonal greeting, note or birthday cards or recognizing significant family events (ie, sympathy cards).
3. Provide adequate feedback about present health status after each visit.
4. Consider participant's ideas and choices in selecting alternatives for scheduling visits to minimize any source of difficulties.
5. Involve participant in activities at the center to sustain interest as a participating member of the team.
6. Consider having occasional group meetings with participants to share study information and/or provide on-going education.
7. Provide recognition for completion of tasks/visits.

8. Provide the annual EDIC gift to participants either at the time of the visit, or via mail.
9. Supplies donated by diabetes product companies to the EDIC study should be given to the participant at the time of their visit as an expression of appreciation for their participation. These products may differ year to year, and can include donated supplies to supplement their usual diabetes care and self-management efforts. These might include study wide donations of insulin, blood glucose meters, strips for the meters, discount forms, pedometers or other supplies as made available to the study.
10. Recognize that participation may decline in a given year. However, participants may be willing to return for subsequent years if recontacted. Thus, except in rare instances, all EDIC participants should be recontacted at least annually, even when they declined to participate in prior years, unless they have formally withdrawn their consent to continue contact and participation. Refer to Chapter 13, Changes in Follow-up Schedule.

## APPENDIX 26.1

04/30/09

## INSTRUCTIONS FOR EDIC TRAVEL FORMS SUBMITTED TO CWRU WHEN OVER 100 MILES EACH WAY

Statement of Travel Expense for Participant Reimbursement:

Use this form when reimbursing participant directly, or reimbursing Coordinator for funds advanced to participant.

Indicate Clinic number, reason for visit (annual, cMRI, other). Date of Expense should be date of visit.

Current rate per mile will change subject to changes in IRS rate. As of 1/1/09 trips, the reimbursement rate is \$0.55 per mile.

If the participant's trip will cost over \$500.00, approval from Dr. Gubitosi-Klug needs to be obtained in advance. If the arrangement is to pay the participant for only a portion of the trip, adjust the number of miles, not the dollar amount. (Example: If paying \$200.00 flat rate, divide  $200/.55 = 363.64$  miles).

Partial hotel and meal reimbursements are OK.

Send to Case the original bills and receipts. If an original is not available, include a note to that effect.

Parking at meters or other situations where a receipt is not issued may be paid.

Send a note indicating that the meter does not issue receipts. It will be decided on a case-by-case basis.

Case will pay the mileage rate, OR cost of a rental car and gas for that car. They will not pay both mileage and rental car cost.

Travel reimbursements must be submitted to Case within one year of the date the trip was taken, or the participant will not be reimbursed.

Travel Invoice for Institutional Reimbursement:

Use this form when Case will be reimbursing your hospital or university for payments they have already made to the participant.

If your institution already has an invoice form, please use that rather than this generic form. Send copies of the receipts, originals will be retained by your institution.

If you or someone in your department will be creating invoices using the generic form, please number them with identifying letters (MGH, USF, etc.) and starting with 01, number consecutively. If your institution prepares invoices in their own format, they will have their unique invoice numbers. The same information is required as when preparing the individual travel expense form. The travel expense form is not needed, if reimbursing the institution. If you deal with a hotel which will allow Case to pay the hotel directly, please continue with filling out the travel expense form, and attach the original hotel bill. We will be able to pay the hotel using their own invoice form.

Copies of current travel forms from Case Western Reserve University CCC can be found at the EDIC web site: <https://www.bsc.gwu.edu/edic/index.cgi>  
From the home page, go to the SC page, and Statement of Expense page.

## APPENDIX 26.2

STAFF TRANSITION GUIDELINES  
EDIC Study

This document provides guidance to the clinical centers regarding the pending departure of a principal investigator or study coordinator from the EDIC Study.

## A. DEPARTURE OF THE EDIC PRINCIPAL INVESTIGATOR

Once it has been determined that the principal investigator will be leaving the clinical site or leaving his/her position as the PI, the following activities should occur:

1. Notify the Study Co-Chairs (S.Genuth, D.Nathan) via email or telephone of the impending departure as soon as confirmed
  - a. Include tentative timeline for departure
  - b. Provide background information, as applicable
  - c. Include information about any early discussions that have occurred locally regarding identification of a replacement
2. Notify the Clinical Coordinating Center (R. Gubiosti-Klug) via email or telephone
  - a. Provide name and CV of candidate
  - b. Submit proposal for transition plan with timeline
  - c. Fiscal support (if any) for the transition period will be reviewed and determined via individual discussions between the clinical center and the Clinical Coordinating Center
  - d. The sub-contract with the clinical site will be modified by the CCC after approval by the Executive Committee and the NIDDK
3. Identify Replacement PI
  - a. Each institution participating in the EDIC Study must identify a replacement for the current principal investigator; the principal investigator is considered “key personnel” per the NIDDK contract
  - b. The name and CV of the locally-recommended candidate should be submitted to the Executive Committee and the NIDDK
  - c. The Executive Committee and the NIDDK must review and approve the candidate prior to the candidate assuming the responsibilities of PI at the clinical center
4. Develop Transition Plan
  - a. Allow time for the transition of duties from the current to the new PI
  - b. Review responsibilities specific to the protocol implementation: IRB, participant interactions, data management, EDIC committee assignment (if transferable)
  - c. Review responsibilities specific to the institution: contract, budget, personnel management
  - d. Incorporate training/communication opportunities with the study coordinator
  - e. Ensure that EDIC certification activities are completed (see Manual of Operations)
  - f. Determine who will be available as local back-up for the incoming PI
  - g. Provide information about study group meetings and associated responsibilities

- h. Review EDIC committee structure (DQA, AMC, Research Review, Publications); notify DCC of new PI's committee preference (should be a different committee than the one the SC is currently participating on)
- i. Provide resource information for the DCC, CCC, and Executive Committee
- j. Provide information and timelines for all outstanding activities that require follow-up by the new PI

## B. DEPARTURE OF THE EDIC COORDINATOR

Once it has been determined that the study coordinator will be leaving the clinical site or leaving the position as EDIC coordinator, the following activities should occur:

1. Notify the Study Co-Chairs (S.Genuth, D.Nathan) and the Data Coordinating Center (P. Cleary) via email or telephone of the impending departure as soon as confirmed
  - a. Include tentative timeline for departure
  - b. Provide background information, as applicable
  - c. Include information about any early discussions that have occurred locally regarding identification of a replacement
2. Notify the Clinical Coordinating Center (R. Gubiosti-Klug) via email or telephone
  - a. Provide name and CV of candidate
  - b. Submit proposal for transition plan with timeline
  - c. Fiscal support (if any) for the transition period will be reviewed and determined via individual discussions between the clinical center and the Clinical Coordinating Center
3. Identify Replacement Coordinator
  - a. Each institution participating in the EDIC Study has the responsibility to identify a replacement for the current study coordinator
  - b. The name of the locally-recommended replacement and qualifications should be submitted to the Executive Committee
4. Develop Transition Plan
  - a. Allow time for the transition of duties from the current to the new coordinator
  - b. Review responsibilities specific to the protocol implementation: IRB, participant interactions, data management, EDIC committee assignment (if transferable), sample disposition and storage, study supplies
  - c. Review Manual of Operations, Orientation Manual, website resources, and responsibilities of Data Coordinating Center staff
  - d. Review pertinent information about study participants; include update regarding recently completed and pending study visits
  - e. Provide direction regarding location of all supplies and materials associated with the EDIC study
  - f. Ensure EDIC certification activities have been initiated and, preferably, completed (see Manual of Operations)
  - g. Review responsibilities specific to the institution: contract, budget, personnel management, training
  - h. It is ideal to allow sufficient overlap of time between the current and pending coordinator to ensure orientation, training, problem-solving and participant continuity
    - i. Determine who will be available as local back-up for the incoming coordinator
  - j. Provide information about study group meetings and associated responsibilities

- k. Review EDIC committee structure (DQA, AMC, Research Review, Publications); notify DCC of new SC's committee preference (should be a different committee than the one the PI is currently participating on)
- l. Provide information and timelines for all outstanding activities that require follow-up by the new coordinator
- m. Provide resource information for the DCC, CCC, and Executive Committee

#### C. TRANSITION RESOURCES AVAILABLE

- a. EDIC Study Website: <https://www.bsc.gwu.edu/edic/index.cgi>
- b. Manual of Operations (under Resource tab on website)
- b. Orientation Manual for EDIC Center Staff (under Resource tab on website)
- c. Orientation conference calls: with incoming coordinator and chairs of Adherence Monitoring and Data Quality Control Committees
- d. Coordinator mentor: mentoring provided by established coordinator at another clinical site

## 27. HEALTH CARE DELIVERY QUESTIONNAIRE

### 27.1 Introduction

Data will be collected with a standardized questionnaire (Form 070) at each annual visit to determine the health care received by the EDIC patient during the previous 12 months. In addition, specific items pertaining to diabetes care will be obtained. Ask the patient to complete the questionnaire. In order to enhance the uniformity of the data across patients within an EDIC clinical center and across the 28 clinical centers, a set of definitions for the various terms employed in the questionnaire was adopted. The Study Coordinator reviews these definitions with the patient prior to asking the patient to complete the form. The following sections provide these terms, definitions, and specific instructions for each item on the Health Care Delivery Questionnaire.

### 27.2 Health Care Terms and Definitions

**Co-Payment** - The amount of money you pay out of your pocket at the time you receive medical care.

**Network** - All the Primary Care Physicians, specialists, hospitals, urgent care centers, and/or other health care providers who are contracted with the insuring group to provide medical care services under the agreed terms of coverage.

**Primary Care Physician** - The plan member's personal doctor and main source of medical care.

**Provider** - A general name for any doctor, hospital, or medical service in the network.

**Indemnity** - An insurance program in which the insured person is required to render payment for services received and is then reimbursed for the covered expenses on a fee-for-service basis.

**Health Maintenance Organization (HMO)** - An organized system of health care that arranges in advance with a specific network of doctors, hospitals, and providers to give care to members and pays them directly for their services. Benefits are available **only** from network providers except during a medical emergency. Plan members are required to select a participating Primary Care Physician (PCP). Generally, services of a specialty care provider can only be received by referral from the selected PCP (with the exception of participating Gynecologists and Dentists). Co-payments are required of the plan member and are due when service is rendered, generally until a specified out-of-pocket maximum is reached.

**Preferred Provider Organization (PPO)** - A medical care plan that has contractual agreements with a network of medical care providers to provide medical services to plan members. Plan members **do not** have to select a participating Primary Care Physician (PCP) to enroll in the plan; s/he may select the provider of their choice. Medical benefits vary based upon whether the plan member selects a provider inside or outside of the network. Participating providers must be used to receive in-network benefits. The plan member is responsible for paying deductibles and coinsurance fees until specified out-of-pocket maximums are reached.

**Point-of-Service (POS) Plan** - A medical care plan that has contractual agreements with a network of medical care providers to provide medical services to plan members. Plan members

must select a Primary Care Physician (PCP) that is in the network and who is not a specialist; however, s/he have the option to self-refer to most specialists in the network without prior written authorization or referrals from their PCP. Medical benefits vary based upon whether the plan member selects a provider inside or outside of the network. If the provider is inside of the network, the plan member is responsible for paying a minimal co-payment in addition to the established premium with the insuring group. If the provider is outside of the network, the plan member must obtain authorization from their PCP and may be susceptible to a deductible, in addition to a higher co-payment.

**Medicaid** - A federal program administered and operated individually by participating state and territorial governments that provides medical benefits to eligible low-income persons needing health care. The program's costs are shared by the federal and state governments. In many areas, Medicaid programs have contracted with HMO's or PPO's to provide services.

**Medicare** - A nationwide, federally administered health insurance program that covers the costs of hospitalization, medical care, and some related services for eligible persons. In many areas, Medicare has contracted with HMO's or PPO's to provide services. Medicare has two parts:

**Part A** covers inpatient costs for Medicare patients. Medicare pays for pharmaceuticals provided in hospitals, but not for those provided in outpatient settings. Also called *Supplementary Medical Insurance Program*.

**Part B** covers outpatient costs for Medicare patients.

**Fee-for-Service Reimbursement** - The traditional health care payment system, under which physicians and other providers receive a payment that does not exceed their billed charge for each unit of service provided.

### 27.3 Instructions to Complete the Health Care Delivery Questionnaire

This questionnaire should be completed by all patients at each annual visit. When completing the questionnaire, the information requested pertains to the previous 12 months or since the patient's last EDIC visit, whichever is the lesser. The term health insurance coverage also implies the receipt of any health care benefits. If the patient misses the in-clinic assessment, the questionnaire can be mailed to the patient and completed at home. The patient should then mail the completed questionnaire to the Study Coordinator. Study Coordinators will review the form for completeness, copy it, and send the original to the Data Coordinating Center in the monthly mailing.

#### A. Identifying Information

This section should be completed by the Study Coordinator prior to giving or sending the form to the patient.

1. Clinic Number: Two-digit number assigned during the DCCT.
2. Patient ID Number: Five-digit number assigned during the DCCT. Include the Patient ID Number in the space provided on each consecutive page in the upper left hand corner.

3. Patient's Initials: First letter of first, middle, and last name in that order. If patient has no middle initial or name, use "X". This was set at the beginning of EDIC and is not changeable.
4. Date Form Completed: Enter month, day, and year using leading zero for days, months, and years when appropriate, e.g., September 17, 2000 would be "09/17/00".
5. EDIC Follow-Up Visit: Enter appropriate annual visit number using leading zeros.

## B. Health Care Insurance Coverage

Please note: For all questions, "during the past 12 months" should be interpreted to mean "during the past 12 months or since the last EDIC visit, whichever is the lesser".

1. Patient should indicate whether there was any time during the past 12 months, that s/he did not have health insurance coverage or health care benefits by checking "yes" or "no". S/he should include any time their insurance coverage had been terminated, suspended, or had a lapse for any reason. If the patient is unsure, s/he should check "uncertain". If their answer is "no", s/he should go to item #4a.
2. If the patient's answer to item #1 was "yes", s/he should indicate the total number of months that s/he was uninsured in the past 12 months, rounded to the nearest month, e.g., If the patient was uninsured 2 months and 21 days s/he should enter "3" months.
3. Patient should indicate whether or not s/he currently has health insurance coverage by checking "yes" or "no". If the patient is unsure, s/he should check "uncertain".
- 4a. If the patient has had any health insurance coverage in the past 12 months, s/he should list the name(s) of their plan(s). If s/he has had coverage with more than one company, s/he should list the names of them all.
- 4b. If the patient has had any health insurance coverage in the past 12 months, s/he should describe their insurance plan(s) by checking all plans that apply (a-c). If the patient has an individual plan that is paid for by an employer or other party, item 4ba should be checked.
- 4c. If the patient has had any health insurance coverage in the past 12 months, s/he should indicate which type(s) of health insurance s/he have had by checking all types that apply (a-d). If the patient has a type of health insurance coverage that is not listed, s/he should specify the type of health insurance coverage by writing it in the space provided in item (e). Patients receiving Veteran's Administration health benefits and patients in the Canadian health plan should check item 4e and specify.
5. If the patient **currently** has health insurance, s/he should indicate whether or not their health insurance provides coverage (complete or partial coverage, after co-payment and/or deductibles) for any of the items listed by checking "yes" or "no" (a-cc). If the patient is unsure of their coverage for a particular item, s/he should check "uncertain". If the patient does not currently have health insurance coverage, s/he should go to Section C.

### C. Health Care Providers and Sources of Care

1. Patient should indicate where s/he usually goes to receive diabetes health care services by checking only one location (a-g). If the location where the patient usually visits is not listed, s/he should specify by writing the location in item (h). If there is no single, that is regular, location where the patient goes to receive diabetes health care services, s/he should indicate so by checking item (i).
2. Patient should indicate who s/he visit to receive diabetes health care services at the location indicated in item #1, by checking only one provider (a-b). If the provider that the patient usually visits is not listed, s/he should check item (c) and specify by writing the provider's professional title in item (c). If the patient does not currently have a diabetes health care provider, s/he should indicate so by checking item (d).
3. Patient should indicate if the provider indicated in item #2 was a member of the DCCT staff or is a current member of the EDIC staff by checking "yes" or "no". "Not Applicable" should be checked if no provider was seen by the patient in the past 12 months.
4. Patient should indicate where s/he usually goes to receive general health care services by checking only one location (a-f). If the EDIC evaluation is the only source of general health care, s/he should check item (g). If there is no single, that is regular, location where the patient goes to receive general health care services, s/he should indicate so by checking item (h).
5. Patient should indicate whom s/he visits to receive general health care services at the location indicated in item #3, by checking only one provider (a-b). If the provider that the patient usually visits is not listed, s/he should check item (c) and specify by writing the provider's professional title in item (c). If the patient does not currently have a general health care provider, s/he should indicate so by checking item (d).
6. Patient should indicate if their general health care provider was the same provider of their diabetes care by checking "yes" or "no". "Not Applicable" should be checked if no general provider or no diabetes care provider was seen by the patient in the past 12 months.
7. The patient should indicate whether or not s/he have visited their EDIC clinic in the past 12 months for any health care services unrelated to the EDIC study, by checking "yes" or "no". If the patient answered "yes" for this question, s/he should also enter the number of visits s/he has had to the clinic in the past 12 months that were unrelated to the EDIC study.
8. The patient should indicate if EDIC evaluations have been the **only**, that is sole health care services s/he have received in the past 12 months by checking "yes" or "no".
9. The patient should indicate if s/he has seen any of the listed health care providers (a - x) for any reason in the past 12 months. If s/he answered "yes" to an indicated health care provider, the patient should also enter the total number of visits s/he **has** made to that particular provider in the past 12 months. If the patient has seen a health care provider that is not listed, s/he should specify by checking "yes", writing the professional title of that provider in item (y), and writing the total number of times s/he have visited that provider in the past 12 months. If the patient has not seen any health care provider other than those previously listed, s/he should check "no" in item (y). All visits occurring in the same day to any of the providers listed in item 9a or 9b should be counted as one visit. Only outpatient visits should be recorded. Patients should not include EDIC evaluations in response to this question.

#### D. Hospitalization and Other Health Care Services Used

1. The patient should indicate if s/he was admitted overnight to a hospital for any reason in the past 12 months by checking “yes” or “no”. This does not include emergency room visits or same day procedures. If the patient answered “no” to this question, s/he should go to item D.2.

1a. If the patient answered yes to item #1 and has been admitted overnight to a hospital, s/he should write the total number of **times** s/he have been admitted overnight to any hospital during the past 12 months.

1b. If the patient answered yes to item #1 and has been admitted overnight to a hospital, s/he should write the total number of **nights** s/he have stayed in any hospital during the past 12 months.

1c. If the patient has been admitted to a hospital at any time, for any reason during the past 12 months, s/he should write the date (month, day, and year) s/he was admitted, the total number of nights s/he stayed in the hospital for that particular admission, the hospital name, as well as the city and state of that hospital. A separate entry should be made for each time the patient was admitted to a hospital. Patient should attach a separate sheet if needed.

2. The patient should indicate if s/he was seen for any reason in the past 12 months in a hospital emergency room by checking “yes” or “no”. Patient should not include urgent care or walk-in clinic visits. If the patient answered “no” to this question, s/he should go to item D.3.

2a. If the patient answered yes to item #2, s/he should write the total number of times s/he was seen in a hospital emergency room during the past 12 months.

2b. Patient should indicate how many of the times s/he was seen in a hospital emergency room were related to their diabetes by writing in the number.

3. The patient should indicate if s/he was a patient at any time in the past 12 months in a nursing home or convalescent facility by checking “yes” or “no”. If the patient answered “no” to this question, s/he should go to item D.4.

3a. If the patient answered yes to item #3, s/he should write the total number of nights s/he spent in a nursing home or convalescent facility in the past 12 months.

3b. If the patient has been admitted to a nursing home or convalescent facility in the past 12 months, the patient should list the date (month, day, and year) s/he was admitted, the total number of nights s/he stayed in the facility, the institution name, as well as the city and state of that institution. A separate entry should be made for each time the patient was admitted to a nursing home or convalescent facility. Patient should attach a separate sheet if needed.

4. The patient should indicate any laboratory tests, or procedures that s/he have had during the past 12 months by checking “yes” or “no” to all that apply (a-q). If s/he answered “yes” to an indicated laboratory test or procedure, the patient should also enter the total number of times that s/he had the procedure in the past 12 months. The patient should not include any tests or procedures that may have been done while s/he was hospitalized, or any evaluations performed as part of their EDIC visit.

5. The patient should indicate if s/he have had any other laboratory tests or evaluations in the past 12 months that were not listed in item #4, by checking “yes” or “no”. If the patient answered “yes”, s/he should specify the name of the medical treatment by writing it in the space provided.

6. The patient should indicate if s/he has had any other medical treatments in the past 12 months that were not listed in item #4, by checking “yes” or “no”. If the patient answered “yes”, s/he should specify the name of the medical treatment by writing it in the space provided.

7. The patient should indicate the total number of days s/he have missed of work, school and/or usual activity in the past 12 months related to any illness, including any days spent in a hospital, nursing home or convalescent facility.

7a. The patient should indicate the total number of the days missed of work, school, and/or usual activity that were related to their diabetes.

### **E. Participation in Other Research Projects**

1. The patient should indicate whether or not s/he have been asked to participate in any other health related research projects in the past 12 months by checking “yes” or “no”. If the patient answered “no” to this question, s/he should go to Section F.

2. If the patient answered “yes” to item #1, s/he should indicate whether or not s/he actually participated in the research project by checking “yes” or “no”. If the patient answered “no” to this question, s/he should go to Section F.

3. If the patient answered “yes” to item #2, s/he should indicate what the research project involved by checking “yes” or “no” to all that apply (a-g). If the research project involved something that is not listed, the patient should check “yes” in item (h) and specify by writing in the space provided.

### **F. Access to Health Care Services**

1. The patient should indicate whether s/he **did not** see a doctor or other health care provider for any health problem or condition for any reason during the past 12 months, by checking “yes” or “no”. If the patient answered “no” to this question, s/he should go to item #3.

2. If the patient answered “yes” to item #1, s/he should indicate why s/he did not see a doctor or other health care provider for the problem or condition, by checking “yes” to all that apply (a-n). If the reason is not listed, s/he should check item (o) and specify by writing in the space provided.

3. The patient should indicate whether s/he **delayed** seeing a doctor or other health care provider for any health problem longer than s/he should have, by checking “yes” or “no”. If the patient answered “no” to this question, s/he stop and return the completed questionnaire.

4. If the patient answered “yes” to item #3, s/he should indicate why s/he delayed seeing a doctor or other health care provider for the problem or condition, by checking “yes” to all that apply (a-n). If the reason is not listed, s/he should check item (o) and specify by writing in the space provided.

#### **27.4 Release of Medical Information**

Patient consent to release medical records will be needed to obtain information to verify hospitalizations, emergency room visits, and information as requested by the Morbidity and Mortality Committee. A consent to release medical records will also be needed if the patient desires to have copies of his/her EDIC results sent to their healthcare provider. Local institution release of medical record forms can be utilized or adapted for these purposes.

## 28. EDIC OUTCOMES: CENTRAL CLASSIFICATION PROCEDURES

### 28.1 Introduction

In multicenter studies, the burden is on the collaborating clinical center to identify and report the events that have been defined as outcomes by the study protocol. In order to have an accurate classification and to remove noise from the reported events, an unbiased objective central review of all reported outcomes should be conducted. The review should include validation against established criteria in a consistent fashion by individuals with appropriate clinical and methodological expertise. The Mortality and Morbidity Review Committee (MMRC) will consist of two clinical center principal investigators, the Director of the Central ECG Reading Unit (CERU), and one or more content/clinical experts from within or outside the study group.

In a study such as EDIC, the patient's treatment group in the DCCT and the patient's current mode of diabetes treatment are known. Therefore, there is the risk that the reporting of all mortality, cause-specific mortality, and other morbidities may be influenced by that information. Thus, this is another compelling reason for the EDIC to establish a detailed classification process.

### 28.2 Fatal Outcomes and Documentation Requirements

EDIC outcomes that will be classified will require external record documentation in addition to the EDIC data form. In the following section, we present the required documentation for each outcome.

NOTE: All non-EDIC medical Records submitted to the Data Coordinating Center for the purpose of event verification should be redacted by the clinic prior to submission to the DCC. Each page should be labeled with the patient's EDIC number and initials.

In the case of a death, the clinic should submit a narrative written description of circumstances surrounding the death including any possible relation to hypoglycemia to the Data Coordinating Center. Information may be obtained from patient records and interviews with family members, friends or other witnesses. Any pertinent information about the subject's emotional state prior to death should be included if available. The method of insulin delivery should not be mentioned in the clinic report. If mention cannot be avoided, segregate discussion of diabetes treatment into one separate paragraph.

Death Procedures specified in Chapter 12 of the Manual of Operations should be reviewed at the time the clinic learns of the death of an EDIC volunteer. Immediately (within 24 hours) upon learning of the death, the Study Coordinator is to notify the Coordinating Center by telephone. Form 140, Notification of Death, should be submitted as soon as possible. It is extremely important that the clinic submit copies of all sources of information used to complete the form. This includes medical and hospital records and those items requested in Section D of the Form 140: death certificate, autopsy report, and interviews. For a small fee, non-relatives can obtain death certificates from many states by contacting that state's vital records departments.

In the case of deaths not medically attended, essential information can often only be obtained from interviews with third parties. Accordingly, if unavailable from other sources, the clinic should make reasonable efforts to interview persons likely to have knowledge of events preceding the death and/or witnesses to the event which led to the death.

If a police report was filed, a copy should be obtained and submitted. The police report may contain interviews with witnesses and hence relieve the clinic staff of the need to conduct separate interviews.

If the clinic believes it prudent to interview a family member(s), friend(s) or other witnesses a summary of the interview(s) should be submitted. The interview with a family member should include, whenever possible, whether the patient had any medical or psychosocial problems within ten days of death.

Finally, the clinic should report in a written narrative whether it believes diabetes contributed to a death by natural causes or whether hypoglycemia contributed to an accidental death, and why.

### **28.3 Other Outcomes**

#### **28.3.1 Non-fatal**

*Myocardial Infarction.* In addition to the Verification of Cardiovascular Event (Form 090), the clinic should submit copies of the initial ECG taken at the time of the event, and the last ECG taken prior to discharge or after abortive therapy. Also submit enzyme reports and hospital records. In a later section, criteria that are more specific are provided for classification of this event.

*Confirmed Non-Acute Myocardial Infarction.* Central reading of serial annual ECGs will serve as the basis for this diagnosis. The DCCT baseline ECG will be read in comparison with each EDIC ECG that is detected with a computer algorithm as abnormal.

*Coronary Artery Disease.* The need for coronary artery bypass surgery, percutaneous transluminal coronary angioplasty, coronary stent, balloon dilatation, atherectomy, or other coronary revascularization. The clinic should complete the Verification of Cardiovascular Event (Form 090). Copies of hospital records or the outpatient report, if the procedure was performed on outpatient basis, should be obtained.

*Arrhythmia.* The following types of arrhythmia are to be reported to the Data Coordinating Center by completing the Verification of Cardiovascular Event (Form 090), but only those arrhythmias that include hospitalization will be adjudicated by the MMRC.

1. atrial fibrillation
2. atrial flutter
3. atrial tachycardia
4. junctional tachycardia
5. ventricular tachycardia
6. ventricular fibrillation
7. Ventricular premature complexes
  - a) multifocal
  - b) runs of three or more
  - c) six or more per minute
8. second degree AV block
9. complete AV block

The official EDIC classification of the arrhythmia will be made by the Central ECG Reading Unit.

*Angina.* The clinic should submit Verification of Cardiovascular Event Form 090 (which incorporates the Standardized Rose Questionnaire on cardiac events), the angiography report, the results of non-invasive tests and the stress thallium exercise echocardiograph report.

*Congestive Heart Failure (CHF).* Congestive heart failure is defined as AT LEAST one symptom from EACH of the following two categories:

Category A: Paroxysmal nocturnal dyspnea, dyspnea at rest, or orthopnea

Category B: Marked limitation of physical activity caused by heart disease. Patients are comfortable at rest, but less than ordinary physical activity (for example, walking one or two blocks on level surface or climbing one flight of stairs in normal conditions) causes fatigue, shortness of breath, palpitations, or anginal pain (New York Heart Association Functional Classification III).

Note: CHF might also be associated with the following symptoms: rales, ankle edema, tachycardia, cardiomegaly by chest x-ray, chest x-ray characteristics of CHF, S3 gallop, jugular venous distention, high BNP (brain natriuretic peptide) level, low LV ejection fraction, or echo results showing characteristics of CHF. Although these symptoms may be used by the MMRC to adjudicate a CHF episode, they will not be used by Study Coordinators to define a CHF episode.

*Intermittent Claudication.* The questions contained within the Annual Medical History and Physical Examination (Form 002) will be used to support the diagnosis of intermittent claudication.

*End Stage Renal Disease (Acute vs. Chronic Renal Failure).* Renal Failure will be defined in EDIC as the receipt of a kidney transplant or an initial dialysis event. However, it is important to distinguish an Acute Renal Failure event with the onset of Chronic Renal Failure. All Renal Failure events must be confirmed through adjudication by the Mortality and Morbidity Review Committee (MMRC). Chronic Renal Failure is also known as End-Stage Renal Disease (ESRD).

Acute Renal Failure (ARF) is the sudden loss of the ability of the kidneys to remove waste and concentrate urine without losing electrolytes. While ARF is potentially life-threatening and may require intensive treatment, it often can be resolved after the underlying cause has been treated. This is not the case with Chronic Renal Failure (CRF): CRF requires either dialysis or kidney transplant. Thus, CRF in the EDIC Study will be defined by the need for ongoing dialysis treatment or kidney transplant. While a single kidney transplant can treat CRF, dialysis must be done on a weekly basis to treat CRF. The need for a single dialysis treatment or dialysis during a single hospital stay will define ARF in the EDIC Study.

Diabetes is a major cause of CRF, but it is not known to be a cause of ARF. At the same time, there are many causes of CRF other than diabetes. One other cause of CRF is unresolved ARF. For a list of causes of ARF and CRF, see Recommended Readings on Renal Failure at the end of this chapter.

To distinguish whether Renal Failure is Acute or Chronic, the clinic will: (1) complete Form 096 (Verification of Renal Failure Event) and (2) submit supporting medical records to the DCC. The preferred supporting medical record is Form CMS-2728; a hospital discharge summary should be used when the Form CMS-2728 is not available. The DCC will provide its own document,

the Renal Patient Report, which summarizes renal function throughout EDIC, to help the MMRC adjudicate the renal failure event. The MMRC will review and adjudicate the report of renal failure event by completing Form 151 (Morbidity Review Form: Myocardial Infarction and Other Cardiovascular Outcomes). Based on the adjudication, the renal failure event will be defined by timing (Acute or Chronic), treatment (dialysis or transplant), the need for continued Chronic Renal Failure treatment (i.e., dialysis), and whether Chronic Renal Failure is newly diagnosed at this event or if it had been a condition that had been present for some time.

The date or year of the beginning of the renal failure event will be sought, but this might be difficult to obtain, especially in cases of chronic renal failure, which are distinguished by slow onset.

*Renal Insufficiency.* Central Biochemistry Laboratory evaluation of renal function (i.e. serum creatinine  $\geq 2$  mg/dl or ESRD (see the previous section).

*MDRD GFR  $\leq 60$  ml/min/1.73m<sup>2</sup>.* Central Biochemistry Laboratory evaluation of renal function as GFR  $\leq 60$  ml/min/1.73m<sup>2</sup>.

*Microalbuminuria.* Central Biochemistry Laboratory evaluation of 4-hour renal collection for urinary albumin excretion rate  $\geq 28\mu\text{g}/\text{min}$  ( $\geq 40\text{mg}/24\text{hours}$ ).

*Albuminuria.* Central Biochemistry Laboratory evaluation of 4-hour renal collection for urinary albumin excretion rate  $\geq 208 \mu\text{g}/\text{min}$  ( $\geq 300\text{mg}/24\text{hours}$ ).

For each outcome based on urinary albumin excretion rate, any value that appears to be unreliable will be sent to the Data Quality Assurance Committee for follow-up and subsequent labeling as to either “valid” or “invalid”.

*Blindness, loss of vision, in one or both eyes.* Defined as visual acuity score, 20/200 from the EDIC Form 030, Ophthalmic Examination and Visual Acuity.

*Stroke (formerly known as CVA).* Stroke is defined as rapid onset of a persistent neurologic deficit attributable to an obstruction or rupture of the arterial system (including stroke occurring during a procedure such as angiography or surgery) (Dreyer PI, 2004). The neurologic deficit is not known to be secondary to brain trauma, tumor, infection or other non-ischemic cause.

Strokes due to a clot are categorized as ischemic strokes, while those occurring due to a bleed are categorized as hemorrhagic strokes. Although strokes are generally known to affect the cerebral cortex (brain tissue), they can also affect other structures close to the brain, such as: (a) brain stem (including the cerebellum, medulla oblongata, and the cranial nerves), (b) the spinal cord, & (c) the retina. Strokes can also be categorized as fatal or non-fatal.

Strokes may be confirmed by radiography (MRI, CT, MR or CT Angiography, or Angiogram of the Head), but require description of onset and duration of symptoms to correlate radiologic findings with symptoms.

Thus, the Clinic should submit Form 091 and the following types of medical records:

1. Neurology notes (such as a SOAP note from a neurologist or a neurology consultation note)
2. Diagnostic tests (such as MRI, CT, MR or CT Angiography, or Angiogram of the Head)
3. Hospital discharge summary that includes administration of tPA, fibrinogen, clotbuster, or surgery

Neurology notes define the clinical history of present illness, describing the neurologic symptoms and when they started and stopped. Diagnostic tests (such as MRI, CT, MR or CT Angiography, or Angiogram of the Head) should also be sent to the DCC.

The hospital discharge summary that includes administration of tPA or surgery is also important. In the past, the rule of thumb was, if symptoms last at least 24 hours, then the lesion is likely a stroke. However, many institutions now have “stroke protocols” that dictate treatment (including administration of tPA, fibrinogen, clotbuster, or surgery) within a matter of hours (of the onset of symptoms).

*Transient Ischemic Attack (TIA).* TIA is a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction (i.e., is not an ischemic stroke) (Easton JD et al., 2009). Clinic should submit Form 091 and the following types of medical records:

1. Neurology notes (such as a SOAP note from a neurologist or a neurology consultation note)
2. Diagnostic tests (such as MRI, CT, MR or CT Angiography, or Angiogram of the Head)
3. Hospital discharge summary

*The use of time to distinguish stroke from TIA.* As TIAs have historically been considered miniature versions of strokes, it has been the neurologist’s challenge to distinguish one from the other. In 1978, the World Health Organization (WHO) published a definition of stroke as a “neurological deficit of cerebrovascular cause that persists beyond 24 hours or is interrupted by death within 24 hours (WHO, 1978). This “24-hour definition” was used around the world for at least two decades. Then in 2002, a group of prominent American neurologists found the “24-hour definition” to be “*misleading in that many patients with transient <24-hour events actually have associated cerebral infarction* (Easton JD et al., 2009).” In addition, this group also determined that the “<1-hour definition” for TIA was also not useful because “*the 1-hour time point, like the 24-hour time point, does not accurately distinguish between patients with or without acute cerebral infarction* (Easton JD et al., 2009).” Thus, this group proposed a new definition for TIA:

*“Transient Ischemic Attack (TIA) is a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction (Easton JD et al., 2009).”*

Since the new definition was adopted, EDIC has updated their stroke and TIA definitions.

In order to distinguish suspected stroke from TIA events in EDIC, Coordinators should determine the duration of the suspected stroke or TIA event. This information can be obtained by asking the patient or someone representing the patient. Event duration should be categorized as lasting “<10 minutes,” “1 hour,” “<24 hours,” or “≥24 hours.”

*Peripheral Vascular Disease.* Amputation of a lower extremity, arterial events requiring bypass or angioplasty. Clinic should submit medical records or laboratory vascular studies with the Form 092.

## 28.4 Review Preparation

The Data Coordinating Center reviews reports of death and other outcomes for consistency with study definitions and completeness of supporting documentation. When the DCC is satisfied

that a reportable outcome is as fully documented as possible, the supporting documentation is edited so that the subject's treatment group assignment is masked to the extent possible. Patient's name, address, social security number, telephone number, and the same for relatives, will be masked by the Clinic prior to submission of records to the DCC. The DCC will mask any reference to treatment group or insulin delivery prior to review by the MMRC. Any additional information, such as history of hypoglycemia, will be included in the patient file if necessary.

#### **28.4.1 Actual Review of Deaths and Other Outcomes**

Death secondary to cardiovascular disease or sudden death is one of the primary cardiovascular outcomes in the EDIC. Immediate and underlying causes, as well as other significant conditions present at death, can usually be assessed from a death certificate.

However, to be recorded on a death certificate, the disease must have either initiated the sequence of morbid events leading directly to death or it must have otherwise contributed to death. The standard certificate has only four or five lines in which to list all the causes of death. Since diabetes tends to be associated with other causes of death, the diagnosis may compete with other causes for space on the certificate. Finally, incomplete clinical knowledge about the decedent and lack of understanding of proper completion of the death certificate may contribute to the incomplete recording of diagnosis. Each death report will be sent to the members of the MMRC. They will review the material documenting the death. They will complete Form 152 and return it to the DCC.

Periodically the DCC sends a set of cases for review to the MMRC. The reviewers have the option of 1) completing the review; 2) requesting additional information about the outcome; 3) requesting information that was edited to mask diabetes treatment; or 4) requesting review by a specialist. If a specialist review is requested, it will be obtained and provided to all reviewers. Requests for additional information will be passed on to the clinical centers and, if available, will also be provided to all reviewers. Responses are returned to the DCC.

When all reviews have been received, the DCC tabulates the results to determine whether there is agreement. If three reviewers agree in their conclusions, the review will be judged complete. If there is disagreement among the committee members, the event is adjudicated by discussion at a meeting of the committee. The DCC will prepare a summary of these classifications and comments by Committee members to be used during the adjudication meeting.

During the adjudication meeting there will be an effort to reach consensus classification of each event; agreement among three of the members will be the basis for consensus. Additional information may be requested by the reviewers in which case discussion may be tabled for final decision at a later time. Events that require unmasking are noted in the final tabulations.

#### **28.5 Definition of Myocardial Infarction**

Myocardial infarction is defined as the death of part of the myocardium due to an occlusion of a coronary artery from any cause, including spasm, embolus, thrombus, or the rupture of a plaque. The PEACE algorithm for classifying MI includes elements of the medical history, results of cardiac enzyme determination, and ECG readings. PEACE definition of MI includes events that occurred during surgery and MIs aborted by thrombolytic therapy or interventional procedures.

The differentiation of **definite MI** vs. **probable MI** vs. **aborted MI** will be made by the **Mortality and Morbidity Review Committee**. MI occurring as a consequence of, or during surgery, will be differentiated from “spontaneous” MI(s).

**Table 28.1**  
**Definition of Criteria for Diagnosis of Myocardial Infarction**

ECG Pattern/Symptoms	Cardiac Enzymes*			
	Abnormal	Equivocal	Incomplete	Normal
<b>Cardiac pain present:</b>				
Evolving Q wave and evolving ST-T Abnormalities	Definite MI	Definite MI	Definite MI	Definite MI
Equivocal Q wave evolution; or evolving ST-T abnormalities; or new left bundle branch block	Definite MI	Definite MI	Probable MI	No MI
Q waves or ST-T abnormalities suggestive of an MI and not classified as above	Definite MI	Probable MI	No MI	No MI
Other ECG, ECG absent or uncodable	Definite MI	No MI	No MI	No MI
	Cardiac Enzymes*			
ECG Pattern/Symptoms	Abnormal	Equivocal	Incomplete	Normal
<b>Abnormalities:</b>				
Equivocal Q wave evolution; or evolving ST-T abnormalities; or new left bundle branch block	Definite MI	Probable MI	No MI	No MI
Q waves or ST-T abnormalities suggestive of an MI and not classified above	Probable MI	No MI	No MI	No MI
Other ECG, ECG absent or uncodable	No MI	No MI	No MI	No MI

\* See Table 28.2 - Cardiac Enzymes for definitions.

### **28.5.1 Aborted Myocardial Infarction**

A diagnosis of aborted MI must meet all of the following criteria:

- Symptoms and ECG evidence for acute MI at presentation.
- Intervention (e.g., thrombolytic therapy) is followed by resolution of ECG changes.
- All cardiac enzymes are within normal limits.

### **28.5.2 Definition of Criteria for Diagnosis of Myocardial Infarction** **Cardiac Pain**

Cardiac pain is defined as:

Chest, jaw, throat or arm pain, discomfort, or tightness of at least 15 minutes duration probably due to myocardial ischemia.

**And** an absence of a definite non-cardiac cause of chest pain.

### **Electrocardiographic Criteria**

Clinical Centers should request first and last ECGs for each CVD hospitalization.

#### **Recommended Readings for ECG Interpretation:**

Crow, R.S., Prineas, R.J., Jacobs, D.R., et al. (1989). A new epidemiologic classification system for Interim Myocardial Infarction for Serial Electrocardiographic Changes. *American Journal of Cardiology*, 64:454-461.

Dubin, D. (1996). *Rapid interpretation of EKG's*, 5th edition. Tampa, Florida; Cover Publishing Co.

Goldschlager, N., and Goldman, M.J. (1989). *Principles of Clinical Electrocardiography*, 3rd edition. Norwalk, CT; Appleton Lange.

### **Cardiac Enzyme Criteria**

Pertinent enzyme results (as defined below) include those recorded in the hospital chart for days one through four after hospital admission, or days one through four after an in-hospital CHD event. Information on any non-ischemic causes for elevated enzymes will be obtained from the hospital discharge summary. Clinical centers should provide laboratory normal ranges for these cardiac enzymes (CK, CK-MB, LDH and troponin).

#### **Abnormal Cardiac Enzymes**

Cardiac enzymes may be defined as abnormal if they meet one of the three following criteria:

##### I. Creatine Kinase Heart Fraction (CK-MB)

CK-MB is listed as elevated in the lab report in one of the following ways (note the total CK may be elevated for other reasons and there may be non-ischemic causes for the elevated CK-MB such as cardiac surgery, cardiac defibrillation, severe muscle trauma, rhabdomyolysis):

CK-MB is  $\geq$  twice the upper limit of normal for that hospital lab,

**or** CK-MB  $\geq$  10% of total CK,

**or** CK-MB listed as “present” (if that lab uses the criterion of “present” or “absent” without reporting a numeric value).

##### 2. Lactate Dehydrogenase (LDH)

LDH<sub>1</sub>  $\geq$  LDH<sub>2</sub> and there is no evidence of other disease associated with elevated LDH (e.g., hemolytic disease, *Pneumocystis carinii*, etc.),

**or** LDH<sub>1</sub>  $\geq$  twice the upper limit of normal in the absence of LDH<sub>2</sub>.

3. Total CK and total LDH are both at least twice the upper limit of normal (not necessarily on the same day) and there is no known non-ischemic cause (e.g., cardiac surgery, cardiac defibrillation, severe muscle trauma, rhabdomyolysis) for the elevated CK and no evidence of hemolytic disease.

4. Troponin  $\geq$  twice the upper limit of normal.

### Equivocal Cardiac Enzymes

Cardiac enzymes will be classified as equivocal if they do not meet criteria for abnormal enzymes and meet one of the following criteria:

CK-MB is greater than the upper limit of normal but less than 2X the upper limit of normal, is 5 - 9% of total CK or, is "weakly present".

LDH is greater than the upper limit of normal but less than 2X the upper limit of normal.

Either total CK or total LDH, but not both, is at least twice the upper limit of normal.

Both total CK and total LDH are between the upper limit of normal and twice the upper limit of normal (not necessarily on the same day.)

Troponin is between the upper limit of normal and twice the upper limit of normal.

A summary of the enzyme diagnostic criteria is given in Table 28.2 - **Algorithm for Enzyme Diagnostic Criteria** and can be used to evaluate cardiac enzyme criteria in Table 28.1 - **Definition of Criteria for Diagnosis of Myocardial Infarction**.

**Table 28.2**  
**Algorithm for Enzyme Diagnostic Criteria**

Enzyme	Abnormal	Equivocal	Normal
Troponin	$\geq 2x$ ULN	ULN < Troponin < 2x ULN	WNL
CK-MB	$\geq 2x$ ULN or $\geq 10\%$ of total CK or "present" without quantification	ULN < CK-MB < 2x ULN or $5\% \leq$ of total CK < 10% or "weakly present"	WNL or < 5% of total CK
Total CK/total LDH	Total CK <b>and</b> total LDH $\geq 2x$ ULN	Total CK <b>or</b> total LDH (but not both) $\geq 2x$ ULN or ULN < total CK <b>and</b> total LDH < 2x ULN	Total CK WNL or total LDH WNL
LDH <sub>1</sub> and/or LDH <sub>2</sub>	LDH <sub>1</sub> $\geq$ LDH <sub>2</sub> or LDH <sub>1</sub> $\geq 2x$ ULN	ULN < LDH <sub>1</sub> < 2x ULN	LDH <sub>1</sub> < LDH <sub>2</sub> or LDH <sub>1</sub> WNL

ULN = upper limit of normal

WNL = within normal limit

## 28.6 Definition of Diabetes-Related Death

Diabetes-related death is defined as death due to one of the following:

- Myocardial infarction
- Stroke
- Peripheral vascular disease
- Renal disease
- Hyperglycemia or hypoglycemia
- Sudden death

## 28.7 Categorization of Renal Failure Events

When adjudicating whether a renal failure event is acute or chronic, the Renal Patient Report will be used. This report summarizes the course of renal function on one patient throughout the duration of the EDIC Study. This report specifically shows trends in levels of the following renal function parameters for one patient: a) AER, b) serum creatinine, c) creatinine clearance, & d) cystatin C. In CRF, the following trend may be seen over several years:

1. an increase in AER,
2. followed by an increase in serum creatinine,
3. followed by a decline in creatinine clearance.

On the other hand, ARF would be consistent with a sudden increase in AER and serum creatinine with a sudden decrease in creatinine clearance.

Observing the trends in renal function throughout EDIC will help the MMRC decide whether a RF event is ARF, CRF, or neither.

### Recommended Readings on Renal Failure:

*Medline Plus Medical Encyclopedia (website) for Acute Kidney Failure, Viewed 26 September, 2008, <<http://www.nlm.nih.gov/MEDLINEPLUS/ency/article/000501.htm>>*

*Medline Plus Medical Encyclopedia (website) for Chronic Renal Failure, Viewed 26 September, 2008, <<http://www.nlm.nih.gov/MEDLINEPLUS/ency/article/000471.htm>>*

## 28.8 Symptoms, Causes, and Categories of Stroke

Three important mechanisms in the development of stroke are (a) high blood pressure, and (b) atherosclerosis, and (c) weakening of blood vessel walls. When (a) and (b) occur together, this increases the risk of developing ischemic stroke. When (a) and (c) occur together, this increases the risk of developing hemorrhagic stroke.

### 28.8.1 Ischemic Stroke Symptoms

Strokes are commonly recognized by symptoms. TIAs may also have the same symptoms, but are generally of shorter duration. Symptoms involving semi-consciousness but not involving paralysis may resemble hypoglycemia.

Stroke/TIA symptoms depend on what part of the brain is damaged. In some cases, a person may not even be aware that he or she has had a stroke/TIA event.

Symptoms depend on the severity of the lesion and what part of the brain is affected. These may include:

- Muscle weakness in the face, arm, or leg (usually just one side)
- Loss of motor coordination
- Numbness or tingling on one side of the body
- Trouble speaking or understanding others who are speaking
- Problems with eyesight, including double vision, partial- or total-loss of vision
- Altered consciousness

#### 28.8.1.1 Categorizing Ischemic Stroke by Location

To distinguish strokes by location, strokes can be referred to by location where the lesion occurs, such as: “cerebral infarction” & “retinal infarction. Other examples of categorizing stroke by location of lesion include:

- (a ) a basal ganglia infarction is an infarct in the basal ganglia region of the brain
- (b ) a right hemispheric stroke is an infarct in the right hemisphere of the brain
- (c ) a lacunar stroke results from an infarct of one of the penetrating arteries that supply blood to deep brain tissue.

Alternative methods for categorizing ischemic stroke by location:

The Oxford Community Stroke Project classification (OCSP, also known as the Bamford or Oxford classification) determines under which “region” a set of neurologic deficits belongs to. Regional categories include: total anterior circulation infarct (TACI), partial anterior circulation infarct (PACI), lacunar infarct (LACI) or posterior circulation infarct (POCI) (Bamford J et al., 1991; Bamford JM, 2000).

#### 28.8.1.2 Categorizing Ischemic Stroke by Causal Mechanism

If there is atherosclerotic buildup in the walls of the arteries located in the brain or that carry blood to the brain (such as the carotid arteries), then this increases the risk of ischemic stroke. Over time, as plaque builds up in the arterial walls, the arterial lumen narrows, which increases the risk that the blood will clot.

Ischemic strokes are caused by a blockage of flow through a blood vessel. Blockage can occur in many different ways. From a trial known as TOAST (Trial of Org 10172 in Acute Stroke Treatment), a classification system was derived that is based on causal mechanism. TOAST classification includes the following categories (Adams HP Jr., 1993; Donnan GA et al., 2008):

- a) thrombosis or embolism due to atherosclerosis of a large artery
- b) embolism of cardiac origin
- c) occlusion of a small blood vessel
- d) other determined cause (such as systemic hypoperfusion or venous thrombosis)
- e) undetermined cause

Undetermined cause can be from two possible causes, no cause identified, or incomplete investigation (Adams HP Jr., 1993; Donnan GA et al., 2008). Ischemic stroke without an obvious explanation is categorized as "cryptogenic (Donnan GA et al., 2008)."

### **28.8.1.3 Risk Factors for Ischemic Stroke**

As mentioned previously, high blood pressure is the strongest risk factor for ischemic stroke. Another important risk factor for ischemic stroke is high cholesterol and heart disease. In addition, the following risk factors may also increase the risk for ischemic stroke:

- a) Atrial fibrillation (a type of arrhythmia)
- b) Diabetes
- c) Family history of stroke
- d) Increasing age

## **28.8.2 Hemorrhagic Stroke**

Hemorrhagic strokes occur because of trauma to the brain that causes a ruptured blood vessel. Traumatic mechanisms that cause such events include: falls, vehicular accidents (such as motor vehicles, trains, or aircraft), sports-related hits (in boxing or getting hit by a fast-moving ball such as in baseball). Some hemorrhagic strokes are not caused by trauma, but result from a rupture of blood vessels in the brain (such as an arteriovenous malformation or brain aneurism).

### **28.8.2.1 Hemorrhagic Stroke Symptoms**

Hemorrhagic stroke symptoms are generally characterized by three symptoms: severe headache, diminished consciousness, and possibly vomiting and/or seizures. Depending on the severity of the bleed, the consciousness can be anywhere between slightly diminished (for example, the patient may seem confused or disoriented) to completely lost (for example, if a patient faints, gets "knocked-out," or goes into a coma).

Patients with hemorrhagic strokes may also present with focal neurologic symptoms resembling ischemic stroke or TIA. However, most ischemic strokes or TIAs do not have headaches, vomiting, or seizures.

### **28.8.2.2 Categorizing Hemorrhagic Stroke by Location**

Like ischemic strokes, hemorrhagic strokes are also categorized by the location where the lesion occurs. Examples of terms used to define hemorrhagic strokes include "cerebral

hemorrhage” & “retinal hemorrhage.” However, they are also categorized by the location of the bleed in relation with the skull and brain tissue.

Hemorrhagic stroke is distinguished based on the location of the bleed in reference to the skull and brain tissue:

1. Intracranial hemorrhage is the accumulation of blood anywhere within the skull vault. Without immediate treatment (i.e., surgery), an intracranial hemorrhage will lead to a stroke.
2. Among intracranial hemorrhages, a distinction is made between intra-axial hemorrhage (blood inside the brain) and extra-axial hemorrhage (blood inside the skull but outside the brain).
  - a. Intra-axial hemorrhage (intracerebral) types:
    - i. *intraparenchymal hemorrhage* (blood in the brain tissue)
    - ii. *intraventricular hemorrhage* (blood in the ventricular system)
  - b. Extra-axial hemorrhage types:
    - i. *epidural hematoma* (bleeding between the dura mater and the skull),
    - ii. *subdural hematoma* (bleeding in the subdural space)
    - iii. *subarachnoid hemorrhage* (bleeding between the arachnoid mater and pia mater).

Most of the hemorrhagic strokes consist of either (a) primary intracerebral or (b) subarachnoid hemorrhage (Donnan GA, et al., 2008).

### 28.8.2.3 Risk Factors for Hemorrhagic Stroke

Hemorrhagic strokes can result from insufficient management of a variety of brain hemorrhage conditions that differ by location of the bleed:

- a. Intra-axial hemorrhage types:
  - iv. Intracerebral hemorrhage (blood in the brain tissue)
    1. It is usually caused by hypertension (The Internet Stroke Center, 2011).
    2. Rarely, it is caused by trauma, infections, tumors, blood clotting deficiencies, and abnormalities in blood vessels (The Internet Stroke Center, 2011).
    3. Among patients between 18-49 years of age, risk factors include: hypertension, diabetes, menopause, cigarette smoking, excessive alcohol consumption, & regular consumption of caffeine (Qureshi AI et al., 2001; Feldmann E et al., 2005).
    4. Among patients between 45 – 90 years of age, risk factors include: advanced age, hypertension, diabetes, smoking, & high cholesterol (Qureshi AI et al., 2001; Poels MM et al., 2010).
- b. Extra-axial hemorrhage types:
  - v. Epidural hematoma (bleeding between the dura mater and the skull)
    1. For epidural hematoma, risk factors include: falls, motor vehicle collisions, assault (Tallon JM et al., 2008).
  - vi. Subdural hematoma (in the subdural space)
    1. For subdural hematoma, risk factors include: advanced age, hemodialysis (for renal failure), & the use of antiplatelet or anticoagulant medications (Torihashi K et al., 2008; Power A et al., 2010)
  - vii. Subarachnoid hemorrhage (between the arachnoid mater and pia mater).

1. High blood pressure, smoking, excessive alcohol intake, and family history are risk factors for subarachnoid hemorrhage, while high BMI seems to protect against subarachnoid hemorrhage (van Gijn J, 2007; Sandvei MS et al., 2009).

#### **28.8.2.4 Categorizing Hemorrhagic Stroke by Causal Mechanism**

Hemorrhagic strokes are often triggered by a) direct trauma to the head or b) violent movement of the body that causes brain structures to be injured (such as acceleration-deceleration trauma or whiplash). Examples of these traumatic mechanisms include: falls, vehicular accidents (such as motor vehicles, trains, or aircraft), sports-related hits (in boxing or getting hit by a fast-moving ball such as in baseball).

Hemorrhagic strokes are more likely in some individuals due to having defects in the blood vessels of the brain that make this more likely (such as an arteriovenous malformation or brain aneurism).

Hemorrhagic ischemic stroke may also result from ischemic change to a part of the brain, such as the blood-brain barrier ("hemorrhagic transformation") (Qureshi AI et al., 2001; Donnan GA et al., 2008).

#### **28.8.3 Categories of Stroke/TIA as outcomes for adjudication by the MMRC**

**Strokes will be classified based on whether it was hemorrhagic or ischemic. The differentiation of definite stroke vs. probable stroke vs. aborted stroke vs. no stroke will be made by the Mortality and Morbidity Review Committee.**

An **aborted ischemic stroke** will be defined as a stroke that was prevented from forming due to timely administration of thrombolysis (i.e., tPA). An **aborted hemorrhagic stroke** will be defined as a stroke that was prevented from occurring due to timely surgical intervention (i.e., repair of a vascular defect).

**In addition, Strokes occurring “as a consequence of surgery or during surgery” will be differentiated from “spontaneous” strokes.**

Summary of categories for adjudicating Stroke or TIA in EDIC

- As with other adjudicated EDIC outcomes, Strokes and TIAs will be adjudicated by the MMRC.
- Like angina, TIAs will be adjudicated as
  - a) Confirmed TIA
  - b) Unconfirmed TIA
  - c) Not Meeting Criteria For TIA Outcome
- Like MIs, Strokes will be adjudicated as
  - a) Definite Ischemic Stroke
  - b) Probable Ischemic Stroke
  - c) Definite Primary Intracerebral Hemorrhagic Stroke
  - d) Probable Primary Intracerebral Hemorrhagic Stroke
  - e) Definite Subarachnoid Hemorrhagic Stroke
  - f) Probable Subarachnoid Hemorrhagic Stroke

- g) Aborted Ischemic Stroke (Stroke Aborted By Thrombolysis)
- h) Aborted Hemorrhagic Stroke (Stroke Aborted By Surgery)
- i) Other type of Stroke
- j) No Stroke
- Strokes will also be adjudicated as
  - a) Stroke not occurring as a result of or during a procedure (such as surgery or angiography; Spontaneous Stroke)
  - b) Stroke occurring a result of or during a procedure (such as surgery or angiography)

#### **28.8.4 Terms Used to Describe Stroke or TIA**

- Aborted stroke – a stroke that was prevented from forming.
  - Aborted ischemic stroke will be defined as a stroke that **was** prevented from forming due to timely administration of thrombolytic therapy (i.e., tPA).
  - Aborted hemorrhagic stroke will be defined as a stroke that was **prevented** from occurring due to timely surgical intervention (i.e., repair of an arteriovenous malformation or brain aneurism).
- Clot – solidified blood.
- Cryptogenic – of unknown origin
- Embolus – a clot travelling from another site that **blocks** flow in an artery in or near the brain.
- Hemorrhagic ischemic stroke – hemorrhage in region of cerebral infarction as a result of ischemic change to blood-brain barrier (Qureshi et al., 2001).
- Infarction – permanent and irreversible damage from blocking flow of blood to tissue (such as brain tissue). Infarction results from prolonged and untreated ischemia.
- Ischemia – temporary and reversible damage from blocking flow of blood to tissue (such as brain tissue).
- Thrombus – a locally-formed clot that blocks flow through a blood vessel.
- Systemic hypoperfusion - general decrease in blood supply, such as in shock.

#### **28.8.5 References for Stroke and TIA**

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## 29. COMPUTED TOMOGRAPHY (CT) SCAN

### 29.1 Background and Goals

The Epidemiology of Diabetes Interventions and Complications (EDIC) is studying risk factors and measures of cardiovascular disease that relate to the progression of subclinical to clinical disease. An integral part of this study is the measurement of coronary artery calcium using either an electron beam computed tomography (EBCT) scanner or a sub-second, multi-row scanner (which we will refer to as SUBCT). [Note: One clinic will use a non multi-row detector, but it will nevertheless be classified as a SUBCT scanner for our purposes in this chapter.] Coronary calcium will be assessed in relation to the risk of future cardiac events, and from repeated scans the progression of coronary calcium will be related to risk factors and risk of future events.

The regularly and comprehensively monitored cohort of 1418 subjects is ideally suited to address these important issues. Retention of the cohort is 95%. HbA1c, blood pressure, serum lipids and urine albumin levels, as well as any history of coronary events, have been recorded in detail through uniform methods in central laboratories by certified personnel according to a common protocol in detail for more than ten years and will continue to be documented for at least five more years. Moreover, in a collaborative study known as “Markers and Mechanisms of Macrovascular Disease in IDDM” with the Medical University of South Carolina, a large number of other putative risk factors for cardiovascular disease are being measured in the same cohort. These include homocysteine, oxidized LDL cholesterol, kallikreins, as well as approximately 20 candidate genes related to these and other risk factors. It is also noteworthy that this DCCT/EDIC cohort has responded enthusiastically to the recent addition of the above measurements by the Medical University of South Carolina.

Measurement of coronary calcium in this particular group of Type 1 diabetic subjects is scientifically attractive for several reasons: 1) it provides a direct means for simultaneously testing multiple hypotheses about the role of recognized and putative risk factors in the development of coronary atherosclerosis in Type 1 diabetes; 2) it provides an opportunity to test the significance of coronary calcium as a risk factor for future coronary events in Type 1 diabetes; 3) it permits a direct comparison between coronary calcium and intimal-medial wall thickness of the carotid arteries determined by ultrasonography as measures of atherosclerosis and as indicators of future coronary heart disease events in Type 1 diabetes.

The ultimate clinical value of performing CT on the subjects could be very great. The information gained could allow us to determine which risk factors are the most important for cardiovascular disease. This would help direct future intervention strategies for prevention of cardiovascular disease. The data could tell us when coronary atherosclerosis begins in the course of Type 1 diabetes, and, therefore, the optimal time for effective primary prevention measures. The data could also help to define the role of coronary calcium in screening asymptomatic patients at especially high risk for cardiovascular disease. More accurate identification of high-risk Type 1 diabetic individuals would make the application of further, often invasive, diagnostic procedures more efficacious and lead to prompt and effective treatment, when indicated.

## 29.2 Scanning Centers and Equipment

The Data Coordinating Center (DCC) asked 23 scanning centers to join the study. Of these 23, 19 sites have indicated that they are interested in participating. Each of these 19 centers has either EBCT or SUBCT capability.

Each scanning site has a unique, two-digit numeric identification number. The identification number should be used on all forms that ask for the “Site ID” or “Scanning Site ID”. The ID numbers of the scanning sites are given in Table 29.1.

**Table 29.1 Scanning Center Identification (ID) Numbers**

<b>Site ID</b>	<b>Scanner Type</b>	<b>Site Name</b>
50	EBCT	Heartscan, Pittsburgh, PA
51	SUBCT	Cleveland Clinic, Cleveland, OH
52	SUBCT	Johns Hopkins University Hospital, Baltimore, MD
53	EBCT	University of Pennsylvania, Philadelphia, PA
54	EBCT	St. Francis Hospital, Roslyn, NY
55	EBCT	Beth Israel Deaconess Medical Center, Boston, MA
56	EBCT & SUBCT	Mayo Clinic, Rochester, MN
57	SUBCT	Fairview University Medical Center, Minneapolis, MN
58	EBCT	University of Iowa, Iowa City, IA
59	EBCT	Lifetest Cardiac Imaging, Nashville, TN
60	EBCT	LifeScore, San Diego, CA
62	SUBCT	Medical University of South Carolina, Charleston, SC
63	EBCT	Lifetest Cardiac Imaging, Sarasota, FL
64	SUBCT	Washington University at St. Louis, St. Louis, MO
65	EBCT	University of Texas Southwestern, Dallas, TX – EBCT
67	SUBCT	Northwestern University, Chicago, IL
68	SUBCT	Heart Hospital of New Mexico, Albuquerque, NM
69	SUBCT	St. John Hospital & Medical Center, Detroit, MI
71	SUBCT	Center for Diagnostic Imaging, Mountlake Terrace, WA

## 29.3 EDIC Clinic ID

Each EDIC clinic has a unique, two-digit numeric identification number. The identification number should be used on all forms that ask for the “EDIC Clinic ID”. The ID numbers of the EDIC clinics are given in Table 29.2.

**Table 29.2 EDIC Clinic Identification (ID) Numbers**

<b>Site ID</b>	<b>Site Name</b>
01	Case Western Reserve University, Cleveland, OH
02	University of Pennsylvania, Philadelphia, PA
03	Cornell University, New York City, NY
04	Henry Ford Hospital, Detroit, MI
05	Joslin Diabetes Center, Boston, MA
06	Massachusetts General Hospital, Boston, MA
07	Mayo Foundation, Rochester, MN
08	Medical University of South Carolina, Charleston, SC

09	International Diabetes Center, Minneapolis, MN
10	University of Iowa, Iowa City, IA
11	University of Minnesota, Minneapolis, MN
12	University of Missouri, Columbia, MO
13	University of Pittsburgh, Pittsburgh, PA
14	University of Tennessee, Memphis, TN
15	University of Texas Southwestern, Dallas, TX
16	University of Toronto, Toronto, Ontario, Canada
17	University of Washington, Seattle, WA
18	University of Western Ontario, London, Ontario, Canada
19	Vanderbilt University, Nashville, TN
20	Washington University, St. Louis, MO
21	Yale University, New Haven, CT
22	Albert Einstein College of Medicine, Bronx, NY
23	Northwestern University, Chicago, IL
24	University of California-San Diego, San Diego, CA
25	University of Maryland-Baltimore, Baltimore, MD
26	University of New Mexico, Albuquerque, NM
27	University of South Florida, Tampa, FL
41	University of Michigan, Ann Arbor, MI

## **29.4 Qualifications of Personnel**

### **29.4.1 Scanning Center Personnel**

Each scanning center has a designated principal investigator (PI) who is responsible for the performance of the CT examinations at his/her EDIC scanning center. These PIs should monitor the study closely to ensure adherence to the CT protocol, including following the approved procedures for scanning, data transmission, and maintenance of appropriate quality control procedures. They should also supervise each technologist and provide necessary on-site training, supplementing that which will be provided by the CT Reading Center personnel.

Scanning Center technologists should have appropriate knowledge of cross-sectional anatomy, physiology, and pathology as related to the heart. Technologists must be certified as RTs in their state. It is recommended that technologists also have at least two years of experience in chest computed tomography. The technologist should also have a basic knowledge of cardiac CT, computer software applications, data formatting, and experience with the workstations and procedures used in data formatting/transmission.

Each technologist involved in the study should also have a complete understanding of this protocol and be experienced at providing breath-holding instruction, ECG gating, and operating the EBCT or SUBCT equipment. To ensure quality control, each scanning center should have designated CT technicians who will perform the EDIC examinations, once appropriate training has been provided.

Training sessions will be mandated for all technicians participating in the EDIC study. Ideally, approximately 1,400 participants will be scanned among the 19 centers during the initial (1-year) examination, however this process may take up to two years. Participants will receive repeated scans during a subsequent follow-up examination in future years.

Each center will be responsible for scanning variable numbers of the cohort of 1381 individuals. For purposes of increased reliability and quality control, each subject will be scanned twice during each session.

#### **29.4.2 Further Training and Certification**

For full certification, all technicians will be required to submit three sample images, performed and transmitted to the Reading Center according to protocol. Immediate feedback will be given. A telephone call will be made to technologists, as needed, to discuss areas for improvement and possible solutions to problems.

A designated CT Reading Center investigator or representative will travel to each of the scanning centers. The instructor will teach the CT scanning protocol to the technologists at the scanning centers and allow time for discussion. These visits will take half of one working day each and will concentrate on obtaining adequate and optimal scan images using the scanning protocol. Each scanning center technologist will perform at least two studies under the supervision of the instructor. On successful completion of this session, the instructor will approve continuing technologist certification.

On successful completion of this session, the instructor will approve continuing technologist certification. The instructor will complete the EDIC Form 124, the CT Certification/Site Visitor Checklist (see Appendix A), to evaluate the performance of the technician(s) during the site visit. The instructor will also complete a site visit report (see Appendix B). The instructor should FAX copies of both of these forms to the DCC at 301-881-4471 and retain copies for the Reading Center files.

#### **29.4.3 Reader Training and Certification**

Readers will be trained by the director of the Reading Center. After training, each reader will undergo a certification exam conducted by the Reading Center director. The following essential elements will comprise this exam:

1. Logging on and off of the work station
2. Appropriate choosing of subjects
3. Boxing and correcting the phantom regions
4. Tracing, including pruning of arterial tree
5. Scoring and editing of lesions
6. Editing when necessary the summary of scores
7. Completing the quality assurance menu

The reader will be scored in each component above as either passed or failed. A 100% pass-rate will be necessary for certification. Currently there are two CT readers fully certified in the EDIC reading protocol.

### **29.5 Informed Consent**

Every scanning center must have an IRB-approved informed consent form that includes the IRB approval number. The informed consent regarding this procedure must be signed and in the patient's file prior to the procedure. If more than one informed consent is needed because of institutional requirements, copies of both forms should be sent to the Data Coordinating Center.

## **29.6 Exclusion Criteria**

### **29.6.1 Pregnancy & Breastfeeding Mothers**

CT scans may not be performed on pregnant women. Pregnancy test guidelines will be determined by local EDIC clinic requirements.

It is also recommended that women who are breastfeeding not have this procedure.

### **29.6.2 Large Patients**

EDIC patients who weigh over 300 pounds will be excluded from scanning at sites with EBCT (Imatron) scanners. The weight limit for patients scanned on SUBCT (non-Imatron) scanners is 400 pounds. If a patient weighs between 300 to 400 pounds and wishes to receive the CT scan, the Study Coordinator may schedule the patient for a scan at one of the SUBCT sites, even if the SUBCT site is not the one usually associated with his/her EDIC clinic.

### **29.6.3 Atrial Fibrillation**

Patients who suffer from atrial fibrillation will be excluded from scanning.

### **29.6.4 Previous Radiation Exposure**

Patients who have had more than one computed tomography (CT) scan or radiation therapy during the past year will not be included in the study.

## **29.7 Participant Scheduling**

The Data Coordinating Center will send each clinical center a list of participant IDs. Each scanning center will provide their local clinical center with the days/times when EDIC participants may be scheduled and the clinical center will contact participants to arrange appointments for their CT scan.

When the EDIC Study Coordinator calls the patient to schedule an appointment, the Study Coordinator should ask the patient questions regarding the exclusion criteria. The Study Coordinator should ask the patients their weight; pregnancy and breastfeeding status, if female; if they suffer from atrial fibrillation; and if they have undergone procedures using radiation during the past year. If a patient weighs between 300 to 400 pounds and wishes to receive the CT scan, the Study Coordinator may schedule the patient for a scan at one of the SUBCT sites, even if the SUBCT site is not the one usually associated with their EDIC clinic.

The Study Coordinator will schedule participants for a certain date and time, and, if necessary, will make transportation arrangements for the patients. The Study Coordinator will tell the participant to call the coordinator at least one week prior to the scheduled appointment should the participant need to reschedule for any reason. The Study Coordinator will send a confirmation letter for the appointment to the patient, detailing the time, date, directions to the scanning center, and description of the procedure. Along with the confirmation letter, the patient will receive a brochure (see Appendix C) that includes information about coronary artery calcification and the scan procedure. Patients will be asked to bring the brochure with them when they go to the scanning center as the brochure also contains a page with information for the technologist, including EDIC identifiers and contact information. Two days prior to the scan

date, the Study Coordinator will phone or e-mail the participants to remind them of their appointments and to remind them to bring their patient brochures. If the brochure has been misplaced, the Study Coordinator will provide the patient with the information for the technologist.

The Study Coordinator will complete EDIC Form 116, the CT Scheduling List (see Appendix D), as patients are scheduled for the CT scan. Only newly scheduled patients should be indicated on Form 116. On a weekly basis, the Study Coordinator will FAX a copy of the form to the DCC at 301-881-4471 and keep the original in the clinic files.

## 29.8 Scanning Table and Calibration Phantom

The table mat will have a recess for the calibration pad phantom which will be of identical manufacture at all scanning centers. The phantom is made of tissue equivalent plastic with rods of hydroxyapatite of known radiographic density. The technologist will position the subject so that the phantom will be under the thorax (allowing for calibration of calcium measurements to the known hydroxyapatite density). All patients should be scanned head-first, even if the site typically scans patients feet-first. The phantom is pictured in Figure 29.1.



Figure 29.1

## 29.9 Scanning Procedure

The scanning procedure, consisting of two scans done in succession on each subject, is described below and will require approximately 20 minutes of the subject's time. Achieving maximal accuracy and reproducibility by minimizing respiratory motion requires this duration of time. In unusual cases, this may require as many as 30 minutes of time. For many, the procedure will be completed in 15 minutes or less.

### 29.9.1 Entering the EDIC ID and Acrostic

This very important step must be done correctly to prevent any irretrievable loss of CT data. All necessary information needs to be entered into the system, including your technician certification identification number that is issued by the Data Coordinating Center. All technicians have their own unique technician certification number, which consists of the two-digit scanning site ID followed by a letter.

The patient identification number for the CT project is a nine-digit field consisting of "EDIC" followed by the five-digit EDIC patient ID. The acrostic is an eleven-digit field consisting of "EDIC" followed by the patient's initials (first, middle, last) and then four "X"s. If the patient does not have a middle name, use an "X" for the middle initial. The EDIC ID number must be placed in the ID Field, the acrostic placed in the Name Field, and the technician certification number must be placed in the Tech Initials field. ***Please note that technicians should not enter their initials into the "Tech Initials" field, they should enter their assigned technician ID/certification number.***

Example:

**ID:** EDIC01001      **NAME:** EDICFMLXXXX      **TECH INITIALS:** 51A

The time stamp on each CT record will determine whether the scan is the first or second in the sequence.

### **29.9.2 Preparation of the Subject (3 minutes)**

EDIC participants with atrial fibrillation or who weigh over 300 lbs using an EBCT scanner, or 400 lbs using a SUBCT scanner, will be excluded from scanning. All participants must give informed consent before being scanned. The technologist will ask women if they might be pregnant and will not scan them if they answer affirmatively. The technologist will attach three electrocardiographic electrodes under the left clavicle and on either side of the thorax near the axillae (to maximize the ECG signal).

### **29.9.3 Breath Holding Instruction (3 minutes)**

Before the first chest CT scan, the technologist should spend 15 to 30 seconds with the subject emphasizing the importance of breath holding and immobility during scanning. Note: As additional time is required to obtain a complete scan on the Somatom 4+, technicians that use Somatom 4+ machines may further emphasize to subjects that a slow, steady exhalation is preferable to inhalation, should the subjects feel compelled to breathe before the scanning is completed. Exhalation reduces carbon dioxide levels and is less likely to cause misregistration.

Preliminary study suggests that at least 99.5% will be able to hold their breaths for more than 15 seconds and 80% will be able to hold their breaths for more than 30 seconds. This is based on the South Bay Heart Watch cohort consisting of subjects whose mean age was 62 years at the time of scanning. The EDIC cohort will be younger and will therefore be expected to suffer less from breathing difficulties. Only after the technologist is satisfied that the subject understands the importance of breath holding, will he/she proceed.

### **29.9.4 Checking the Scout Image (1 minute)**

While acquiring an 11 cm scout image that begins 180 mm below the sternal notch, the technologist will instruct the subject to take three deep breaths, and then to hold his/her breath at end-inspiration. This will provide views of the chest on the image monitor at the operator console. From this image, the technologist will check patient centering and choose the position for the highest scan (at the lower margin of the bifurcation of the main pulmonary artery) in the case of EBCT scanners or will position for the initiation of the sub-second, multi-row volume in the case of SUBCT scanners. The couch will be moved to the start position. The technologist will check subject and phantom positioning in the scout image.

The Siemens Volume Zoom and General Electric Lightspeed scan acquisition requires a breath hold ranging from 15 to 25 seconds for the participant depending upon the combination of heart rate and heart length. EBCT scan acquisition requires a breath hold of between 25 and 40 seconds depending on the same factors. The Siemens Somatom 4+ non multi-row detector CT scanner requires a breath hold of at least 35-45 seconds with a slow exhalation permitted if, or when, the participant is not able to hold his or her breath for that length of time.

### 29.9.5 Default Scanner Settings.

The technologist will acquire 35-40 image slices as needed to ensure that the entire heart is scanned. At least 10.5 cm of data in the z direction will be acquired with each scan and the scan Field of View will be 35 cm for all scanners (to incorporate the phantom in the image). For SUBCT scans, prospective cardiac gating will be used with scanner triggering at 50% of the electrocardiographic RR interval. For each scanner, the default settings will be as follows:

- **GE Light Speed** (800 msec rotation time) - 120 kVp, 200 mA, .8 sec scan, 4 x 2.5 mm collimation, sequential axial scans with prospective gating, standard reconstruction, standard filter, retrospective cardiac gating will be used for image selection. Prospective cardiac gating will be used with scanner triggering at 50% of the electrocardiographic RR interval when this is available. If prospective triggering is not available, the step and shoot (cine loop) mode should be used with retrospective image slice selection.
- **GE Light Speed Plus** (500 msec rotation time) - 120 kVp, 320 mA, .5 sec scan, 4 x 2.5 mm collimation, sequential axial scans, with prospective cardiac gating, standard reconstruction. Prospective cardiac gating will be used with scanner triggering at 50% of the electrocardiographic RR interval.
- **Siemens Volume Zoom** (500 msec rotation time) - 140 kVp, 139 mA, .361 sec scan, 4 x 2.5 mm collimation, sequential axial scans with prospective cardiac gating, standard reconstruction (as designated on the VZ). Note: mAs increases to 50. Prospective cardiac gating will be used with scanner triggering at 50% of the electrocardiographic RR interval.
- **Siemens Somatom 4+** (500 msec rotation time) – 140 kVp, 100 mA, 3.0 mm collimation, sequential axial scans with prospective cardiac gating, standard reconstruction filter. Note: mAs increases to 50. Prospective cardiac gating will be used with scanner triggering at 50% of the electrocardiographic RR interval.
- **Marconi MX 8000** (500 msec rotation time) - 120 kVp, 500 mA, .333 sec scan, 4X2.5 mm collimation, sequential axial scans with prospective cardiac gating, standard filter reconstruction, Note: mAs increases to 165. Prospective cardiac gating will be used with scanner triggering at 50% of the electrocardiographic RR interval.
- **Imatron EBCT scanners** - 130 kVp, 630 mA, scan time 100 msec, 3 mm collimation, sharp reconstruction filter. For EBCT scans, prospective cardiac gating will be used with scanner triggering at 80% of the electrocardiographic RR interval. The EBCT scanner table will pause after each table increment of 3 mm (sequential axial scans).

### 29.9.6 Large Patient Scanner Settings

For the SUBCT (non-Imatron) scanners *only*, the mA will be adjusted upwards for larger patients. For **patients > 220 lbs**, the mA will be increased by 25%. Specifically:

- **General Electric LightSpeed scanners** (800 msec rotation time): increase to 250 mA. All other parameters are to remain the same.
- **GE Lightspeed Plus scanners** (500 msec rotation time): increase to 400 mA. All other parameters are to remain the same.
- **Siemens Volume Zoom scanners** (500 msec rotation time): increase to 174 mA. Note: mAs increases to 63. All other parameters are to remain the same.

- **Siemens Somaton 4+ scanners** (500 msec rotation time): increase to 125 mA.  
Note: mAs increases to 63. All other parameters are to remain the same.
- **Marconi MX 8000 scanners** (500 msec rotation time): increase to 625 mA.  
Note: mAs increases to 205. All other parameters are to remain the same.

### **29.9.7 Reconstruction**

The technologist will use the 35 cm field of view and the sharp reconstruction kernel for all EBCT scans and the 35 cm field of view and the standard kernel for all other scans.

### **29.9.8 Imaging (8 minutes)**

Though total imaging time will be approximately 30 to 40 seconds, double scanning will require about 7 to 9 minutes to complete. The technologist will first acquire one entire series of image slices. The technologist will instruct the subject to relax on the table while he/she reconstructs and assesses the adequacy of positioning, ECG gating and lack of respiratory motion. ***The technologist should allow a two minute rest period between scans.*** This will insure some decrease in heart rate and respiratory recovery before the second scan and breath hold.

If the first set of images are adequate and after the two minute rest period, the technologist will acquire another series of image slices while the subject remains immobile and in an identical position. Once again, the technologist will assess the adequacy of the images.

### **29.9.9 Identification, Storage and Transport of Image Data**

The following process will ensure proper scan identification and subject confidentiality. The technologist will record each volunteer's study ID number in the medical record number field of each scan. An eleven-digit acrostic consisting of "EDIC" followed by the patient's initials (first, middle, last) then 4 "X"s (see Section 29.8.1) will be put in the last name field of the header. The date and times of the two scans and the technologist certification number will be identified in the appropriate fields. The technologist will store images in retrievable format on optical disk (MODs). Images will be transferred to a local work station which has an INTERNET interface to be used for transfer to the Reading Center.

## **29.10 Scanner Quality Assurance**

### **29.10.1 Regular Scanner Calibration to Water**

It is strongly recommended that the technologist at each center check the scanner at least weekly using a standard water phantom. These checks will include zeroing and calibrating the scanner unit.

### **29.10.2 CT Calibration Measurements for Quality Assurance**

Each clinical site will have a QCT calibration phantom (Image Analysis Inc) and a TORSO quality assurance (QA) phantom (Image Analysis Inc) containing a central plug with a known concentration of hydroxyapatite (100 mg/cc). The calibration pad contains cylindrical rods and will be contained inside of a recess in the table pad for patient comfort. Periodic

quality assurance scans of the TORSO phantom allow convenient and quick verification of accuracy and precision of CT scanners at different sites.

### 29.10.3 Positioning the Calibration and TORSO Phantoms

Make the table height such that the center of the calibration phantom is located at a distance of 9.2 cm +/- 1.0 cm from isocenter of the scanner field of view, see Figure 29.2. Place the TORSO phantom on top of the calibration phantom (positioned in the couch pad) and using your laser alignment light, adjust the table height until the TORSO center insert is at the location of isocenter (on grid). This is the table height you will use for QA scans with your TORSO phantom.

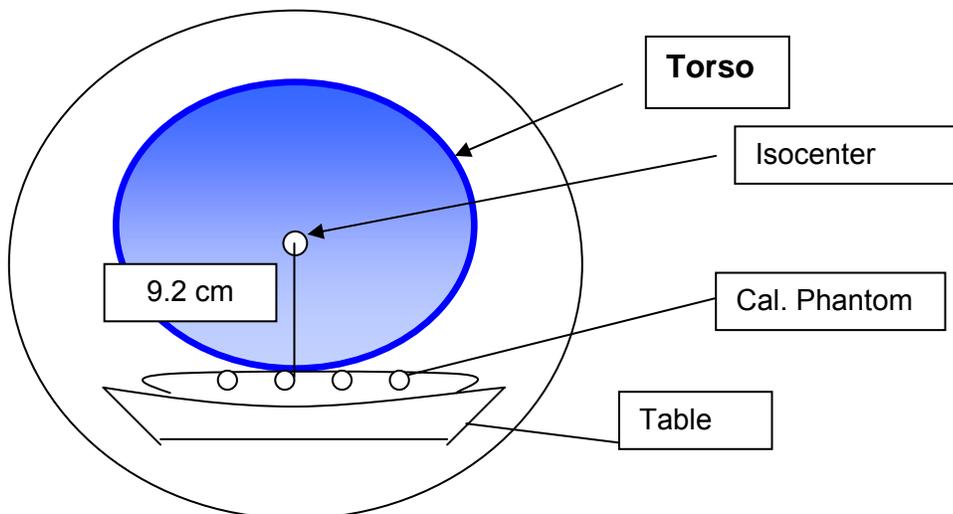


Figure 29.2

### 29.10.4 Scanning Your TORSO QA Phantom

After the correct position has been determined, take a vertical axial slice through the center of the TORSO phantom. Use the same parameters as with patient exams. With SUBCT scanners, you should acquire two centimeters of volume data including the center of the TORSO phantom. Reconstruction should be done with the same parameters as in scanning study subjects.

Display your axial image on the CT monitor and examine it to ensure that it is free of artifacts, such as air gaps and streaks. Ensure that the calibration phantom is included in the field of view. If there are significant artifacts over the calibration phantom, you should discard the image and rescan the phantom.

Using your CT software, place the region of interest (ROI) on the calibration phantom reference samples (0, 50, 100, 200 mg/cc). The 0 sample will be an apparent blank space. Then place an ROI in the TORSO vertebral sample. The ROIs should be as large as practical while remaining completely within the reference cylinder. (We recommend ROIs about 70% of the sample area.) Record the five mean CT numbers within these five ROIs using the Quality Assurance QCT Data Sheet provided (see Appendix E).

Send copies of the QA Data Sheets to the Reading Center by FAX at 310-533-1616 and to the DCC by FAX at 301-881-4471 or e-mail to the DCC. File the Quality Assurance Data Sheet for your records.

### **29.10.5 Instructions to the Reading Center**

Use the QCT software available to the Reading Center that runs on a standard personal computer (PC) using Windows 95. Click on the QXCT-3000 icon on your desktop. Click the enter QA button on the toolbar. A QA data entry screen pops up. Enter the data from the QA data sheets (see Appendix E) from the scanning centers. When all the data is entered, click OK. This will save the data to the QA database and open a window showing the QA report. To discard the entries you have made, click cancel.

The QCT 3000 software computes the calibrated calcium density for the TORSO phantom. The results are displayed in graphic and tabular format. The software also accesses the database and retrieves any previous data on the TORSO phantom. Previous data and calculated changes are displayed in tabular format.

The individual QA TORSO readings should be maintained at within  $\pm 3\%$  of the mean value of all the reading. If the values fall out of range, the scanning site must be notified in order to have the scanner checked by the site's engineers. The Reading Center should also inform the DCC about the issue.

The QA report has three major parts:

- a) Phantom and Scanner Information. This includes the phantom type, the exam number, details of the CT scanner and technique.

Click the image of the phantom which matches the one used at the scanning site and enter the serial number of the phantom.

- b) QA Readings, together with past readings, are plotted in graphical format. The graph is color coded and includes a band that covers the mean  $\pm 3\%$ .
- c) The QA readings are also printed in tabular format by date. The change in the reading is also tabulated. Also shown are the mean and standard deviation of all the readings.

Some common sources that cause poor results include, inappropriate table height (TORSO plug should be at isocenter when scanned), mispositioning of the phantom, old or improper CT calibrations, or use of improper scan parameters.

Given that there are multiple technicians at each scanning center, interscan percent variability will be calculated for each technician by the Reading Center on a quarterly basis. The Reading Center will determine the mean percent difference in scores between all duplicate scans performed by a given technician. Where unacceptable variability exists within a given technician (greater than two standard deviations beyond the mean variability for a given center), the Reading Center will notify the DCC, advise the scanning site, and investigate the reasons for the variability. If necessary, further training or recertification will be arranged.

## 29.11 Alerts

### 29.11.1 Communication of Alerts by the Reading Center

The Reading Center will review all scans within two weeks and will indicate any alerts, including suspected non-coronary pathology. A cardiologist or radiologist investigator will review all scans and will identify eventual alerts. The investigator will telephone both the principal investigator at the EDIC clinic and the Data Coordinating Center and will write a letter (see Appendix F) with copies to both. Pathological findings constituting alerts will include pulmonary infiltrates, pericardial or pleural effusions, tumors, dilatation of the aorta greater than 4 cm and pathological rib fractures.

### 29.11.2 Data Transmission of Studies

The technologist will transmit the studies to the local work stations if this has not been done during scanning. He/she will archive each study locally and leave a copy on the hard disk of the work station until it has been successfully transferred to the Reading Center. He/she will transmit the studies electronically using DICOM transfer on the local workstation to the Reading Center on a given afternoon of each week. The technologist will complete EDIC Form 117, the CT Study Transmission Sheet (see Appendix G), which indicates the patient studies that will be transmitted to the Reading Center. He/she will simultaneously FAX Form 117 to the Reading Center at 310-533-1616 and to the DCC at 301-881-4471.

The CT data manager will check each study to ascertain if it has been completely received. If it has been so received, the study will be put on the queue to be read by the reader. If it has not been received, the data manager will immediately communicate the identity of the study to the scanning site technologist and request that another attempt be made to send that study. The CT data manager will enter the identity, transfer date and time of transfer of each study into a running log (see Appendix H). A copy of the log will be sent weekly to the Data Coordinating Center.

The CT reader will backup studies onto recordable compact discs (CD-Rs) as they are read. The reader will label each disc with a volume name and the date the CD-R was created. The reader will print a directory to be stored with each CD-R. Each CD-R that is archived will thus have a printed list of its contents inserted into its sleeve. The data manager will back check the CD-Rs to be sure that they contain complete studies. After scoring of 20 studies or daily, the traced arteries and ROI files will be stored on the CD-R and on a labeled Zip disk.

### 29.11.3 Data Flow

A complex data flow diagram is contained in Appendix I. In brief, the following listing illustrates the principles of data flow:

1. The Data Coordinating Center (DCC) will keep a list of all ID numbers of subjects that are scanned. This list will be the master list.
2. The scanning tech will FAX to the Reading Center (310-533-1616) and to the DCC (301-881-4471) a separate list of all subjects for whom an INTERNET electronic transmission of images is being attempted (EDIC Form 117).
3. Simultaneous with the FAX in 2, the scanning tech will attempt transmission of images of those subjects.

4. The Reading Center data manager will check the work station for the arrival and completeness of the images corresponding to the ID numbers on the FAXed list.
5. The data manager will log in study ID numbers on an electronic spreadsheet in EXCEL for all studies completely received.
6. The data manager will print this spreadsheet as soon as it is complete and deliver it to the Reading Center director to begin the process of reading.
7. The Reading Center director, or his/her designee, will check all scan studies for non-coronary pathology.
8. The reader will then read the scan studies.
9. The data manager will e-mail the spreadsheet, labeled with the date sent, to the DCC as soon as it is complete.
10. The DCC will check the spreadsheet from the Reading Center against the master list. On a weekly basis, the coordinating center will inform the Reading Center data manager of missing studies.
11. The Reading Center data manager will track down the studies that have not been received by communicating with the scanning sites on a weekly basis.
12. The same procedure will be applied to studies that have not arrived.

#### **29.11.4 Reading Results.**

1. The readers will automatically accumulate results as they read in their results files to create a summary of scores.
2. The data manager will use FTP (File Transport Protocol) to electronically send these results to the Data Coordinating Center every Friday afternoon. The results file will be labeled with the readers' initials and the date and time that it was electronically sent to the DCC.
3. The DCC will alert the data manager whenever expected results are incomplete or not received.

# APPENDICES

## EDIC CT Certification / Site Visitor Checklist

<b>DATE:</b>	<input style="width: 40px; height: 25px;" type="text"/> mo	<input style="width: 40px; height: 25px;" type="text"/> day	<input style="width: 40px; height: 25px;" type="text"/> year	<b>Scanning Center:</b>	
				<b>Technician Name/Number:</b>	
				<b>Site Visitor:</b>	

Please check the appropriate box if technician performance is satisfactory for each line item. Please note any comments or remedial action taken in 'Comments' section if performance was not satisfactory.

### During examination:

1.  Greets participant professionally.
2.  Places calibration pad phantom correctly.
3.  Teaches participant breath-holding technique (at end-inspiration).
4.  Checks that participant is centered prior to the scan.
5.  Selects correct field of view (35 cm) including the phantom.
6.  Selects appropriate ECG triggering (80% for EBCT, 50% for SUBCT scanners per EDIC protocol).
7.  Scans entire heart (at least 35 slices per scan, preferably 40).
8.  Instructs participant to relax between scans.
9.  Assesses the adequacy of positioning, ECG gating, and lack of respiratory motion.
10.  If assessments made in #9 are adequate, immediately acquires another series of 35-40 slices (i.e. repeats entire heart scan a second time) insuring that participant remains immobile and in an identical position.

### Data transmission and quality control:

11.  Transmits images successfully via Internet.
12.  Uses proper EDIC ID labeling on study form.
13.  Demonstrates understanding of QA procedure and frequency of CT calibration using the Calibration and Torso phantoms.
14.  Documents any problems (if they occurred) in obtaining either scan.

Comments: \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_

Supervisor Signature \_\_\_\_\_

Format for EDIC Quality Control CT Site visit reports.  
Please return to the coordinating center with the completed check lists.

Name of Site \_\_\_\_\_

Report Date \_\_\_\_\_

Report Time \_\_\_\_\_

Number of participant studies (2 scans) observed \_\_\_\_\_

Number of Technologists at Visit \_\_\_\_\_

Name of Technologists	Tech Cert. Number	No. of scans observed
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____

Comments on observations regarding the items in the site visit check list.

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Comments on Quality Control Scans of Torso Phantom.

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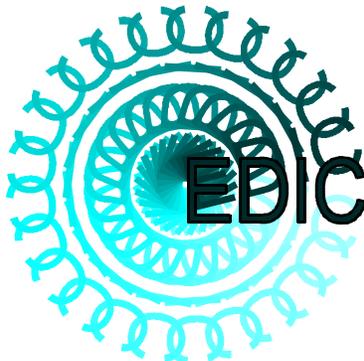


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## **EDIC Patient Brochure**

What You Should Know About the Coronary Calcium CT Scan

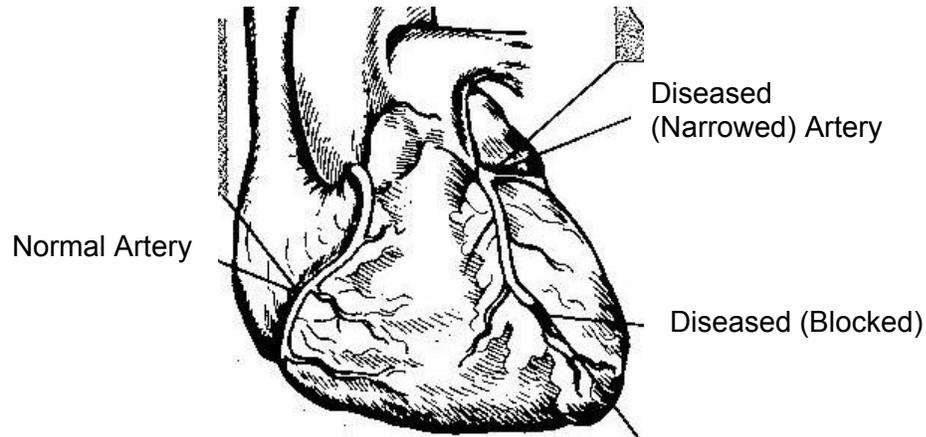
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*Please bring this pamphlet with you when you visit the scanning site.*

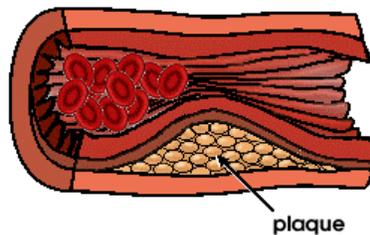
## What You Should Know About the Coronary Calcium CT Scan

### What's coronary artery calcification?

The blood vessels that surround and supply blood to the heart muscle are the coronary arteries.



Coronary artery disease (CAD) occurs when the coronary arteries become narrowed by plaque (a mix of cholesterol and other fats, calcium, and other products carried in the blood). Plaque builds up on the inside of the artery walls and may harden and narrow the arteries. Less blood, oxygen, and other nutrients reach the heart muscle when the arteries are hardened and narrowed. Blocked arteries can lead to chest pain (angina pectoris) or to a heart attack (myocardial infarction).



Plaque often contains calcification, the build-up and hardening of calcium deposits. This bone-like material can be seen by certain types of x-rays, such as computed tomography (CT) scans. Calcification is not normally seen in the artery wall, so when we see it we know that plaque must be present. A CT scanner is able to see very small amounts of calcification in the coronary arteries. CT scans can detect plaque build-up in the heart even in people who have no signs of heart disease.



CT Scan Image of Calcification of the Coronary Arteries



### **What is a CT scan?**

A computed tomography (CT) scan is a special type of x-ray that is used to take pictures from different views of the body, and then uses a computer to show a clear picture of the inside of the body. The type of scanner that will be used in the EDIC study is a very fast x-ray, which can take many pictures of a moving object, such as a beating heart, in a few seconds.

### **Why is the EDIC Study scanning the heart?**

The EDIC Study is interested in the coronary CT scan because there is almost no evidence concerning coronary calcium and coronary artery disease in type 1 diabetes. The CT scan is a tool for spotting narrowed and blocked arteries, the leading cause of heart attacks. It is a tool that may help doctors identify persons at risk for heart disease but may otherwise seem healthy. The scan may show plaque build-up in the arteries that may be missed with other types of tests for the heart. By spotting calcium build-up early, problems may be found when they are easiest to treat. However, calcium in the coronary artery does not mean that you will have a heart attack in the near future. Rather, knowing the amount of calcium in your arteries, along with the results of other tests, will help your doctor know if more tests or treatment are needed. However, there are no proven (by clinical trials) treatments to reduce the amount of calcium in your arteries.

### **What do we hope to learn?**

EDIC is studying risk factors and measures of cardiovascular disease in people with and without signs of heart disease. Calcium in the arteries will be measured to see if it is related to the risk of future heart disease. Repeated scans will let us measure the progress of coronary calcium build-up and the risk for future events. This information could allow us to identify which risk factors are the most important for cardiovascular disease in people with type 1 diabetes. The data could tell us when coronary atherosclerosis, or hardening of the arteries, begins and the best time for prevention. This exam will also help us learn if the CT scan is a good method for screening people who are at risk for heart disease but do not show signs.

Your EDIC clinic will receive all CT scores and will share suggestions for follow-up care with you.

### **What will the EDIC participant learn from the CT scan?**

The CT scan is a modern tool to find out about the risk of future heart disease. A feedback report will be sent to you that shows the coronary calcium scores that are based on the amount of plaque seen in the CT images. People without symptoms may benefit by learning of plaque build-up early enough to slow its development by changing their diet, exercising, or by treating their heart disease risk factors more carefully, such as smoking or blood pressure. Those who already have heart disease will benefit by learning more about the blockage in their arteries. They may stop their heart disease from becoming worse by making lifestyle changes, taking medications, and/or using other forms of medical treatment.

### **What risks are involved with the CT scan?**

CT does involve radiation in the form of x-rays. The effective dose for two CT scans of the heart is about 200 to 300 mrem, depending on the type of scanner used. For comparison, according to NIH, the average effective dose equivalent of background radiation to which a person in the United States is exposed annually is estimated to be about 350 mrem, depending on geographic location. Sources of background radiation include cosmic rays from the sun and stars, radon, and naturally occurring radioactive materials in rocks and soil.

If you have had radiation therapy or more than one CT scan in the past year, suffer from atrial fibrillation, or weigh more than 300 pounds, you will not be asked to participate in the CT Study. If you are pregnant, breastfeeding, or think that you could be pregnant, you should not receive this exam. Please tell your EDIC Study Coordinator if you are pregnant or think that you could be pregnant.



**How should I prepare for the CT exam?**

You should wear comfortable, loose-fitting clothing for your CT exam. Metal objects can affect the image, so do not wear clothing with zippers or snaps. It is suggested that women wear a jog bra, or other undergarment, that is free of metal clasps. You may also be asked to remove jewelry.

**What does the CT exam involve?**

CT scans are safe, painless, and non-invasive, meaning that no needles are used. The exam consists of two scans done one after the other and takes about 20 minutes. You may remain fully clothed, unless there are metal objects in your clothing. The technologist will attach three electrodes to you, one under your left collarbone and one on each side of your chest. You will be taught the importance of holding your breath and staying absolutely still during the scan. You will be asked to take three deep breaths, and then to hold your breath for 15-40 seconds. After the first scan is finished, you will be asked to relax on the table while the technologist reviews the scan. The technologist will then do one more scan while you remain in the same position.

**How were scanning sites chosen for the EDIC CT Study?**

CT scan sites that had the right equipment, were closest to the EDIC clinics, and who agreed to follow EDIC rules were chosen to be involved in the EDIC Study. The type of CT scan that EDIC will be using is relatively new and not all of the EDIC clinics have the equipment needed to do the coronary calcium CT scans. CT scan sites were chosen from both academic and commercial centers across the United States. All of the CT technicians who will be performing the scans have gone to a special training course to learn the EDIC guidelines and to receive EDIC certification.

**If travel to a scanning site is needed, how will it be handled?**

Some travel-related expenses may be paid by EDIC. Your clinic study coordinator will tell you about the EDIC travel policy.

**Sources**

Colorado Heart Imaging  
Radiological Society of North America (RSNA)  
Heart Information Network  
Mayo Clinic  
Harbor-UCLA Research and Education Institute  
National Heart, Blood, and Lung Institute



**Participant Information:**

Name: \_\_\_\_\_

EDIC Patient ID: \_\_\_\_\_ Patient Initials: \_\_\_\_\_

EDIC Clinic: \_\_\_\_\_ Clinic #: \_\_\_\_\_

EDIC Visit (EDIC Year): \_\_\_\_\_

EDIC Study Coordinator: \_\_\_\_\_

EDIC Clinic Phone Number: \_\_\_\_\_

Scanning Site: \_\_\_\_\_ Site #: \_\_\_\_\_

Scanning Site Address: \_\_\_\_\_

\_\_\_\_\_

Scanning Site Phone Number: \_\_\_\_\_

Date of CT Scan: \_\_\_\_\_

Time of CT Scan: \_\_\_\_\_

EDIC CT Technologist Certification #: \_\_\_\_\_

EPIDEMIOLOGY OF DIABETES INTERVENTIONS AND COMPLICATIONS

CT Scheduling List

This mailing list is used whenever the EDIC clinic schedules patients for the CT scan. Please only add newly scheduled patients. Make two copies of this form and distribute as follows:

- (1) Complete and send to the Data Coordinating Center on a weekly basis.  
(FAX: 301-881-4471)
- (2) Send to the Reading Center at Harbor-UCLA. (FAX: 310-533-1616)

Retain the original in clinic files.

Clinic Number:            — —

Date:                    — — | — — | — —  
                              Month    Day    Year

Newly Scheduled Patients

PATIENT ID NUMBER	PATIENT'S INITIALS			PATIENT* WEIGHT (lbs.)	DATE OF SCAN			TIME	EDIC YEAR	SCAN SITE ID #		
	F	M	L		Month	Day	Year					
— — — — —	—	—	—	— — —	— —		— —		— —	_____am/pm	— —	— —
— — — — —	—	—	—	— — —	— —		— —		— —	_____am/pm	— —	— —
— — — — —	—	—	—	— — —	— —		— —		— —	_____am/pm	— —	— —
— — — — —	—	—	—	— — —	— —		— —		— —	_____am/pm	— —	— —
— — — — —	—	—	—	— — —	— —		— —		— —	_____am/pm	— —	— —
— — — — —	—	—	—	— — —	— —		— —		— —	_____am/pm	— —	— —
— — — — —	—	—	—	— — —	— —		— —		— —	_____am/pm	— —	— —
— — — — —	—	—	—	— — —	— —		— —		— —	_____am/pm	— —	— —
— — — — —	—	—	—	— — —	— —		— —		— —	_____am/pm	— —	— —
— — — — —	—	—	—	— — —	— —		— —		— —	_____am/pm	— —	— —

- \* Please note:**
1. Please refer to the Manual of Operations for instructions regarding the scanner settings used with patients who weigh **more than 220 lbs.**
  2. Patients weighing **more than 300 lbs.** are excluded from scans on EBCT machines, but may be scanned on SUBCT machines.
  3. Patients weighing **more than 400 lbs.** are excluded from all scan procedures.



Appendix F

Sample Alert Letter

[Date]

CT Investigator Name  
Address

Dear Dr. [Name]:

I have evaluated the CT scan of the EDIC participant [participant ID number and acronym]. The following finding which constitutes pathology suggesting an urgent referral alert was noted:

Pericardial Effusion	_____	Size	_____	
Pleural Effusion	_____	Location	_____	
Tumor	_____	Location	_____	
Infiltrate	_____	Location	_____	
Fracture	_____	Location	_____	
Aortic Dilation	_____	Location	_____	Diameter _____

If you have any questions, please call me at [phone number].

Sincerely,

[Name of M.D.]

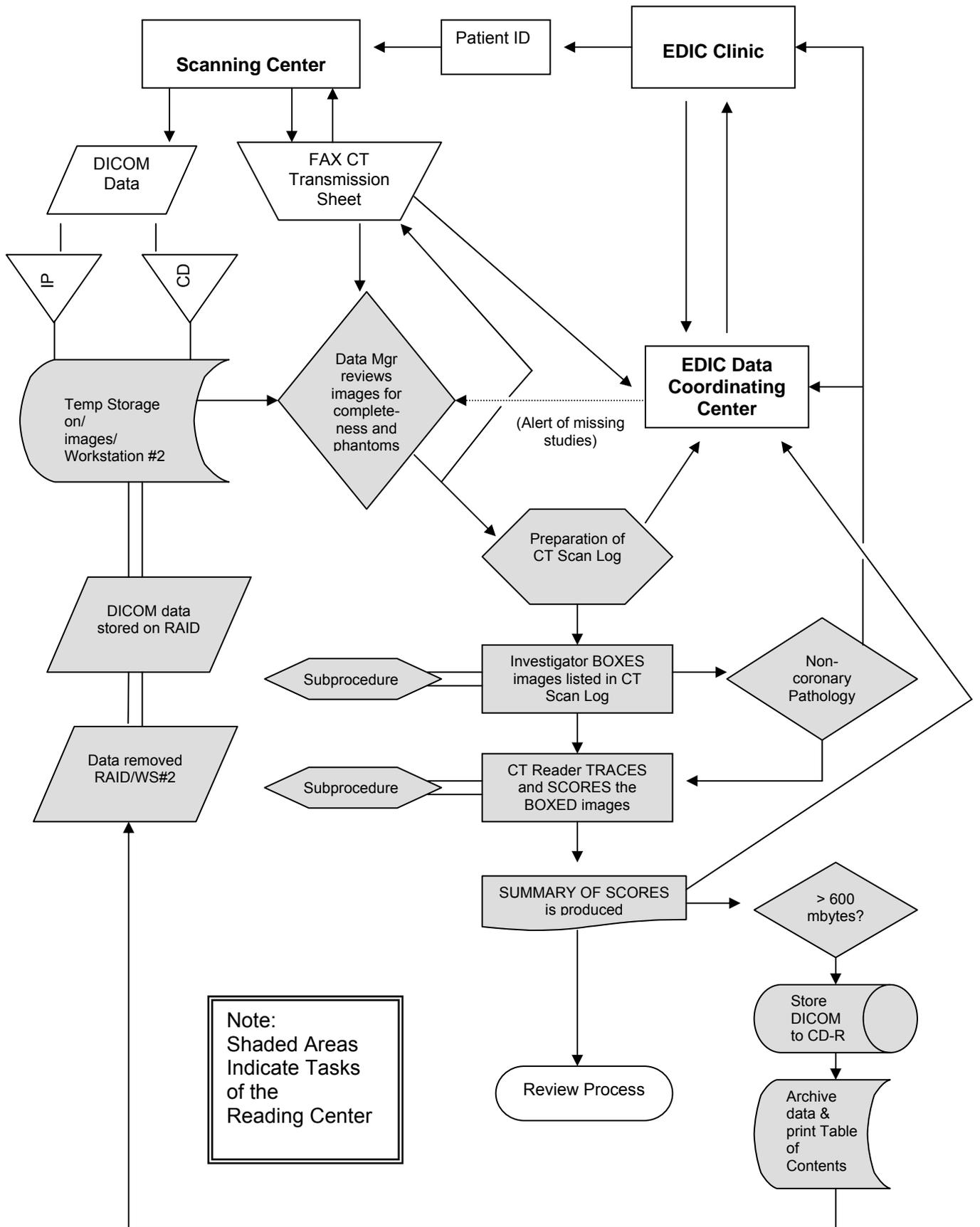
cc: EDIC Coordinating Center





Appendix I

EDIC CT DATA FLOW SHEET



## 30. THE STUDY WEBSITES

### 30.1 Introduction

The DCC maintains three websites for EDIC:

- 1) a secure website: for EDIC personnel: <https://www.dcct-edic.org> or <https://www.bsc.gwu.edu/edic>
- 2) a public website <http://www.dcct-edic.org>
- 3) a password protected website used by EDIC clinical sites to relate information to the DCC. Training for this site provided by the DCC: <https://www2.bsc.gwu.edu/edic>

The only difference in the web addresses is the “s” for secure after the “http”

### 30.2 The Secure Website(s)

The secure EDIC Study website contains six main web pages: Home, Directory, Projects, Schedule of Events, Administrative, and Resources. Navigating through the EDIC web can be achieved by clicking on the menu bar going across the Home page for the six different pages, or by clicking on the identified items within a page. Documents and lists are periodically updated by the DCC. Note the date in grey after the title of the document or list to insure you have the most recent document. See Appendix # for views of the six main web pages.

Those wishing to obtain a User ID and password for the secure websites should send a request to Paddy Cleary. If you forget your password, please call Loretta Dews at the DCC (301-881-9260).

It is the responsibility of the EDIC clinic sites and central units to notify the DCC of changes at the site levels of: investigators, coordinators, certified staff, email changes in address, shipping addresses or other information that impacts the operations and contacts to the clinics or central units.

#### 30.2.1 The Home Page

The home webpage provides links to documents, information, and the other webpages within the study website. It also provides a quick-search method for looking up a single EDIC staff member.

The left sidebar contains links to information such as:

- Study Photos
- DCCT Study
- DCCT/EDIC Précis
- News Bulletins
- EDIC/GoKinD WGA
- UT Tracking
- Ineligible DNA
- Site Location Map (a map of EDIC centers)

The body of the home webpage contains links to the following webpages and information:

- Groups :
  - Study Coordinators
  - Individual Clinic Sites
  - Study Group
- Committees: Containing agendas, minutes, and miscellaneous documents
- **Private Clinic Page that includes clinic specific reports (BMI, Waist Hip, Blood Pressure Sitting, Doppler, ANS and Histogram completion information.)**
- Quick Links
  - EEC Letters
  - Ethnic & Gender Characteristics
  - Publications 1980's
  - Publications 1990's
  - Publications 2000's
  - Staff Desks
  - SI Units for Selected Clinical Data
  - SI Units Conversion Calculator
  - Clinical Trials Registrations
  - Unpublished Manuscripts
  - Important Dates: Meeting Updates
  - Important Dates: Abstracts

Clicking on any of the groups, committees or quick links will allow you to navigate to those requested sites.

The Study Coordinators webpage contains links to the following information and documents:

- End of Year Activities
- Meeting Minutes
- Meeting Agendas
- Miscellaneous Documents
  - Study Coordinators Supply Page
- Travel Documents
- CBL-Poor Venous Access Documents
- Memos

The Study Group webpage contains links to the following information and documents:

- Annual Meeting Agendas
- Annual Meeting Minutes
- Annual EEC Progress Letter
- Correspondence
- DQA Slides
- Miscellaneous Slides
- American Diabetes 68
  - Abstract Letters of Acceptance

- End of Year Activities
- Memos

### **30.2.2 The Directory Page**

This webpage provides multiple methods for searching for EDIC personnel, from the top of the home page, just by clicking on to the Directory.

### **30.2.3 The Projects Page**

This webpage provides a list of all EDIC projects. By selecting a specific project you have links to documents that are project specific to EDIC. Most of the projects include a “Frequently Asked Question” resource for a given project.

- Carotid Ultrasound Study
- Camera – Digital vs Film Study
- Epigenetics Study
- Genetics Study
- CMRI Study
- MUSC – Markers & Mechanisms
- Neurobehavioral Study
- Neurology ANS Study
- Retention Survey Study
- SCOUT Study
- URO-EDIC Study
- URO-EDIC II Study
- UWA/Brunzell

### **30.2.4 The Schedule of Events Page**

This webpage is currently not in use.

### **30.2.5 The Administrative Page**

This webpage contains links to staff lists for displaying or printing (an alternative to the Directory webpage), a link for changing your password, and a document that lists the EDIC study week numbers. The following is an outline of these links and documents:

- Staff
  - Lists for Display
    - All Staff by Last Name
    - All Staff by Location
    - List all Members
  - Printable Lists
    - Staff Email Addresses
    - Staff Phone & Fax Numbers
    - Staff Addresses by Location
    - Staff Addresses by Name

- Find Staff
  - Search for Staff Members
  - Condensed Staff List
- Miscellaneous
  - Change My Password
  - EDIC Week Numbers List

### **30.2.6 The Resources Page**

This webpage contains links to a multitude of study documents, such as protocols, forms, publications, etc. The following is an outline of these documents:

- OHRP Guidelines
  - Institutional Review Board Guidebook – Chapter 6 (02/05/09)
- EDIC Organizational Chart
  - EDIC/DCC Organization
  - EDIC Organizational Chart by Projects
- EDIC and GoKinD WGA
  - Investigator Meeting
- Clinical Trials Registrations
- Quick Staff Directory
- Staff Desks
- Important Dates
  - Meeting Updates
  - Abstract Deadlines
- Certifications
- Ethnic & Gender Characteristics
- General Documents
  - EDIC Protocol
  - Original Study Protocol
  - Manual of Operations
  - SCs Orientation Manual
  - EDIC Forms
  - EDIC Correspondence
  - EDIC Policy of Collaborations
  - Policy Statement on EDIC Volunteers
  - Publication Policy Statement for Studies using PPG & DCCT/EDIC data
  - Policy for EDIC Slides
  - EDIC Publication Policy
  - EDIC CT Close-Out Document
  - EDIC EEC Guidelines for DSMC
  - EDIC Core FAQs
- Publications/Presentations
- Newsletter
  - EDIC Gazette
  - Charleston Chronicle
  - China California Newsletter

### **30.3 The Public Website**

The public website contains five main web pages from the home page: Participating Clinics, Executive Committee, Study Protocol, Published Reprints and Publications/Presentations (<http://www.bsc.gwu.edu/Edic>)

#### **30.3.1 The Home Page**

The Home webpage provides a summary of the study, links to the other webpages, a link—Contact Us—for sending an email to the webmaster, and link—Study Protocol—that brings up a PDF of the most current Study Protocol.

#### **30.3.2 The Study Protocol**

The Study Protocol is the Continuing Follow-Up.

#### **30.3.3 The Participating Clinics Page**

The Participating Clinics webpage lists the EDIC Study Participating Clinics with their Principal Investigators and Study Coordinators.

#### **30.3.4 The Executive Committee Page**

The Executive Committee webpage lists the members of the Executive Committee.

#### **30.3.5 The Published Reprints Page**

The Published Reprints webpage provides links to various reprints of articles published about the DCCT/EDIC study and its findings.

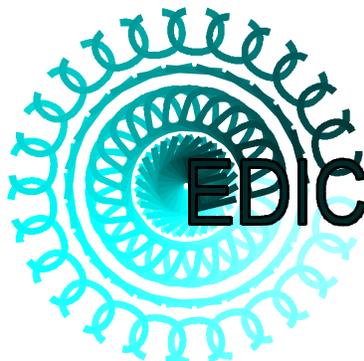
#### **30.3.6 The Publications/ Presentations Page**

The Published Reprints webpage provides links to various reprints of published articles and authors about Diabetes and its findings.

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**Epidemiology of  
Diabetes Interventions  
and Complications**

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CLINICAL CENTER  
CARDIAC MAGNETIC RESONANCE IMAGING  
MANUAL OF OPERATIONS

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**1st Edition July 18, 2007**

Amended 09/10/2007

Amended 01/14/2008

EDIC Data Coordinating Center  
**Biostatistics Center**  
George Washington University  
6110 Executive Boulevard  
Suite 605  
Rockville, Maryland 20852

Summary of Changes September 10, 2007

Revised 1/15/2008

Pages 9&10 **Options for Submitting Training Cases**

1 – Submit volunteer CMRI exams using the EDIC protocol, including the gadolinium portion of the examination.

- Perform 1 exam per technologist to certify that technologist
- Perform a minimum of 2 exams at each site, to certify that site
- *Please do one exam at a time*; we will check it within a day to insure the parameters are correct.

Page 11 **Changes in Entering MRI Scan Header Information**

**Name and ID Field:** EDIC ID # and EDIC Initials Example, if the EDIC ID # is 12345 and the EDIC initials are ABC, followed by the date of the MRI scan. Please enter as follows:

**Example:** EDIC12345ABC(Current Date) where there is NO space between the EDIC

Page 12 **CMRI Scanning Protocol**

1. Starting Blood Pressure
2. Scout views (e.g., 3 plane localizer). One of these views should be an axial view through the middle of the left ventricle.
3. Pseudo 2 chamber localizer. This view is prescribed on a line from the apex of the left ventricle to the mitral valve plane.
4. 4 Chamber (horizontal long axis) Cine (1 slice)
5. Horizontal Tag Cine (3 slices: base, mid, apex)
6. Vertical Tag Cine (3 slices: base, mid, apex. Exact same # of phases and locations as #4)
7. GADOLINIUM IS ADMINISTERED AT THIS POINT (0.2 MMOL/KG) except for Iowa which is 0.15
8. Short Axis Cine (minimum of 12 slices, prescribed base to apex)
9. 2 Chamber (vertical long axis Cine) (1 slice)
10. Short Axis Delay (minimum of 12 slices. Same slice locations as #7)
11. 4 Chamber Delay (1 slice)
12. 2 Chamber Delay (1 slice)
13. Axial Phase Contrast (1 slice, prescribed from at the level of the pulmonary artery)
14. Ending Blood Pressure
15. Ending Heart Rate

Page 15 Data Transmission from the local EDIC CMRI CC by the EDIC CMRI Reading Center (RC)

**Changes for naming the zip folders**

g. Name the zip folder the same as the study ID number. If the study ID number is EDIC12345ABC\_082807, name the zip folder EDIC12345ABC\_082807.

Page 16 **Additional Instructions**

- i. "Yousendit" generates an e-mail message that data has been electronically sent to the RC.
- j. If your center has scanning capabilities, scan the completion and transmittal form (223.1) and attach it to the notification e-mail or fax the completion and transmittal form (223.1) to:

RC Fax #: 410-955-9799

**The information on the MRI completion form will be entered in the EDIC web database by the CMRI staff.**

6.5.2 Alternatively, a CD from the CMRI and the completion and transmittal form (223.1) center can be FedEx'ed to Linda Wilkins at the address below:

## Table of Contents

1. General Principles
2. Guidelines for EDIC Staff and Patient Interactions in the Course of Outcome determinations
3. Eligibility Criteria for CMRI test (with and without Gadolinium injection)
4. Evaluation of serum creatinine prior to CMRI test
  - 1) EDIC Center used on site GCRC or hospital lab
  - 2) EDIC Center suggests that the patient have a serum creatinine drawn-lab agree to pay bill
  - 3) EDIC Center suggests that the patient have a serum creatinine drawn-patient pay bill and get reimbursed
5. Preparation for CMRI Test
  - Qualification for CMRI Technologists
  - CMRI Technologist Training
    - Option for Submitting Training Cases
  - Day of CMRI Appointment
  - Participant Preparation and Instructions
  - Header Information
  - CMRI Scanning Protocol
  - Gadolinium Administered at this point
  - CMRI Technologist, CMRI Exam Quality Control
6. Alerts
  - 6.1 Background and Rationale
  - 6.2 Alerts Triggered at the local EDIC CMRI Clinical Center (cc)
    - 6.2.1 Technologist
    - 6.2.2 CMRI Center Physician
  - 6.3 Alert Status Categories
    - 6.3.1 No alert
    - 6.3.2 Abnormal
    - 6.3.3 Urgent Referral
  - 6.4 Reading Center (RC) Results categories
    - 6.4.1 Normal
    - 6.4.2 Abnormal
    - 6.4.3 Abnormal-Urgent
  - 6.5 Data Transmission fm the Local EDIC CMRI (CC) by the EDIC CMRI Reading Center (RC)
    - 6.5.1 The preferred data transmission method
    - 6.5.2 Alternatively, A CD from the CMRI

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## 6.6 Reading Center (RC) Results Protocol

- 6.6.1 Communication with the local EDIC CMRI (CC) by the EDIC CMRI Reading Center
- 6.6.2 Communication with Data Coordinating Center (DCC)
- 6.6.3 Local EDIC CMRI Reporting of results

## 7. Test Results

## 8. Missed and Make-Up Visits

Appendix A: List of Quest Diagnostic Laboratories near EDIC Clinics

Appendix B: Informed Consent for Participation in the Cardiac MRI in EDIC  
Continuing Follow-Up

- A. Purpose and Background
- B. Voluntary
- C. Study Procedures
- D. Risks and/or Discomfort
- E. Benefits
- F. Cost/Payment
- G. Confidentiality
- H. Contact Information
- I. Record of Information provided

Appendix C: CMRI Forms

- 1. 007.1 CMRI Eligibility & Exclusion
- 2. 220.1 Request for Certification of Cardiac MRI Technologist
- 3. 221.1 CMRI Scheduling List
- 4. 222.1 EDIC MRI Exam QC Evaluation Form
- 5. 223.1 EDIC Cardiac MRI Completion and Transmittal Form

## 1. General Principles

In EDIC year 14 and 15 Cardiac MRI (CMRI test) will be performed and read at the Central CMRI Reading Unit. A standard intravenous CMRI contrast agent that contains gadolinium will be used to identify the presence of myocardial scar (due to prior myocardial infarction). These tests will follow standardized procedures. All visits will be scheduled to coordinate these procedures and examinations with other requirements in order to optimize convenience for the study participants and to minimize costs.

CMRI tests will be scheduled after a recent GFR estimate has been made for the patient. This estimate will come from a recent serum creatinine measurement, which will be obtained through a local laboratory.

If a patient is excluded from the gadolinium portion of the CMRI test (because of low GFR) the majority of the CMRI test will be performed, except for the portion requiring gadolinium injection.

## **2. Guidelines for EDIC Staff and Patient Interactions in the Course of Outcome Determinations**

Although official recording and interpretation of outcome measurements are carried out in the central units, in some instances the process of data collection makes it unavoidable that certain EDIC staff will see or scan results or outcome data before it is transmitted centrally. In these circumstances, patients (and possibly other EDIC staff members or technicians) will naturally be curious as to the results. It is therefore important that by neither manner nor speech, information should not be provided unnecessarily or inappropriately. If in the process of scanning or sample or data collection a staff member or technician is asked for information by a patient, he/she should respond by reminding the patient that all data collected is sent to a central source for analysis and interpretation and that no information is available locally. The patient should be reassured that CMRI radiographs will be examined promptly at central units and that all results will be immediately transmitted to the EDIC center.

It is equally important that other EDIC staff members, including the Principal Investigator, should not be informed spontaneously of any perceived change in results from inspection of radiographs by a technician or by the M.D./Ph.D. in charge. For example, EDIC staff members and technicians must NOT give any indication of alarm after having viewed the CMRI radiographs. Incomplete assessments transmitted casually to some or all other staff members can only generate rumors and speculation that may impact adversely on carrying out the EDIC protocol.

## **3. Eligibility Criteria for CMRI test (with and without Gadolinium injection)**

[amend according to local CMRI inclusion/exclusion criteria].

Inclusion Criteria: Anyone who is a participant in the EDIC study may take part in the EDIC CMRI study UNLESS any of the CMRI exclusion criteria listed below are present.

Exclusion Criteria: [amend to include any local exclusion criteria not listed]

- The patient cannot take part in the EDIC CMRI study if they:
- patient is pregnant.

- patient has a history of any metal in head or eyes.
- patient has a pacemaker, an implanted defibrillator or certain other implanted electronic or metallic devices (such as MRI incompatible aneurysm clip).

The patient cannot take part in the Gadolinium test if the:

- patient is on dialysis, had a kidney transplant, or ever had a GFR < 60.
- patient had an allergic reaction to Gadolinium in the past.

To determine eligibility for the MRI Test with Gadolinium, serum creatinine will be evaluated 1-2 months prior to the CMRI test.

#### **4. Evaluation of serum creatinine prior to CMRI test**

Before participating in the CMRI test, EDIC patients must first have their serum creatinine evaluated. Serum Creatinine evaluation will be done at a local laboratory. A contract has been set up between Quest Diagnostics Laboratory and The George Washington University Biostatistics Center, Biostatistics Center (institution of the EDIC DCC). Quest Diagnostics will provide local laboratories where all EDIC patients can visit for their serum creatinine draw. All invoicing will be done in a manner specified by the contract. All invoices will be sent to the EDIC DCC. For a list of Quest Laboratories near EDIC Clinics, see Appendix A. However, if it is not possible for the patient to get to a Quest Laboratory, then alternative arrangements will be made with another laboratory.

The study coordinator will assist the EDIC patient in making an appointment for their serum creatinine draw. The study coordinator must obtain a “doctor’s order” for the serum creatinine test on the patient’s behalf. The “doctor’s order” should be prescribed by the EDIC Clinic Principal Investigator (PI). The study coordinator will then give the “doctor’s order” to the patient.

While the “doctor’s order” is being requested, the study coordinator will ask the patient for times he/she will be available for a serum creatinine draw. The study coordinator will call the local Quest Laboratory (or another laboratory) to schedule an appointment for the patient to have a serum creatinine draw for a time that the patient states is convenient. For a list of the equipment and supplies needed to carry out the serum creatinine measurement, see Table 1.

The study coordinator will notify the patient of the date and time of the appointment and will give the “doctor’s order” to the patient. This written confirmation should be sent to the patient two weeks before their appointment. The written confirmation should include the date and time, and the estimated time needed to complete the appointment. The written confirmation should be followed by phone contact with the patient two to three days prior to the scheduled appointment.

The patient will then take the “doctor’s order” to their scheduled appointment. The serum creatinine specimen will be sent to Quest’s Central Laboratory to be assayed. The serum creatinine value will faxed to the clinic coordinator.

Alternatively, other laboratories can be used for those clinics that do not have a local Quest laboratory or one located near by. The study can identify a local laboratory not associated with Quest Diagnostics for their patient to have a serum creatinine draw. The

patient will take the “doctor’s orders” to the identified local laboratory for their schedule appointment. The study coordinator will obtain the patient’s serum creatinine value from the local laboratory where the patient’s appointment was scheduled. The study coordinator will then enter the serum creatinine value on the secured EDIC data entry website system using his/her personal computer. The GFR value will be made available on the EDIC website for the study coordinators, so that the patient’s eligibility can be determined for the CMRI test that requires the gadolinium agent. If the patient’s GFR > 60 the study coordinator will complete the screening process with the patient. Note that the alternative laboratories are not covered by the contract and below are the three possible billing scenarios for CMRI requiring serum creatinine draw.

1) EDIC Center used on site GCRC or hospital lab:

If the EDIC patient is having the stat serum creatinine drawn the AM of the CMRI visit (allowing enough time for the results and calculated GFR), then the charges will be channeled institutionally through the GCRC or the EDIC office. (For instance, if a center petitions their CGEC to cover the cost of the serum creatinine as part of a modification of the EDIC Core-Follow-up protocol, the charge would be absorbed and paid by the GCRC. If the GCRC is not paying for the charge, then charges would be channeled to the EDIC account for reimbursement.) In this case, the EDIC PI will write the “doctor’s orders” for obtaining the lab at the beginning of the EDIC visit.

2) EDIC Center suggests that the patient have a serum creatinine drawn locally at a non-Quest laboratory (if, their MD office laboratory or local hospital laboratory) and the laboratory agrees to bill the EDIC center.

(This model was used in GOKIND, and was efficient, keeping the cost out of the participants’ responsibility). It worked best when the study coordinator calls the laboratory after the patient identified the lab to be used, and billing charges and method were discussed between the study coordinator and laboratory personnel. The EDIC PI would write a “doctor’s order” that the patient would be mailed, with instructions developed locally for how to bill the EDIC center.

3) EDIC center suggests that the patient have a serum creatinine drawn locally at a non-Quest laboratory (ie, their MD office laboratory or local hospital laboratory) and the patient pays and gets reimbursed from the center. (This is not ideal).

## 5. Preparation for CMRI Test

Once an EDIC patient is declared eligible for the CMRI test (with or without Gadolinium contrast agent), the study coordinator will schedule a visit to a local radiology center, contracted by EDIC. One visit for a CMRI test will be scheduled for each subject. Table 5.1 is a list of the equipment and supplies needed to carry out the EDIC CMRI test.

In preparation for the CMRI test, the clinic staff will arrange a date and time appropriate for the patient and assure the availability of any staff or laboratory personnel (CMRI technologist) required for that visit. Any necessary appointments will be arranged with the radiology staff at least two weeks in advance. After the necessary arrangements have been made, the visit will be confirmed by mail with the patient. This written confirmation should be sent two weeks before the visit, and should include the date and time of the visit, the estimated time needed to complete the visit, and a specific schedule for the visit including times and locations for seeing various study team members. This written confirmation should be followed by phone contact with the patient two to three days prior to the scheduled visit.

At the same time, the staff person responsible for visit scheduling should make certain that the various clinic team members are aware of the date and time of the visit, and have the necessary forms to complete during that visit.

### **Qualifications for CMRI Technologists**

CMRI technologists should have appropriate knowledge of cross-sectional anatomy, physiology, and pathologic processes with emphasis on cardiac imaging. The preferred level of education is completion of a two-year AMA approved program for diagnostic imaging and a minimum of 2 to 3 years MRI experience. The technologist should have advanced knowledge of CMRI and/or knowledge of computer software applications necessary for performing CMRI.

In addition to the above education and CMRI experience, the EDIC CMRI technologist must have a complete understanding of the EDIC CMRI Imaging Protocol. The CMRI Reading Center (RC) at Johns Hopkins University requires that each Clinical Center (CC) have at least two designated EDIC CMRI technologists. The CMRI technologist must be supervised by a local imaging physician specialist, so that if the technologist is aware of severe pathologic conditions, a local physician can be alerted to provide an immediate medical diagnosis (see Section 6, Alerts).

### **CMRI Technologist Training**

**Experienced** CMRI centers can be qualified for the EDIC protocol by submitting example CMRI examinations, performed in accordance with the EDIC protocol:

#### Options for Submitting Training Cases

1 – Submit two volunteer CMRI exams using the EDIC protocol, including the gadolinium portion of the examination.

- Perform 1 exam per technologist to certify that technologist
- Perform a minimum of two exams at each site, to certify that site
- *Please do one exam at a time; we will check within a day to insure the parameters are correct*

In many centers, volunteers cannot receive gadolinium injection. If this is the case:

2 – a. Submit two volunteer CMRI exams using the EDIC protocol EXCEPT for the portions that require gadolinium injection.

AND b. Submit two anonymized patient CMRI examples of delayed gadolinium imaging for myocardial viability. The delayed gadolinium images must at a minimum contain a stack of short axis slices covering the left ventricle and demonstrating myocardial infarction/scar.

The purposes of these studies is a) to demonstrate CMRI competence and b) to insure that the CMRI RC at John Hopkins can read/import the DICOM images from each center.

***Inexperienced*** CMRI center ***or those that have not performed MRI tagging*** will undergo protocol training sessions. Training will be available for at least 2 technologists from each center. Training will be done over the internet using internet video conferencing (WebEx). These training sessions will last 45-60 minutes. WebEx training will be conducted approximately 3 weeks before EDIC patient CMRI scanning begins.

Upon receipt of the qualifying CMRI exams, the CMRI RC will review the examination for technical adequacy and will complete EDIC Form 222.1 “EDIC CMRI Exam QC Evaluation Form” (See Attachment #2, Form 222.1) for each exam received. Examinations any major protocol deviations or un-evaluable images will be deemed unacceptable and additional training and examinations will need to be submitted for evaluation.

The training sessions will be scheduled in advance and will include members of the EDIC CMRI RC, CMRI radiologist and designated EDIC CMRI technologists.

To access WebEx, a PC with internet connection is required. The EDIC coordinating center will facilitate access to these internet training sessions.

### **Day of CMRI Appointment**

EDIC Form 223.1 “EDIC Cardiac CMRI Completion and Transmittal Form (See Attachment #1, Form 223.1) will be made available to the MRI technologist before the participant arrives for the examination.

During this time, the CMRI technologist will interview the patient and document screening information on EDIC Form 007.1 “CMRI Eligibility & Exclusion” form **used at all EDIC clinical centers** (site dependent). EDIC Form 007.1 can be found on the EDIC website. The participant should be instructed to remove any metallic objects, including jewelry, dentures, hearing aids, hairpins, etc., and secure all items in the participant’s locker. While escorting the participant to the changing area, the CMRI technologist should explain that the procedure will take approximately 60 minutes and should answer any questions that the participant may have.

### **Participant Preparation and Instructions**

Please follow the outline below to expedite participant preparation for the procedure:

1. It is critical to determine if a patient is to receive gadolinium or not. If the patient is to receive gadolinium, then an intravenous angiocath should be started according to local policies. Typically this is a 20-22 gauge angiocath positioned

in the right antecubital vein. This should be done before the patient enters the CMRI suite.

2. All series are performed at resting lung volume (end expiration). Please practice 1-2 breath-holds prior to positioning the patient in the bore of the CMRI scanner. Only after the technologist is satisfied that the participant understands the importance of breath holding for the exam should he/she proceed.
3. ECG leads will be placed on the chest per the CMRI scanner manufacturer recommendations.
4. Place blood pressure cuff on participant's left arm
5. Use a surface coil (cardiac coil, body array coil etc) for all cardiac imaging.
6. The participant should be told that movement, and/or speaking during the exam will cause the images to be less than optimal, and if at all possible to refrain from such activity during the scan. Please provide hearing protection for the participant or headphones with music as available.

For accurate and reproducible MR studies, there is a strong interdependence between cardiac analysis methods and the method of MR image acquisition. The CMRI RC will therefore require CC personnel to strictly adhere to all facets of a standardized MR image acquisition protocol.

### Header Information

Enter the following information into the system. For purposes of archiving and retrieval, it is **imperative** that the EDIC identification number be placed in the **Name Field** and in the **ID Field**. Please follow the example below:

**Name and ID Field:** EDIC ID # and EDIC Initials Example, if the EDIC ID # is 12345 and the EDIC initials are ABC, followed by the date of the CMRI scan. Please enter as follows:

**Example:** EDIC12345ABC (current date) where there is NO space between the EDIC ID and the initials and the initials should be in capital letters.

All other MR fields may be entered according to local CC conventions/ policies. *Enter the correct age, gender, height and patient weight onto the appropriate CMRI scanner fields.*

**ERRORS IN THIS STEP MAY RESULT IN IRRETRIEVABLE LOSS OF CMRI DATA FROM THE STUDY AND  
WOULD REQUIRE THE EXAMINATION TO BE REPEATED**

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### CMRI Scanning Protocol

## Performing the CMRI Scanning Protocol

The CMRI scanning protocol should be followed exactly, and series performed in the order listed below, as well as on the EDIC Form 223.1 "EDIC Cardiac MRI Completion and Transmittal Form":

1. Starting Blood Pressure
2. Scout views (e.g., 3 plane localizer). One of these views should be an axial view through the middle of the left ventricle.
3. Pseudo 2 chamber localizer. This view is prescribed on a line from the apex of the left ventricle to the mitral valve plane.
4. 4 Chamber (horizontal long axis) Cine (1 slice)
5. Horizontal Tag Cine (3 slices: base, mid, apex)
6. Vertical Tag Cine (3 slices: base, mid, apex. Exact same # of phases and locations as #4)  
→ GADOLINIUM IS ADMINISTERED AT THIS POINT (0.2 MMOL/KG) except for Iowa which is 0.15
7. Short Axis Cine (minimum of 12 slices, prescribed base to apex)
8. 2 Chamber (vertical long axis Cine) (1 slice)
9. Short Axis Delay (minimum of 12 slices. Same slice locations as #7)
10. 4 Chamber Delay (1 slice)
11. 2 Chamber Delay (1 slice)
12. Axial Phase Contrast (1 slice, prescribed from at the level of the pulmonary artery)
13. Ending Blood Pressure
14. Ending Heart Rate

If the EDIC Center needs to revise the protocol due to modifications in equipment or software, the revised protocol **MUST BE APPROVED BY THE CMRI RC PI BEFORE SCANNING A EDIC PARTICIPANT.**

CMRI Technologist CMRI Exam Quality Control

Data integrity and quality are of primary importance to the CMRI RC. Each examination received at the CMRI RC will be evaluated for data quality by the CMRI RC PI. Examinations that are classified as non-diagnostic will not be reimbursed to the CMRI CC unless repeated. Monthly reports on data integrity will be distributed to the EDIC data center for compilation and distribution to the CCs. (See Attachment #2, for the “EDIC CMRI Exam QC Evaluation Form,” Form 222.1.)

## 6. Alerts

### 6.1. Background and Rationale

The EDIC CMRI examination is similar to a clinical MRI examination of the heart. The purpose for doing this examination is to identify life-threatening abnormalities may be recognized on the MRI scan. Therefore, initial interpretation of the CMRI needs to be performed at the local CC since the CMRI reading center (RC) may only receive and review images within a 30 day period of the performance of the CMRI. Any abnormalities identified at the CMRI reading center (RC) will be forwarded to the CC and will be documented on the “EDIC Cardiac MRI Completion and Transmittal Form” (Attachment #1, Form 223.1).

EDIC does not assume responsibility for diagnosis and management of its participants. EDIC has assumed an obligation to refer patients to their local physician for medical care.

### 6.2. Alerts Triggered at the local EDIC CMRI Clinical Center (CC)

#### 6.2.1. Technologist

The local EDIC CMRI CC technologist will immediately alert the local EDIC CMRI CC imaging physician of any potentially clinically significant abnormality at the time the EDIC patient is being imaged.

#### 6.2.2. CMRI Center Physician

If the local CMRI CC physician determines that the CMRI abnormality constitutes an alert (immediate or urgent referral), the:

- 1) The local imaging physician will telephone the EDIC Clinic Study Coordinator, who will contact the patient’s physician.
- 2) Arrangements for further medical evaluation will be made through discussions involving the participant, the EDIC Clinic PI, the EDIC Clinic Study Coordinator, and the local EDIC CMRI CC physician.
- 3) An alert will be noted on “EDIC Cardiac MRI Completion and Transmittal Form” (Attachment #1, Form 223.1).

### 6.3. Alert Status Categories

The EDIC CMRI RC PI will record the participant’s alert status in the CMRI results data file at the time of image interpretation.

- 0 = No alert
- 1 = Abnormal
- 2 = Urgent referral

#### 6.3.1. No alert

No findings that would require urgent attention

### 6.3.2. Abnormal

Abnormality that may require urgent medical evaluation (e.g. within 30 days or less) as deemed by the participant's physician

### 6.3.3. Urgent Referral

Abnormality that requires immediate medical evaluation, typically within one to several days following the CMRI examination.

- a.) Phone call and written report to the local EDIC CMRI CC PI or designee.
- b.) If the alert had previously been handled at the local EDIC CMRI CC (see below), then no further action is necessary.
- c.) If the alert had not been triggered at the Local EDIC CMRI CC the Coordinator will contact the EDIC patient and the EDIC Clinic PI. Arrangements for further medical evaluation will be made through discussions involving the EDIC patient, EDIC Clinic PI, study coordinator, and the CMRI RC PI (or a designated replacement). The local EDIC CMRI CC requires direct referral to a hospital or clinic.

***Note that the CMRI reading center (RC) reviews the CMRI examination within 30 days of performance. Also, the reading center (RC) performs a scientific review/ analysis rather than a clinical analysis. Therefore, it is strongly recommended that local review of the CMRI be performed for all EDIC patients immediately after performance of the CMRI examination.***

## 6.4. Reading Center (RC) Results Categories

### 6.4.1. Normal

1. No clinically significant findings
2. Cardiac function parameters: within 2 standard deviations of normal for gender and body size

### 6.4.2. Abnormal

1. Cardiac function parameters: greater than 2 standard deviations of normal for gender and body size
2. Ascending aortic size  $\geq 4.5$  cm – 4.9 cm
3. Possible mass or tumor
4. Any other abnormality deemed by the CMRI RC PI as abnormal

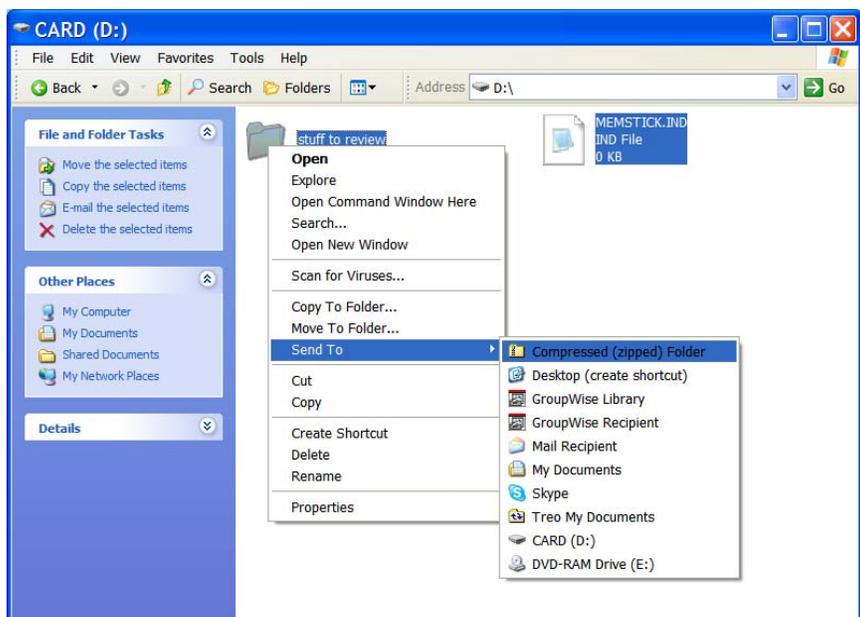
### 6.4.3. Abnormal - Urgent

1. Ascending aortic size  $\geq 5.0$  cm
2. Aortic dissection
3. Definite mass or tumor
4. Cardiac or pulmonary thrombus
5. Any other abnormality deemed by the CMRI RC PI as immediate

## 6.5 Data Transmission from the local EDIC CMRI CC by the EDIC CMRI Reading Center (RC)

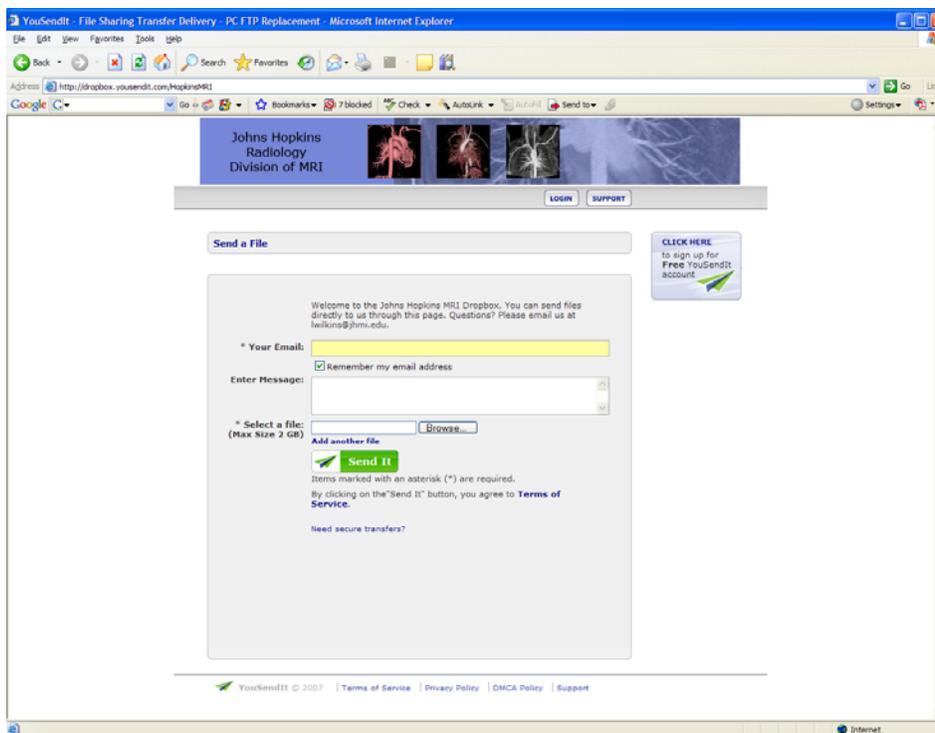
6.5.1 The preferred data transmission method is electronic through secure internet services. Please obtain a CD of the MRI examination from your MRI center and follow the instructions below:

- a. Place the CD in your computer
- b. The CD may automatically play and display a menu. If this occurs, exit the menu/program that displays.
- c. Go to My Computer
- d. Right hand click on the drive that corresponds to the CD, select copy
- e. Go to the desktop on your computer. Select paste. These instructions copy the entire CD to your computer desktop.
- f. Right hand click on the new folder on your desktop. Select “send to: compressed folder”. This will create a new compressed file, with the extension .zip
- g. Name the zip folder the same as the study ID number. If the study ID number is EDIC 12345ABC\_082807, name the zip folder EDIC 12345ABC\_082807.



h. Open Internet Explorer, open the website:  
<http://dropbox.yousendit.com/HopkinsMRI>

1. **At the top of the page** - Click on the link: “**Send a File to Dropbox**”
2. **\* Your Email:** - type in your email address here
3. **Enter Message:** - optional, enter a message you would like to convey to the CMRI RC
4. **\* Select a file** - click on the Browse button to locate the file you are sending to the CMRI RC  
 - select the file (open)  
 - **Click on the “Send It” button**



-You will receive a message “File(s) sent successfully, your file(s) has been sent to Hopkins MRI

-You will receive an email confirmation that your file was sent

- i. “Yousendit” generates an e-mail message that data has been electronically sent to the RC.
- j. If your center has scanning capabilities, scan the MRI Completion and Transmittal form (223.1) and attach it to the notification e-mail or fax the form 223.1 to:

RC Fax Number: (410) 955-9799

The information on the MRI Completion and Transmittal form (223.1) will be entered in the EDIC web database by the CMRI staff.

**The EDIC clinic coordinator should retain a copy of the CD in the patient’s file/ record at the local Clinical Center (CC). The MRI center should maintain a back-up copy of the MRI exam on PACS.**

6.5.2 Alternatively, a CD from your CMRI center and a copy of the MRI Completion and Transmittal form (223.1) can be Fed Ex’ed to Linda Wilkins at the address below:

Attn: Linda Wilkins (Ph 410.955.8216)  
 Dept of Radiology, MRI Building Nelson Basement Room 143  
 Johns Hopkins Hospital  
 600 N Wolfe St  
 Baltimore, MD 21287

6.6. Reading Center (RC) Results Protocol

#### 6.6.1. Communication with the local EDIC CMRI CC by the EDIC CMRI Reading Center (RC)

1. The staff of the EDIC CMRI RC will place the results of patients' CMRI results onto the EDIC secure data-sharing website, for the data manager at the DCC to access and add to the central EDIC database.
2. The participant's CMRI results values will be compared to the expected index ranges for gender and indexed values by body surface area to determine the type of letter he/she will receive.
3. There will be two categories of results letters that a participant could receive:
  - a. Normal for age
  - b. Possible finding
4. Issues concerning the data transfer and data quality will be discussed monthly at CMRI conference calls.
5. The DCC will send the CMRI results letter to the respective EDIC Clinics by electronic mail.

#### 6.6.2. Communication with Data Coordinating Center (DCC)

The referral system is detailed below. Modifications made by individual local EDIC CMRI CCs subject to approval by the CMRI RC and the DCC.

1. The EDIC Clinic Study Coordinator will review each EDIC patient's referral status when the CMRI results letters are received from the DCC.
2. Likewise, the EDIC Clinic Study Coordinator will receive and review any CMRI results data files sent as alerts from the CMRI RC.

#### 6.6.3. Local EDIC CMRI CC Reporting of Results

1. Reporting of results may be made to the EDIC patient, EDIC Clinic PI, or both in the form of a letter or telephone contact. The EDIC Clinic Study Coordinator will make this determination and, if necessary, will consult with the local EDIC CMRI CC PI.

### 7. Test Results

All the results of the serum creatinine tests and GFR calculations will be recorded on the EDIC website data entry system. The timely submission of results of these examinations is the responsibility of the individual EDIC Clinics.

All results of the centrally reviewed CMRI will be mailed to the staff of the EDIC Clinic and it is their responsibility to inform the patient and if necessary the patient's personal physician of these results.

### 8. Missed and Make-Up Visits

For the policy for missed Serum Creatinine or CMRI appointments, see the parts of the Chapter 5 of the EDIC MOO that discuss Missed and Make-Up Visits.

**Appendix A: List of Quest Diagnostic Laboratories near EDIC Clinics**

<b>EDIC CLINIC 01 – Case Western Reserve University</b>				
Quest Diagnostics - University Heights	14100 Cedar Rd Ste 240	Cleveland	OH	44121
Quest Diagnostics - Willoughby	36001 Euclid Ave Ste B1	Willoughby	OH	44094
Quest Diagnostics - Solon	34501 Aurora Rd Ste 103	Solon	OH	44139
Quest Diagnostics - Parma	7441 W Ridgewood Dr Ste 100	Parma	OH	44129
Quest Diagnostics - Mentor	9500 Mentor Ave Ste 120	Mentor	OH	44060
Quest Diagnostics - Fairview Park	20455 Lorain Rd Ste T02	Fairview Park	OH	44126
Quest Diagnostics - Chardon	13221 Ravenna Rd Ste 10	Chardon	OH	44024
Quest Diagnostics - Middleburg Heights	18660 Bagley Rd, Ste 104	Middleburg Heights	OH	44130
Quest Diagnostics - Westlake	24551 Detroit Rd Ste 4	Westlake	OH	44145
Quest Diagnostics - Stow	4465 Darrow Rd	Stow	OH	44224
Quest Diagnostics - Cuyahoga Falls	600 Portage Trl	Cuyahoga Falls	OH	44221
Quest Diagnostics - Fairlawn	3624 W Market St. Suite 105	Fairlawn	OH	44333
Quest Diagnostics - Akron	4125 Medina Rd Ste 202	Akron	OH	44333
Quest Diagnostics - Medina	5010 Grande Blvd	Medina	OH	44256
Quest Diagnostics - Akron	676 S Broadway St Ste 100	Akron	OH	44311
Quest Diagnostics - Green	1587 Boettler Rd Ste 106	Uniontown	OH	44685
Quest Diagnostics - Warren	3915 E Market St Ste 410	Warren	OH	44484
Quest Diagnostics - Canton PSC	4084 Holiday St NW	N. Canton	OH	44718
Quest Diagnostics - Austintown PSC	1570 S Canfield Niles Rd Bldg B	Austintown	OH	44515
Associated Clinical Laboratories - ACL-Meadville PSC	289 North St	Meadville	PA	16335
Quest Diagnostics - Mansfield	339 Cline Ave	Mansfield	OH	44907
Associated Clinical Laboratories - ACL-Fairview PSC	7686 Main St	Fairview	PA	16415
Associated Clinical Laboratories - ACL-Edinboro PSC	448 Erie St Suite 100	Edinboro	PA	16412
Associated Clinical Laboratories - ACL - Zuck Road PSC	4108 Zuck Road	Erie	PA	16506
Associated Clinical Laboratories - ACL Yorktown PSC	2501 W 12th St	Erie	PA	16505
Associated Clinical Laboratories - ACL-West 26th Street PSC	1781 W 26th St	Erie	PA	16508
Associated Clinical Laboratories - ACL-Liberty Street PSC	3315 Liberty St	Erie	PA	16508
Associated Clinical Laboratories - ACL Waterford PSC	991 Route 19 Suite G	Waterford	PA	16441
Quest Diagnostics - Beaver	336 College Ave Ste 4	Beaver	PA	15009
Associated Clinical Laboratories - Patient Service Center and Main Lab	1526 Peach St	Erie	PA	16501
Associated Clinical Laboratories - ACL-Bayfront PSC	350 E Bayfront Pkwy	Erie	PA	16507
Associated Clinical Laboratories - ACL-East 38th Street PSC	2020 E 38th St	Erie	PA	16504
Associated Clinical Laboratories - ACL - East Harbor PSC	4916 Buffalo Rd	Erie	PA	16510
Quest Diagnostics - Cranberry	20826 Route 19	Cranberry Twp	PA	16066
Quest Diagnostics - Ambridge	832 Merchant St	Ambridge	PA	15003
Quest Diagnostics - Seven Fields	100 Northpointe Cir Ste 301	Seven Fields	PA	16046
Quest Diagnostics - Eastpointe Kelly PSC	22850 Kelly Rd	Eastpointe	MI	48021



<b>EDIC CLINIC 02 – University of Penn.</b>				
Quest Diagnostics - North Broad Street	227 N. Broad St	Philadelphia	PA	19107
Quest Diagnostics - Walnut St PSC	828 Walnut St	Philadelphia	PA	19107
Quest Diagnostics - S. Broad Street	2219 S Broad St	Philadelphia	PA	19148
Quest Diagnostics - Bala Cynwyd	4190 City Avenue - Ste. 416	Philadelphia	PA	19131
Quest Diagnostics - Roxborough	525 Jamestown St	Philadelphia	PA	19128
Quest Diagnostics	Cooper River Plaza West 6981 North Park Drive Suite 203	Pennsauken	NJ	08109
Quest Diagnostics - Germantown	2 Penn Blvd Suite 205	Philadelphia	PA	19144
Quest Diagnostics - Juniata	4501 Castor Ave	Philadelphia	PA	19124
Quest Diagnostics - Woodbury	730 N Broad St Suite 125	Woodbury	NJ	08096
Quest Diagnostics - Havertown	2010 W Chester Pike	Havertown	PA	19083
Quest Diagnostics - Springfield	1001 Baltimore Pike Suite 9	Springfield	PA	19064
Quest Diagnostics - Haddonfield PSC	807 Haddon Ave	Haddonfield	NJ	08033
Quest Diagnostics - MacDade Blvd	501 W MacDade Boulevard	Folsom	PA	19033
Quest Diagnostics - Haddon Heights	515 Grove Street Suite 1 A	Haddon Heights	NJ	08035
Quest Diagnostics - Roosevelt Plaza	6555 Roosevelt Blvd.	Philadelphia	PA	19149
Quest Diagnostics - Cottman Avenue PSC	700 Cottman Ave	Philadelphia	PA	19111
Quest Diagnostics - Maple Shade	19 W Main St	Maple Shade	NJ	08052
Quest Diagnostics - Cherry Hill PSC	1040 Kings Hwy Suite 102	Cherry Hill	NJ	08034
Quest Diagnostics - Flourtown	1107 Bethlehem Pike	Flourtown	PA	19031
Quest Diagnostics - Frankford Avenue	7526 Frankford Ave	Philadelphia	PA	19136
Quest Diagnostics - Welsh Road	2417 Welsh Rd	Philadelphia	PA	19114
Quest Diagnostics - Moorestown	502 Pleasant Valley Ave	Moorestown	NJ	08057
Quest Diagnostics - Abington PSC	1419 Old York Rd	Abington	PA	19001
Quest Diagnostics - Stratford	215 E Laurel Rd Suite 102	Stratford	NJ	08084
Quest Diagnostics - Camden County UDS	1101 White Horse Rd	Voorhees	NJ	08043
Quest Diagnostics - Bustleton	9808 Bustleton Avenue	Philadelphia	PA	19115
Quest Diagnostics - Voorhees	1010 Haddonfield Berlin Rd Suite 400	Voorhees	NJ	08043
Quest Diagnostics - Norristown PSC	720--730 E Johnson Highway	Norristown	PA	19401
Quest Diagnostics - Devon	227 W Lancaster Ave	Devon	PA	19333
Quest Diagnostics	1437 Dekalb St	Norristown	PA	19401
Quest Diagnostics - Marlton	4 Eves Dr # A	Marlton	NJ	08053
Quest Diagnostics - KOP	491 Allendale Road Ste300	King Of Prussia	PA	19406
Quest Diagnostics - Horsham	200 Lakeside Dr Ste 230	Horsham	PA	19044
Quest Diagnostics	1012 W 9th Avenue 1st Floor	King of Prussia	PA	19406
Quest Diagnostics - Turnersville	188 Fries Mill Rd Bldg. H	Turnersville	NJ	08012
Quest Diagnostics - Sewell	302 Hurffville Crosskeys Rd Suite A- 2	Sewell	NJ	08080
Quest Diagnostics - Street Road	210 E. Street Road 3rd Floor, Ste 3D	Feasterville	PA	19053
Quest Diagnostics - Paoli PSC	15 Industrial Blvd Ste Suite A-101	Paoli	PA	19301
Quest Diagnostics - Rancocas Valley PSC	220 Sunset Rd Suite 5D	Willingboro	NJ	08046
Quest Diagnostics - Concordville PSC	736 Baltimore Pike Suite 9	Concordville	PA	19331
Quest Diagnostics - Medford	175 Route 70	Medford	NJ	08055
Quest Diagnostics - Silverside PSC	2700 Silverside Rd Ste 1b	Wilmington	DE	19810

Quest Diagnostics - Mount Holly	1613 Route 38	Lumberton	NJ	08060
Quest Diagnostics - Liberty Town Plaza	412 Sicklerville Rd Ste 106	Sicklerville	NJ	08081
Quest Diagnostics - Lansdale	1050 S Broad St	Lansdale	PA	19446
Quest Diagnostics - Foulk Road PSC	1403 Foulk Rd Ste 103	Wilmington	DE	19803
Quest Diagnostics - Richboro	130 Almshouse Rd	Richboro	PA	18954
Quest Diagnostics - Oaks	Oaks Corporate Center 450 Cresson Boulevard, Suite 305	Phoenixville	PA	19460
Quest Diagnostics - Collegeville	555 2nd Ave	Collegeville	PA	19426
Quest Diagnostics - Chalfont PSC	1700 Horizon Dr Suite 205	Chalfont	PA	18914
Quest Diagnostics - West Chester	600 E Marshall St	West Chester	PA	19380
Quest Diagnostics - Hidden Meadow	2131 N Broad St	Lansdale	PA	19446
Quest Diagnostics - Woodbourne	1609 Woodbourne Rd	Levittown	PA	19057
Quest Diagnostics - Trappe	545 W Main St	Collegeville	PA	19426
Quest Diagnostics - Langhorne	586 Middletown Blvd Suite C-11	Langhorne	PA	19047
Quest Diagnostics - Fairless Hills	333 N Oxford Valley Road Suite 203	Fairless Hills	PA	19030
Quest Diagnostics - Trolley Square PSC	Delaware Ave & Clayton St Trolley Square, Suites 3b-4b	Wilmington	DE	19806
Quest Diagnostics - Harleysville	484 Harleysville Pike	Harleysville	PA	19438
Quest Diagnostics - Exton	80 W Welsh Pool Rd Ste 102	Exton	PA	19341
Quest Diagnostics - Pennsville PSC	181 N Broadway	Pennsville	NJ	08070
Quest Diagnostics - Souderton Square	708 Route 113	Souderton	PA	18964
Quest Diagnostics - Doylestown	Routes 313 & 611 Baliwick Campus, Suite 45	Doylestown	PA	18901
Quest Diagnostics - Downingtown	308 E Lancaster Ave	Downingtown	PA	19335
Quest Diagnostics - Hammonton PSC	777 White Horse Pike Ste D3	Hammonton	NJ	08037
Quest Diagnostics - New Castle	525 E Basin Rd	New Castle	DE	19720
Quest Diagnostics - Millcreek PSC	4512 Kirkwood Hwy Ste 100	Wilmington	DE	19808
Quest Diagnostics - Thorndale	3508 Lincoln Hwy	Thorndale	PA	19372
Quest Diagnostics - Trenton	Lexington Mews Office Center 795 Parkway Avenue Unit A-7	Trenton	NJ	08618
Quest Diagnostics - Pottstown PSC	1569 Medical Dr	Pottstown	PA	19464
Quest Diagnostics - Stoney Batter	5311 Limestone Rd Suite 202	Wilmington	DE	19808
Quest Diagnostics - Hor-Omega PSC	A98 100 Omega Drive	Newark	DE	19713
Quest Diagnostics - Hamilton	1225 Whitehorse Mercerville Rd Suite 201	Hamilton	NJ	08619
Quest Diagnostics - Gilbertsville	1050 E Philadelphia Ave	Gilbertsville	PA	19525
Quest Diagnostics - Lawrenceville PSC	168 Franklin Corner Rd Bldg. 2, Suite 1D	Lawrenceville	NJ	08648
Quest Diagnostics - Bridgeton PSC	216 Laurel Heights Dr	Bridgeton	NJ	08302
Quest Diagnostics - Newark Main St	249 E Main Street	Newark	DE	19711
Quest Diagnostics - Vineland	3071 E Chestnut Ave Suite A-3	Vineland	NJ	08360
Quest Diagnostics - Quakertown	1532 Park Ave Suite 103.	Quakertown	PA	18951
Quest Diagnostics	2848 S Delsea Dr Suite 2-C	Vineland	NJ	08360
Quest Diagnostics - East Greenville	622 Gravel Pike	East Greenville	PA	18041
Quest Diagnostics - Glasgow PSC	2600 Glasgow Ave Ste 100	Newark	DE	19702
Quest Diagnostics - Millville PSC	1601 N 2nd St Street Unit C-9	Millville	NJ	08332
Quest Diagnostics	300 Biddle Avenue Suite 202	Newark	DE	19702
Quest Diagnostics - West Grove PSC	1101 Baltimore Pike, Suite 209	West Grove	PA	19390
Quest Diagnostics - Birdsboro	321 N Furnace St	Birdsboro	PA	19508
Quest Diagnostics - Princeton	601 Ewing St Suite C-22	Princeton	NJ	08540

Quest Diagnostics - FLEMINGTON	309 WALTER E. FORAN BLVD. TOWNE CENTRE	FLEMINGTON	NJ	08822
Quest Diagnostics - Emmaus	1040 Chestnut St	Emmaus	PA	18049
Quest Diagnostics - Mays Landing	5429 Harding Hwy Suite 102	Mays Landing	NJ	08330
Quest Diagnostics - Hellertown	The Shoppes at Hellertown 25 Main Street	Hellertown	PA	18055
Quest Diagnostics - Exeter	4400 Perkiomen Ave	Reading	PA	19606
Quest Diagnostics - Middletown PSC	Ketley Professional Plaza - 114 Sandhill Drive Suite 202	Middletown	DE	19709
Quest Diagnostics - Cedar Crest	1251 S Cedar Crest Blvd	Allentown	PA	18103
Quest Diagnostics - Bethlehem- Delaware Avenue	406 Delaware Ave	Bethlehem	PA	18015
Quest Diagnostics - Shillington Shopping Center	520 E Lancaster Ave	Shillington	PA	19607
Quest Diagnostics - Allen Street	1608 W Allen St	Allentown	PA	18102
Quest Diagnostics - Jamesburg	333 Forsgate Dr Ste 203	Jamesburg	NJ	08831
Quest Diagnostics - Absecon	76 W Jimmie Leeds Rd Ste 403	Galloway	NJ	08205
Quest Diagnostics - Fairgrounds Square Mall	3050 N 5th Street Hwy	Reading	PA	19605
Quest Diagnostics - Bethlehem- Westgate Dr	2045 Westgate Dr Bldg Ste104	Bethlehem	PA	18017
Quest Diagnostics - Toms River 2	600 Mule Road, Unit 24A	Toms River	NJ	08755
Quest Diagnostics - Berkshire	Berkshire Mall 1665 State Hill Road	Wyomissing	PA	19610
Quest Diagnostics - Bethlehem-Reeve Drive	4333 Easton Ave Suite A	Bethlehem	PA	18020
Quest Diagnostics - Manahawkin	1322 Route 72 West, Suite 202 Corner of Barnacle Dr.	Manahawkin	NJ	08050
Quest Diagnostics - Easton- 22nd Street	229 S 22nd St	Easton	PA	18042
Quest Diagnostics - FREEHOLD	260 Mounts Corner Drive	Freehold	NJ	07728
Quest Diagnostics - TOMS RIVER COMMONS	548 Commons Way Bldg E	Toms River	NJ	08755
Quest Diagnostics - Somerset	49 Veronica Ave Ste 203	Somerset	NJ	08873
Quest Diagnostics - Linwood PSC	222 New Rd Ste 103	Linwood	NJ	08221
Quest Diagnostics - Easton-	3601 Nazareth Rd	Easton	PA	18045
Quest Diagnostics - MANALAPAN	46-50 Franklin Lane, Suite 202	Manalapan	NJ	07726
Quest Diagnostics - Howell	400 Candlewood Commons, Bldg. 4	Howell	NJ	07731
Quest Diagnostics - EAST BRUNSWICK	1020 Route 18 Unit 007 - Route 18 Shopping Center	East Brunswick	NJ	08816
Quest Diagnostics - PSC-BOUND BROOK	601 West Union Ave.	Bound Brook	NJ	08805
Quest Diagnostics - New Brunswick	77 Church Street	New Brunswick	NJ	08901
Quest Diagnostics - Nazareth	25 Soute Broad Street Suite 102	Nazareth	PA	18064
Quest Diagnostics - Ephrata PSC	112 N Reading Rd	Ephrata	PA	17522
Quest Diagnostics - Ventnor PSC	6508 Ventnor Ave	Ventnor City	NJ	08402
Quest Diagnostics - Ocean City	6th and Central Ave	Ocean City	NJ	08226
Quest Diagnostics - PSC-BRICK	1608 Route 88 Ste 114	Brick	NJ	08724
Quest Diagnostics - Dover PSC	1102 South Dupont Highway	Dover	DE	19901
Quest Diagnostics - Hamburg	400-B South 4th Street	Hamburg	PA	19526
Quest Diagnostics - Warren	37 Mountain Blvd Suite #5	Warren	NJ	07059
Quest Diagnostics - Aberdeen PSC	219 W Bel Air Ave Ste 3	Aberdeen	MD	21001
Quest Diagnostics - Edison - Amboy	1199 Amboy Ave # Storea-4	Edison	NJ	08837

Avenue				
Quest Diagnostics - South Plainfield	904 Oak Tree Ave Ste K	South Plainfield	NJ	07080
Quest Diagnostics - Lancaster PSC	215 Granite Run Dr	Lancaster	PA	17601
Quest Diagnostics - Edison-James Street	102 James St Suite 201	Edison	NJ	08820
Quest Diagnostics - HOLMDEL	704 N Beers St	Holmdel	NJ	07733
Quest Diagnostics - PSC-Bernardsville	1 Anderson Rd Ste 101	Bernardsville	NJ	07924
Quest Diagnostics - HAZLET	1 Bethany Rd Building 5, Suite 67	Hazlet	NJ	07730
Quest Diagnostics - Neptune	1809 Corlies Ave Floor 2	Neptune	NJ	07753
Quest Diagnostics - Bangor	418 Blue Valley Drive Route 512	Bangor	PA	18013
Quest Diagnostics - Staten Island - Tottenville	7001 Amboy Road, Store A-4 Tottenville Square Shopping Center	Staten Island	NY	10307
Quest Diagnostics - Oakhurst	1900 Highway 35, Suite 101 Ocean Park Cente	Oakhurst	NJ	07755
Quest Diagnostics - Myerstown	725 E Lincoln Ave	Myerstown	PA	17067
Quest Diagnostics - Hackettstown	137 Mountain Ave Ste 2	Hackettstown	NJ	07840
Quest Diagnostics - Red Bank	240 Maple Ave	Red Bank	NJ	07701
Quest Diagnostics - LITTLE SILVER	200 White Rd Ste 104 Little Silver Commons	Little Silver	NJ	07739
Quest Diagnostics - Westfield	189 Elm St Lower Level	Westfield	NJ	07090
Quest Diagnostics - Rio Grande PSC	1500 Delsea Drive (Rt 47)	Rio Grande	NJ	08242
Quest Diagnostics - Staten Island 4855 Hylan Blvd	4855 Hylan Blvd	Staten Island	NY	10312
Quest Diagnostics - Old Emmorton Commons	2227 Old Emmorton Rd	Bel Air	MD	21015
Quest Diagnostics - Bel Air: North Ave	4 C North Ave Suite 405	Bel Air	MD	21014
Quest Diagnostics - Bel Air: MacPhail Rd	620 W MacPhail Rd Ste 103	Bel Air	MD	21014
Quest Diagnostics - STATEN ISLAND - RICHMOND AVEN	3733 Richmond Ave	Staten Island	NY	10312
Quest Diagnostics - Morristown	101 Madison Ave Ste 101	Morristown	NJ	07960
Quest Diagnostics - STATEN ISLAND - 3311 HYLAN	3311 Hylan Blvd	Staten Island	NY	10306
Quest Diagnostics - Roselle	711 E 1st Ave Store #17	Roselle	NJ	07203
Quest Diagnostics - UNION-CHESTNUT	440 Chestnut St Unit 102	Union	NJ	07083
Quest Diagnostics - UNION-MORRIS	2333 Morris Ave Ste A-121	Union	NJ	07083
Quest Diagnostics - PSC-Cedar Knolls	8 Saddle Rd Suite 204	Cedar Knolls	NJ	07927
Quest Diagnostics - Randolph	477 Route 10 East Suite 203	Randolph	NJ	07801
Quest Diagnostics - STATEN ISLAND - 2627A HYLAN	2627a Hylan Blvd	Staten Island	NY	10306
Quest Diagnostics - STATEN ISLAND - WILLOWBROOK	651 Willowbrook Road Suite 101	Staten Island	NY	10314
Quest Diagnostics - Lebanon	Rt 422 West	Lebanon	PA	17042
Quest Diagnostics - East Stroudsburg	314 Lincoln Avenue Pocono Plaza	East Stroudsburg	PA	18301
Quest Diagnostics - Milford	975 N Dupont Hwy	Milford	DE	19963
Quest Diagnostics - Staten Island-Todt Hill Road	78 Todt Hill Rd Ste 109	Staten Island	NY	10314
Quest Diagnostics - STATEN ISLAND - 1361 HYLAN	1361 Hylan Blvd	Staten Island	NY	10305
Quest Diagnostics - Livingston	349 E Northfield Rd Ste 203	Livingston	NJ	07039
Quest Diagnostics - West Orange	769 Northfield Ave Ste LI3	West Orange	NJ	07052
Quest Diagnostics - Pottsville	1851 W End Ave	Pottsville	PA	17901
Quest Diagnostics - PSC-Bayonne	686-692 Broadway, 3rd Floor	Bayonne	NJ	07002

Quest Diagnostics - STATEN ISLAND - 81 RANDALL	81 Randall Ave	Staten Island	NY	10301
Quest Diagnostics - Denville	Main Street (Route 53) and Luger Road	Denville	NJ	07834
Quest Diagnostics - Parsippany	50 Cherry Hill Rd Ste 103	Parsippany	NJ	07054
Quest Diagnostics - Newark	24 Commerce St Fl 4	Newark	NJ	07102
Quest Diagnostics - BROOKLYN - BAYRIDGE	7601 4th Ave	Brooklyn	NY	11209
Quest Diagnostics - BROOKLYN-BENSONHURST	15 Bay 29th St Room 2B	Brooklyn	NY	11214
Quest Diagnostics - Whitmarsh	8114 Sandpiper Cir Ste 115	Nottingham	MD	21236
Quest Diagnostics - Kearny	206 Bergen Ave Suite A5	Kearny	NJ	07032
Quest Diagnostics - Brooklyn - Boro Park	5102 13th Ave	Brooklyn	NY	11219
Quest Diagnostics - PSC-Brooklyn- 48th Street	949 48th St	Brooklyn	NY	11219
Quest Diagnostics - MONTCLAIR	49 Claremont Avenue	Montclair	NJ	07042
Quest Diagnostics - York PSC	1748 6th Ave	York	PA	17403
Quest Diagnostics - BROOKLYN - EAST 14TH ST	1660 E 14th St Ste LL2	Brooklyn	NY	11229
Quest Diagnostics - Seven Square Park PSC	9110 Philadelphia Rd Ste 212	Baltimore	MD	21237
Quest Diagnostics - Brooklyn Newkirk Avenue	1416 Newkirk Ave	Brooklyn	NY	11226
Quest Diagnostics - Jersey City	600 Pavonia Ave	Jersey City	NJ	07306
Quest Diagnostics - BROOKLYN - PARK SLOPE	348 13th St Suite 102	Brooklyn	NY	11215
Quest Diagnostics - Hazelton	20 N Laurel St	Hazleton	PA	18201
Quest Diagnostics - BROOKLYN HEIGHTS	120 Atlantic Ave	Brooklyn	NY	11201
Quest Diagnostics - Harford Road PSC	8035 Harford Road Suite B	Baltimore	MD	21234
Quest Diagnostics - Lewes PSC	1526 Savannah Rd	Lewes	DE	19958
Quest Diagnostics - BROOKLYN - PIERREPONT	146 Pierrepont St	Brooklyn	NY	11201
Quest Diagnostics - BROOKLYN - RALPH AVENUE	2035 Ralph Ave Ste B1	Brooklyn	NY	11234
Quest Diagnostics - NYC - MOTT ST	41 Mott St Fl 4	New York	NY	10013
Quest Diagnostics - Clifton	881 Allwood Rd, Suite 103	Clifton	NJ	07012
Quest Diagnostics - NYC - GREENWICH AVE	119 Greenwich Ave # 5	New York	NY	10014
Quest Diagnostics - NYC - West 14th Street	314 West 14th St. Lower Level	New York	NY	10014
Quest Diagnostics - Totowa	500 Union Blvd	Totowa	NJ	07512
Quest Diagnostics - NYC - WEST 16TH ST	269 West 16th Street Lower Level	New York	NY	10011
Quest Diagnostics - Rutherford	17 Sylvan St	Rutherford	NJ	07070
Quest Diagnostics - Lutherville	1205 York Rd Ste 15a	Lutherville	MD	21093
Quest Diagnostics - New York Seventh Avenue	275 Seventh Avenue Between 25th & 26th Streets	New York	NY	10001
Quest Diagnostics - Dundalk	7544 Holabird Ave	Baltimore	MD	21222
Quest Diagnostics - York Crossings	York Crossings 2189 York Crossing Drive	York	PA	17408

Quest Diagnostics - NYC - 247 3RD AVENUE	247 Third Ave Rm 303	New York	NY	10010
Quest Diagnostics - West New York	4914-4922 Kennedy Blvd. Suite 206	West New York	NJ	07093
Quest Diagnostics - NYC - EAST 36TH STREET	137 E 36th St	New York	NY	10016
Quest Diagnostics - BUTLER	1395 Route 23S Unit C-1	Butler	NJ	07405
Quest Diagnostics - BROOKLYN - GREENPOINT	147 Greenpoint Ave First Floor	Brooklyn	NY	11222
Quest Diagnostics - PSC- West 58th Street	330 West 58th Street Suite 203	New York	NY	10019
Quest Diagnostics - NYC - 115 E 57TH ST	115 E 57th St Ste 1530	New York	NY	10022
Quest Diagnostics - NYC - EAST 61ST STREET	115 E 61st St	New York	NY	10021
Quest Diagnostics - NYC - E 67TH ST	235 E 67th St Rm 201	New York	NY	10021
Quest Diagnostics - Queens-Howard Beach	Lindenwood Village Shopping Center 82-29 153rd Avenue	Howard Beach	NY	11414
Quest Diagnostics - NYC - EAST 76TH ST	65 E 76th St	New York	NY	10021
Quest Diagnostics - Wayne	401 Hamburg Tpke Ste 203	Wayne	NJ	07470
Quest Diagnostics - NYC - WEST 86TH ST	2 W 86th St Apt 1a	New York	NY	10024
Quest Diagnostics - NYC - 66 E 86TH ST	66 E 86th St	New York	NY	10028
Quest Diagnostics - NYC - 115 E. 86th Street	115 E 86th St	New York	NY	10028
Quest Diagnostics - QUEENS - MIDDLE VILLAGE	7121 Eliot Ave	Middle Village	NY	11379
Quest Diagnostics - NYC-1651 3rd Avenue	1651 3rd Ave Fl 2	New York	NY	10128
Quest Diagnostics - North Haledon	535 High Mountain Rd	North Haledon	NJ	07508
Quest Diagnostics - Queens-Astoria	27-47 Crescent Street	Astoria	NY	11102
Quest Diagnostics - Harrisburg PSC	4824 Londonderry Rd	Harrisburg	PA	17109
Quest Diagnostics - Queens-Jackson Heights	75-35 31st Ave	Jackson Heights	NY	11372
Quest Diagnostics - FAIRLAWN	33-00 Broadway Suite 305	Fair Lawn	NJ	07410
Quest Diagnostics - Queens-Forest Hills	7010 Austin St	Forest Hills	NY	11375
Quest Diagnostics - Hackensack	385 Prospect Ave	Hackensack	NJ	07601
Quest Diagnostics - Teaneck	179 Cedar Ln Suite E	Teaneck	NJ	07666
Quest Diagnostics - Garwyn Medical	2300 Garrison Blvd Ste 206	Baltimore	MD	21216
Quest Diagnostics - Cedarhurst PSC	222 Rockaway Tpke, Suite 5	Cedarhurst	NY	11516
Quest Diagnostics - NYC-West 168th Street	607 W 168th St	New York	NY	10032
Quest Diagnostics - Naylor's Court PSC	4000 Old Court Rd Suite 102	Pikesville	MD	21208
Quest Diagnostics - ENGLEWOOD	25 Rockwood Pl Ste 1	Englewood	NJ	07631
Quest Diagnostics - QUEENS - JAMAICA	12614 Merrick Blvd	Jamaica	NY	11434
Quest Diagnostics - Owings Mills: Crossroads Drive	21 Crossroads Drive Bldg B -Suite 245	Owings Mills	MD	21117
Quest Diagnostics - Cross Roads PSC #2	23 Cross Roads Suite 120	Owings Mills	MD	21117
Quest Diagnostics - Paramus	275-277 Forest Ave	Paramus	NJ	07652
Quest Diagnostics - Ridgewood	127 Union St	Ridgewood	NJ	07450
Quest Diagnostics - Queens - Flushing	41-61 Kissena Blvd Ste 25	Flushing	NY	11355

Quest Diagnostics - Crain Hwy PSC	1412 N. Crain Hwy Suite 3A	Glen Burnie	MD	21061
Quest Diagnostics - Englewood Cliffs	464 Hudson Ter	Englewood Cliffs	NJ	07632
Quest Diagnostics - Linglestown PSC	2021 Linglestown Rd	Harrisburg	PA	17110
Quest Diagnostics - Wilkens Ave. PSC	4660 Wilkens Ave SUITE 201	Baltimore	MD	21229
Quest Diagnostics - Frederick Villa	5411 Old Frederick Rd Ste 9	Baltimore	MD	21229
Quest Diagnostics - Main Street PSC	750 Main St Suite 306	Reisterstown	MD	21136
Quest Diagnostics - Catonsville: Maiden Choice	724 Maiden Choice Ln Ste 101	Catonsville	MD	21228
Quest Diagnostics - Seaford PSC	808 Middleford Rd	Seaford	DE	19973
Quest Diagnostics - Bronx-Arthur Avenue	2385 Arthur Ave Suites 201 & 202	Bronx	NY	10458
Quest Diagnostics - Queens-Bayside	4401 Francis Lewis Blvd	Bayside	NY	11361
Quest Diagnostics - Randallstown/ Old Court	5400 Old Court Rd Ste 102	Randallstown	MD	21133
Quest Diagnostics - Camp Hill	3401 Hartzdale Dr	Camp Hill	PA	17011
Quest Diagnostics - Oakwood PSC	7845 Oakwood Rd Ste 304	Glen Burnie	MD	21061
Quest Diagnostics - Hospital Drive PSC	200 Hospital Dr Ste 103	Glen Burnie	MD	21061
Quest Diagnostics - BRONX - WILLIAMSBRIDGE	2015 Williamsbridge Rd	Bronx	NY	10461
Quest Diagnostics - EMERSON	452 Old Hook Rd Suite 1A	Emerson	NJ	07630
Quest Diagnostics - Rockville Centre PSC	165 North Village Avenue Suite 103	Rockville Centre	NY	11570
Quest Diagnostics - BRONX - WESTCHESTER	3250 Westchester Ave Ste 105	Bronx	NY	10461
Quest Diagnostics - Floral Park PSC	265 Jericho Tpke	Floral Park	NY	11001
Quest Diagnostics - Hanover	1157 Eichelberger St Suite 3A	Hanover	PA	17331
Quest Diagnostics - Ramsey	500 N Franklin Tpke Fl 2	Ramsey	NJ	07446
Quest Diagnostics - Great Neck PSC	287 Northern Blvd. Suite 100	Great Neck	NY	11021
Quest Diagnostics - Lake Success PSC	2001 Marcus Ave Suite 98W, Lobby Level	Lake Success	NY	11042
Quest Diagnostics - Millville	200 Atlantic Ave Suite A	Millville	DE	19967
Quest Diagnostics - Bestgate PSC	820 Bestgate Rd	Annapolis	MD	21401
Quest Diagnostics - Mount Vernon	105 Stevens Ave Ste 205	Mount Vernon	NY	10550
Quest Diagnostics - Freeport PSC	101 South Bergen Place 2nd Floor	Freeport	NY	11520
Quest Diagnostics - Conte PSC	116 Defense Hwy Ste 401	Annapolis	MD	21401
Quest Diagnostics - Hempstead PSC	230 Hilton Avenue Room 220	Hempstead	NY	11550
Quest Diagnostics - Suffern	Indian Rock Shopping Center Route 59 & Hemion Road	Suffern	NY	10901
Quest Diagnostics - Ellicott City	9055 Chevrolet Dr Ste 101	Ellicott City	MD	21043
Quest Diagnostics - Manhasset PSC	1165 Northern Blvd Suite 404	Manhasset	NY	11030
Quest Diagnostics - Garden City PSC	520 Franklin Ave Suite 104	Garden City	NY	11530
Quest Diagnostics - Yonkers	970 N Broadway Ste 205	Yonkers	NY	10701
Quest Diagnostics - Westminster Washington Heights	222 Washington Road	Westminster	MD	21157
Quest Diagnostics - Mineola PSC	156 First Street Lower Level	Mineola	NY	11501
Quest Diagnostics - Tappan	111 Route 303 Ste 109	Tappan	NY	10983
Quest Diagnostics - New Rochelle	150 Lockwood Ave	New Rochelle	NY	10801

**EDIC CLINIC 03 – Cornell University**

Quest Diagnostics - NYC - E 67TH ST	235 E 67th St Rm 201	New York	NY	10019
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Quest Diagnostics - NYC - 66 E 86TH ST	66 E 86th St	New York	NY	10028
Quest Diagnostics - NYC-1651 3rd Avenue	1651 3rd Ave Fl 2	New York	NY	10128
Quest Diagnostics - PSC- West 58th Street	330 West 58th Street Suite 203	New York	NY	10019
Quest Diagnostics - NYC - WEST 86TH ST	2 W 86th St Apt 1a	New York	NY	10024
Quest Diagnostics - Queens-Astoria	27-47 Crescent Street	Astoria	NY	11102
Quest Diagnostics - NYC - EAST 36TH STREET	137 E 36th St	New York	NY	10016
Quest Diagnostics - BROOKLYN - GREENPOINT	147 Greenpoint Ave First Floor	Brooklyn	NY	11222
Quest Diagnostics - NYC - 247 3RD AVENUE	247 Third Ave Rm 303	New York	NY	10010
Quest Diagnostics - New York Seventh Avenue	275 Seventh Avenue Between 25th & 26th Streets	New York	NY	10001
Quest Diagnostics - NYC - WEST 16TH ST	269 West 16th Street Lower Level	New York	NY	10011
Quest Diagnostics - NYC - West 14th Street	314 West 14th St. Lower Level	New York	NY	10014
Quest Diagnostics - NYC - GREENWICH AVE	119 Greenwich Ave # 5	New York	NY	10014
Quest Diagnostics - Queens-Jackson Heights	75-35 31st Ave	Jackson Heights	NY	11372
Quest Diagnostics - West New York	4914-4922 Kennedy Blvd. Suite 206	West New York	NJ	07093
Quest Diagnostics - NYC - MOTT ST	41 Mott St Fl 4	New York	NY	10013
Quest Diagnostics - QUEENS - MIDDLE VILLAGE	7121 Eliot Ave	Middle Village	NY	11379
Quest Diagnostics - NYC-West 168th Street	607 W 168th St	New York	NY	10032
Quest Diagnostics - BROOKLYN - PIERREPONT	146 Pierrepont St	Brooklyn	NY	11201
Quest Diagnostics - BROOKLYN HEIGHTS	120 Atlantic Ave	Brooklyn	NY	11201
Quest Diagnostics - Jersey City	600 Pavonia Ave	Jersey City	NJ	07306
Quest Diagnostics - Queens-Forest Hills	7010 Austin St	Forest Hills	NY	11375
Quest Diagnostics - Queens - Flushing	41-61 Kissena Blvd Ste 25	Flushing	NY	11355
Quest Diagnostics - Bronx-Arthur Avenue	2385 Arthur Ave Suites 201 & 202	Bronx	NY	10458
Quest Diagnostics - BROOKLYN - PARK SLOPE	348 13th St Suite 102	Brooklyn	NY	11215
Quest Diagnostics - Englewood Cliffs	464 Hudson Ter	Englewood Cliffs	NJ	07632
Quest Diagnostics - ENGLEWOOD	25 Rockwood Pl Ste 1	Englewood	NJ	07631
Quest Diagnostics - BRONX - WILLIAMSBRIDGE	2015 Williamsbridge Rd	Bronx	NY	10461
Quest Diagnostics - Queens-Howard Beach	Lindenwood Village Shopping Center 82-29 153rd Avenue	Howard Beach	NY	11414
Quest Diagnostics - Teaneck	179 Cedar Ln Suite E	Teaneck	NJ	07666
Quest Diagnostics - PSC-Brooklyn- 48th Street	949 48th St	Brooklyn	NY	11219
Quest Diagnostics - Rutherford	17 Sylvan St	Rutherford	NJ	07070
Quest Diagnostics - BRONX -	3250 Westchester Ave Ste 105	Bronx	NY	10461

WESTCHESTER				
Quest Diagnostics - Brooklyn Newkirk Avenue	1416 Newkirk Ave	Brooklyn	NY	11226
Quest Diagnostics - Queens-Bayside	4401 Francis Lewis Blvd	Bayside	NY	11361
Quest Diagnostics - Brooklyn - Boro Park	5102 13th Ave	Brooklyn	NY	11219
Quest Diagnostics - BROOKLYN - RALPH AVENUE	2035 Ralph Ave Ste B1	Brooklyn	NY	11234
Quest Diagnostics - BROOKLYN - BAYRIDGE	7601 4th Ave	Brooklyn	NY	11209
Quest Diagnostics - Kearny	206 Bergen Ave Suite A5	Kearny	NJ	07032
Quest Diagnostics - Hackensack	385 Prospect Ave	Hackensack	NJ	07601
Quest Diagnostics - BROOKLYN - EAST 14TH ST	1660 E 14th St Ste LL2	Brooklyn	NY	11229
Quest Diagnostics - BROOKLYN-BENSONHURST	15 Bay 29th St Room 2B	Brooklyn	NY	11214
Quest Diagnostics - QUEENS - JAMAICA	12614 Merrick Blvd	Jamaica	NY	11434
Quest Diagnostics - Newark	24 Commerce St Fl 4	Newark	NJ	07102
Quest Diagnostics - Mount Vernon	105 Stevens Ave Ste 205	Mount Vernon	NY	10550
Quest Diagnostics - STATEN ISLAND - 81 RANDALL	81 Randall Ave	Staten Island	NY	10301
Quest Diagnostics - Great Neck PSC	287 Northern Blvd. Suite 100	Great Neck	NY	11021
Quest Diagnostics - PSC-Bayonne	686-692 Broadway, 3rd Floor	Bayonne	NJ	07002
Quest Diagnostics - Clifton	881 Allwood Rd, Suite 103	Clifton	NJ	07012
Quest Diagnostics - Paramus	275-277 Forest Ave	Paramus	NJ	07652
Quest Diagnostics - New Rochelle	150 Lockwood Ave	New Rochelle	NY	10801
Quest Diagnostics - FAIRLAWN	33-00 Broadway Suite 305	Fair Lawn	NJ	07410
Quest Diagnostics - Lake Success PSC	2001 Marcus Ave Suite 98W, Lobby Level	Lake Success	NY	11042
Quest Diagnostics - Floral Park PSC	265 Jericho Tpke	Floral Park	NY	11001
Quest Diagnostics - Manhasset PSC	1165 Northern Blvd Suite 404	Manhasset	NY	11030
Quest Diagnostics - STATEN ISLAND - 1361 HYLAN	1361 Hylan Blvd	Staten Island	NY	10305
Quest Diagnostics - Staten Island-Todt Hill Road	78 Todt Hill Rd Ste 109	Staten Island	NY	10314
Quest Diagnostics - MONTCLAIR	49 Claremont Avenue	Montclair	NJ	07042
Quest Diagnostics - Yonkers	970 N Broadway Ste 205	Yonkers	NY	10701
Quest Diagnostics - STATEN ISLAND - WILLOWBROOK	651 Willowbrook Road Suite 101	Staten Island	NY	10314
Quest Diagnostics - EMERSON	452 Old Hook Rd Suite 1A	Emerson	NJ	07630
Quest Diagnostics - Port Washington PSC	14 Vanderventer Ave Suite 105	Port Washington	NY	11050
Quest Diagnostics - Cedarhurst PSC	222 Rockaway Tpke, Suite 5	Cedarhurst	NY	11516
Quest Diagnostics - STATEN ISLAND - 2627A HYLAN	2627a Hylan Blvd	Staten Island	NY	10306
Quest Diagnostics - Roslyn Heights PSC	One Expressway Plaza Suite 116	Roslyn Heights	NY	11577
Quest Diagnostics - Mineola PSC	156 First Street Lower Level	Mineola	NY	11501
Quest Diagnostics - Totowa	500 Union Blvd	Totowa	NJ	07512
Quest Diagnostics - Roselle	711 E 1st Ave Store #17	Roselle	NJ	07203
Quest Diagnostics - Ridgewood	127 Union St	Ridgewood	NJ	07450
Quest Diagnostics - STATEN ISLAND - 3311 HYLAN	3311 Hylan Blvd	Staten Island	NY	10306

Quest Diagnostics - Garden City PSC	520 Franklin Ave Suite 104	Garden City	NY	11530
Quest Diagnostics - Hempstead PSC	230 Hilton Avenue Room 220	Hempstead	NY	11550
Quest Diagnostics - Tappan	111 Route 303 Ste 109	Tappan	NY	10983
Quest Diagnostics - UNION-CHESTNUT	440 Chestnut St Unit 102	Union	NJ	07083
Quest Diagnostics - Rockville Centre PSC	165 North Village Avenue Suite 103	Rockville Centre	NY	11570
Quest Diagnostics - UNION-MORRIS	2333 Morris Ave Ste A-121	Union	NJ	07083
Quest Diagnostics - North Haledon	535 High Mountain Rd	North Haledon	NJ	07508
Quest Diagnostics - West Orange	769 Northfield Ave Ste LI3	West Orange	NJ	07052
Quest Diagnostics - Glen Cove PSC	Three Village Square	Glen Cove	NY	11542
Quest Diagnostics - Livingston	349 E Northfield Rd Ste 203	Livingston	NJ	07039
Quest Diagnostics - Wayne	401 Hamburg Tpke Ste 203	Wayne	NJ	07470
Quest Diagnostics - STATEN ISLAND - RICHMOND AVEN	3733 Richmond Ave	Staten Island	NY	10312
Quest Diagnostics - White Plains	280 Dobbs Ferry Rd Sprain Brook Medical Center	White Plains	NY	10607
Quest Diagnostics - Staten Island 4855 Hylan Blvd	4855 Hylan Blvd	Staten Island	NY	10312
Quest Diagnostics - Freeport PSC	101 South Bergen Place 2nd Floor	Freeport	NY	11520
Quest Diagnostics - Rye Brook	14 Rye Ridge Plz Ste 155	Rye Brook	NY	10573
Quest Diagnostics - Tarrytown	200 South Broadway Suite 102	Tarrytown	NY	10591
Quest Diagnostics - Westfield	189 Elm St Lower Level	Westfield	NJ	07090
Quest Diagnostics - Staten Island - Tottenville	7001 Amboy Road, Store A-4 Tottenville Square Shopping Center	Staten Island	NY	10307
Quest Diagnostics - Nanuet	420 Nanuet Mall S Unit 307	Nanuet	NY	10954
Quest Diagnostics - Ramsey	500 N Franklin Tpke Fl 2	Ramsey	NJ	07446
Quest Diagnostics - Syosset PSC	175 Jericho Turnpike Suite 304	Syosset	NY	11791
Quest Diagnostics - Greenwich-Deerfield Dr	2 1/2 Dearfield Dr	Greenwich	CT	06831
Quest Diagnostics - Bethpage PSC	4276 Hempstead Tpke	Bethpage	NY	11714
Quest Diagnostics - Seaford PSC	850 Hicksville Road Suite 114	Seaford	NY	11783
Quest Diagnostics - Edison-James Street	102 James St Suite 201	Edison	NJ	08820
Quest Diagnostics - Plainview PSC	146A Manetto Hill Rd. Suite 101	Plainview	NY	11803
Quest Diagnostics - Suffern	Indian Rock Shopping Center Route 59 & Hemion Road	Suffern	NY	10901
Quest Diagnostics - Edison - Amboy Avenue	1199 Amboy Ave # Storea-4	Edison	NJ	08837
Quest Diagnostics - BUTLER	1395 Route 23S Unit C-1	Butler	NJ	07405
Quest Diagnostics - South Plainfield	904 Oak Tree Ave Ste K	South Plainfield	NJ	07080
Quest Diagnostics - PLEASANTVILLE	174 Marble Ave Ste 1	Pleasantville	NY	10570
Quest Diagnostics - Parsippany	50 Cherry Hill Rd Ste 103	Parsippany	NJ	07054
Quest Diagnostics - HAZLET	1 Bethany Rd Building 5, Suite 67	Hazlet	NJ	07730
Quest Diagnostics - New City	151 N Main St Unit 307	New City	NY	10956
Quest Diagnostics - Morristown	101 Madison Ave Ste 101	Morristown	NJ	07960
Quest Diagnostics - PSC-Cedar Knolls	8 Saddle Rd Suite 204	Cedar Knolls	NJ	07927
Quest Diagnostics - Massapequa Park PSC	Southgate Shopping Center 4900 Merrick Road, 2nd Floor	Massapequa Park	NY	11762
Quest Diagnostics - Pomona	978 Route 45 Ste 202	Pomona	NY	10970
Quest Diagnostics - HOLMDEL	704 N Beers St	Holmdel	NJ	07733
Quest Diagnostics - Denville	Main Street (Route 53) and Luger Road	Denville	NJ	07834

Quest Diagnostics - Stamford-Mill River	80 Mill River Street	Stamford	CT	06902
Quest Diagnostics - Red Bank	240 Maple Ave	Red Bank	NJ	07701
Quest Diagnostics - Stamford-Summer Street	1250 Summer St Ste 203	Stamford	CT	06905
Quest Diagnostics - Pulaski Road PSC	180 E Pulaski Rd	Huntington Station	NY	11746
Quest Diagnostics - LITTLE SILVER	200 White Rd Ste 104 Little Silver Commons	Little Silver	NJ	07739
Quest Diagnostics - Huntington PSC	195 E Main St Suite D	Huntington	NY	11743
Quest Diagnostics - Warren	37 Mountain Blvd Suite #5	Warren	NJ	07059
Quest Diagnostics - New Brunswick	77 Church Street	New Brunswick	NJ	08901
Quest Diagnostics - Stamford-Buxton Farm Rd.	30 Buxton Farm Rd	Stamford	CT	06905
Quest Diagnostics - Mt Kisco	83 South Bedford Road Floor 3	Mt. Kisco	NY	10549
Quest Diagnostics - EAST BRUNSWICK	1020 Route 18 Unit 007 - Route 18 Shopping Center	East Brunswick	NJ	08816
Quest Diagnostics - PSC-Bernardsville	1 Anderson Rd Ste 101	Bernardsville	NJ	07924
Quest Diagnostics - Randolph	477 Route 10 East Suite 203	Randolph	NJ	07801
Quest Diagnostics - Babylon PSC	400 Montauk Hwy Suite 116	Babylon	NY	11702
Quest Diagnostics - Darien	557 Post Rd	Darien	CT	06820
Quest Diagnostics - PSC-BOUND BROOK	601 West Union Ave.	Bound Brook	NJ	08805
Quest Diagnostics - Somerset	49 Veronica Ave Ste 203	Somerset	NJ	08873
Quest Diagnostics - Oakhurst	1900 Highway 35, Suite 101 Ocean Park Cente	Oakhurst	NJ	07755
Quest Diagnostics - Commack PSC	2171 Jericho Turnpike Suite 102	Commack	NY	11725
Quest Diagnostics - MANALAPAN	46-50 Franklin Lane, Suite 202	Manalapan	NJ	07726
Quest Diagnostics - Peekskill	2 Stowe Rd 5th Floor - Suite 15	Peekskill	NY	10566
Quest Diagnostics - Norwalk-148 East Ave	148 East Avenue	Norwalk	CT	06851
Quest Diagnostics - Norwalk Cross St	40 Cross St	Norwalk	CT	06851
Quest Diagnostics - Norwalk-91 East Ave	91 East Ave	Norwalk	CT	06851
Quest Diagnostics - Bay Shore PSC	8 Saxon Avenue, Suite D	Bay Shore	NY	11706
Quest Diagnostics - Neptune	1809 Corlies Ave Floor 2	Neptune	NJ	07753
Quest Diagnostics - Jamesburg	333 Forsgate Dr Ste 203	Jamesburg	NJ	08831
Quest Diagnostics - Hauppauge PSC	490 Wheeler Rd. Suite 190	Hauppauge	NY	11788
Quest Diagnostics - Brooksite Drive PSC	9 Brooksite Drive	Smithtown	NY	11787
Quest Diagnostics - FREEHOLD	260 Mounts Corner Drive	Freehold	NJ	07728
Quest Diagnostics - Smithtown PSC	222 Middle Country Road Suite 107	Smithtown	NY	11787
Quest Diagnostics - Ridgefield	38a Grove St	Ridgefield	CT	06877
Quest Diagnostics - Howell	400 Candlewood Commons, Bldg. 4	Howell	NJ	07731
Quest Diagnostics - Fairfield-Post Road	1305 Post Rd Ste 101	Fairfield	CT	06824
Quest Diagnostics - CARMEL	Barns Office Center - 667 Stoneleigh Ave Bldg N, Suite 115	Carmel	NY	10512
Quest Diagnostics - West Sayville PSC	The Bayview Building 233 Montauk Highway	West Sayville	NY	11796
Quest Diagnostics - Princeton	601 Ewing St Suite C-22	Princeton	NJ	08540
Quest Diagnostics - Hackettstown	137 Mountain Ave Ste 2	Hackettstown	NJ	07840
Quest Diagnostics - East Setauket PSC	100-10 South Jersey Avenue Heritage Square, Suite 10	East Setauket	NY	11733
Quest Diagnostics - East Setauket PSC	23 Technology Dr. Suite 2	East Setauket	NY	11733

Quest Diagnostics - Fairfield-Black Rock	2150 Black Rock Turnpike	Fairfield	CT	06825
Quest Diagnostics - PSC-Brewster	Clock Tower Commons, 601 Route 22	Brewster	NY	10509
Quest Diagnostics - Goshen	30 Hatfield Ln	Goshen	NY	10924
Quest Diagnostics - PSC-BRICK	1608 Route 88 Ste 114	Brick	NJ	08724
Quest Diagnostics - Selden PSC	235 Boyle Rd	Selden	NY	11784
Quest Diagnostics - Trumbull -Park Ave	5520 Park Ave	Trumbull	CT	06611
Quest Diagnostics - Port Jefferson PSC	1010 Route 112 2nd Floor	Port Jefferson Station	NY	11776
Quest Diagnostics - Bridgeport-2660 Main St	2660 Main St	Bridgeport	CT	06606
Quest Diagnostics - Bridgeport-Beechmont	3180 Main St Beechmont Building	Bridgeport	CT	06606
Quest Diagnostics - Bridgeport-Commerce Park	4695 Main St	Bridgeport	CT	06606
Quest Diagnostics - FLEMINGTON	309 WALTER E. FORAN BLVD. TOWNE CENTRE	FLEMINGTON	NJ	08822
Quest Diagnostics - Stratford-Lordship	555 Lordship Blvd	Stratford	CT	06615
Quest Diagnostics - Bridgeport-1450 Barnum Ave	1450 Barnum Ave	Bridgeport	CT	06610
Quest Diagnostics - Newburgh	347 Fullerton Ave	Newburgh	NY	12550
Quest Diagnostics - Trumbull-White Plains Rd	888 White Plains Rd	Trumbull	CT	06611
Quest Diagnostics - Danbury-Germantown	7 Germantown Rd	Danbury	CT	06810
Quest Diagnostics - Medford PSC	570 Expressway Dr S Suite1-J	Medford	NY	11763
Quest Diagnostics - Lawrenceville PSC	168 Franklin Corner Rd Bldg. 2, Suite 1D	Lawrenceville	NJ	08648
Quest Diagnostics - East Patchogue PSC	Brookhaven Professional Park 285 Sills Road, Building 8, Suite A	East Patchogue	NY	11772
Quest Diagnostics - Fishkill	982 Main St Ste 9	Fishkill	NY	12524
Quest Diagnostics - Stratford-Main Street	2890 Main Street	Stratford	CT	06614
Quest Diagnostics - Trumbull-Technology Dr	115 Technology Dr	Trumbull	CT	06611
Quest Diagnostics - Bethel	83b Stony Hill Rd	Bethel	CT	06801
Quest Diagnostics - Hamilton	1225 Whitehorse Mercerville Rd Suite 201	Hamilton	NJ	08619
Quest Diagnostics - Milford-Bridgeport Ave	2044 Bridgeport Avenue	Milford	CT	06460
Quest Diagnostics - Milford-Noble Ave	88 Noble Ave	Milford	CT	06460
Quest Diagnostics - Trenton	Lexington Mews Office Center 795 Parkway Avenue Unit A-7	Trenton	NJ	08618
Quest Diagnostics - TOMS RIVER COMMONS	548 Commons Way Bldg E	Toms River	NJ	08755
Quest Diagnostics - Shelton	515 Bridgeport Ave	Shelton	CT	06484
Quest Diagnostics - Toms River 2	600 Mule Road, Unit 24A	Toms River	NJ	08755
Quest Diagnostics - Derby	299 Seymour Ave	Derby	CT	06418
Quest Diagnostics - Wading River PSC	6144 Route 25A Building B, Suite 8	Wading River	NY	11792
Quest Diagnostics - Center Moriches PSC	760-8 Montauk Highway	Center Moriches	NY	11934
Quest Diagnostics - Ansonia	158 Main St	Ansonia	CT	06401
Quest Diagnostics - Southbury	385 Main St S	Southbury	CT	06488

Quest Diagnostics - Fairless Hills	333 N Oxford Valley Road Suite 203	Fairless Hills	PA	19030
Quest Diagnostics - Langhorne	586 Middletown Blvd Suite C-11	Langhorne	PA	19047
Quest Diagnostics - West Haven-Main Street	385 Main Street	West Haven	CT	06516
Quest Diagnostics - West Haven-Campbell Avenue	687 Campbell Avenue	West Haven	CT	06516
Quest Diagnostics - Woodbourne	1609 Woodbourne Rd	Levittown	PA	19057
Quest Diagnostics - Poughkeepsie - South Avenue	205 South Ave Ste 203	Poughkeepsie	NY	12601
Quest Diagnostics - New Milford	120 Park Ln	New Milford	CT	06776
Quest Diagnostics - New Haven-Orchard Street	200 Orchard St	New Haven	CT	06511
Quest Diagnostics - New Haven-Sherman Avenue	136 Sherman Avenue, Suite 02	New Haven	CT	06511
Quest Diagnostics - New Haven-Church Street	2 Church St S Ste 115	New Haven	CT	06519
Quest Diagnostics - New Haven-Temple Street	60 Temple Street Temple Medical Building	New Haven	CT	06510
Quest Diagnostics - Bangor	418 Blue Valley Drive Route 512	Bangor	PA	18013
Quest Diagnostics - Poughkeepsie-Dutchess Tpke	695 Dutchess Tpke Suite 102	Poughkeepsie	NY	12603
Quest Diagnostics - East Stroudsburg	314 Lincoln Avenue Pocono Plaza	East Stroudsburg	PA	18301
Quest Diagnostics - Riverhead PSC	74 Commerce Drive, Suite 2	Riverhead	NY	11901
Quest Diagnostics - East Haven	190 Main Street	East Haven	CT	06512
Quest Diagnostics - Richboro	130 Almshouse Rd	Richboro	PA	18954
Quest Diagnostics - New Paltz	Cherry Hill Plaza 246 Main Street, Suite 202	New Paltz	NY	12561
Quest Diagnostics - Easton- 22nd Street	229 S 22nd St	Easton	PA	18042
Quest Diagnostics - Doylestown	Routes 313 & 611 Baliwick Campus, Suite 45	Doylestown	PA	18901
Quest Diagnostics - Street Road	210 E. Street Road 3rd Floor, Ste 3D	Feasterville	PA	19053
Quest Diagnostics - Hamden-Whitney Avenue	2200 Whitney Ave Ste 210	Hamden	CT	06518
Quest Diagnostics - Rancocas Valley PSC	220 Sunset Rd Suite 5D	Willingboro	NJ	08046
Quest Diagnostics - Branford-1008 Main St	1008 Main St	Branford	CT	06405
Quest Diagnostics - Easton-	3601 Nazareth Rd	Easton	PA	18045
Quest Diagnostics - Hamden-Dixwell	3000 Dixwell Ave	Hamden	CT	06518
Quest Diagnostics - Branford-144 North Main St	144 North Main St	Branford	CT	06405
Quest Diagnostics - Hyde Park	7 Pine Woods Rd Suite #6	Hyde Park	NY	12538
Quest Diagnostics - North Haven	12 Village St Ste 103	North Haven	CT	06473
Quest Diagnostics - Mount Holly	1613 Route 38	Lumberton	NJ	08060
Quest Diagnostics - Waterbury-West Main Street	1389 West Main Street, Suite 125	Waterbury	CT	06708
Quest Diagnostics - Nazareth	25 Soute Broad Street Suite 102	Nazareth	PA	18064
Quest Diagnostics - Bethlehem-Reeve Drive	4333 Easton Ave Suite A	Bethlehem	PA	18020
Quest Diagnostics - Waterbury-Westwood	60 Westwood Avenue	Waterbury	CT	06708

Ave				
Quest Diagnostics - Prospect	166 Waterbury Rd	Prospect	CT	06712
Quest Diagnostics - Bustleton	9808 Bustleton Avenue	Philadelphia	PA	19115
Quest Diagnostics - Waterbury East Main	2457 E Main St	Waterbury	CT	06705
Quest Diagnostics - Manahawkin	1322 Route 72 West, Suite 202 Corner of Barnacle Dr.	Manahawkin	NJ	08050
Quest Diagnostics - Cheshire	673 S Main St	Cheshire	CT	06410
Quest Diagnostics - Welsh Road	2417 Welsh Rd	Philadelphia	PA	19114
Quest Diagnostics - Hellertown	The Shoppes at Hellertown 25 Main Street	Hellertown	PA	18055
Quest Diagnostics - Horsham	200 Lakeside Dr Ste 230	Horsham	PA	19044
Quest Diagnostics - Chalfont PSC	1700 Horizon Dr Suite 205	Chalfont	PA	18914
Quest Diagnostics - Medford	175 Route 70	Medford	NJ	08055
Quest Diagnostics - Abington PSC	1419 Old York Rd	Abington	PA	19001
Quest Diagnostics - Frankford Avenue	7526 Frankford Ave	Philadelphia	PA	19136
Quest Diagnostics - Bethlehem- Delaware Avenue	406 Delaware Ave	Bethlehem	PA	18015
Quest Diagnostics - Wallingford-South Elm Street	15 South Elm Street	Wallingford	CT	06492
Quest Diagnostics - Guilford	669 Boston Post Rd	Guilford	CT	06437
Quest Diagnostics - Cottman Avenue PSC	700 Cottman Ave	Philadelphia	PA	19111
Quest Diagnostics - Moorestown	502 Pleasant Valley Ave	Moorestown	NJ	08057
Quest Diagnostics - Hidden Meadow	2131 N Broad St	Lansdale	PA	19446
Quest Diagnostics - Bethlehem- Westgate Dr	2045 Westgate Dr Bldg Ste104	Bethlehem	PA	18017
Quest Diagnostics - Roosevelt Plaza	6555 Roosevelt Blvd.	Philadelphia	PA	19149
Quest Diagnostics - Quakertown	1532 Park Ave Suite 103.	Quakertown	PA	18951
Quest Diagnostics - Thomaston	130 S Main St	Thomaston	CT	06787
Quest Diagnostics - Souderton Square	708 Route 113	Souderton	PA	18964
Quest Diagnostics - Wallingford-North Main	850 North Main Street Ext	Wallingford	CT	06492
Quest Diagnostics - Marlton	4 Eves Dr # A	Marlton	NJ	08053
Quest Diagnostics - Maple Shade	19 W Main St	Maple Shade	NJ	08052
Quest Diagnostics - Juniata	4501 Castor Ave	Philadelphia	PA	19124
Quest Diagnostics - Madison	11 Woodland Road	Madison	CT	06443
Quest Diagnostics - Lansdale	1050 S Broad St	Lansdale	PA	19446
Quest Diagnostics - Cherry Hill PSC	1040 Kings Hwy Suite 102	Cherry Hill	NJ	08034
Quest Diagnostics - Kingston-Washington Avenue	380 Washington Ave Suite A	Kingston	NY	12401
Quest Diagnostics - Kingston - Grand Street	5 Grand St	Kingston	NY	12401
Quest Diagnostics - Southington	55 Meriden Avenue, Suite 1F	Southington	CT	06489
Quest Diagnostics - Flourtown	1107 Bethlehem Pike	Flourtown	PA	19031
Quest Diagnostics - Germantown	2 Penn Blvd Suite 205	Philadelphia	PA	19144
Quest Diagnostics - Meriden	816 Broad Street, Ste 22	Meriden	CT	06450
Quest Diagnostics - Allen Street	1608 W Allen St	Allentown	PA	18102
Quest Diagnostics - Torrington	30 Peck Rd	Torrington	CT	06790
Quest Diagnostics - Haddonfield PSC	807 Haddon Ave	Haddonfield	NJ	08033
Quest Diagnostics	Cooper River Plaza West 6981	Pennsauken	NJ	08109

	North Park Drive Suite 203			
Quest Diagnostics - Voorhees	1010 Haddonfield Berlin Rd Suite 400	Voorhees	NJ	08043
Quest Diagnostics - Harleysville	484 Harleysville Pike	Harleysville	PA	19438
Quest Diagnostics - Camden County UDS	1101 White Horse Rd	Voorhees	NJ	08043
Quest Diagnostics - Roxborough	525 Jamestown St	Philadelphia	PA	19128
Quest Diagnostics - Emmaus	1040 Chestnut St	Emmaus	PA	18049
Quest Diagnostics - Cedar Crest	1251 S Cedar Crest Blvd	Allentown	PA	18103
Quest Diagnostics - Haddon Heights	515 Grove Street Suite 1 A	Haddon Heights	NJ	08035
Quest Diagnostics - Bristol	935 Farmington Avenue	Bristol	CT	06010
Quest Diagnostics - Red Hook	7385 S Broadway 2nd Floor	Red Hook	NY	12571
Quest Diagnostics - Norristown PSC	720--730 E Johnson Highway	Norristown	PA	19401
Quest Diagnostics - North Broad Street	227 N. Broad St	Philadelphia	PA	19107
Quest Diagnostics - Walnut St PSC	828 Walnut St	Philadelphia	PA	19107
Quest Diagnostics - Bala Cynwyd	4190 City Avenue - Ste. 416	Philadelphia	PA	19131
Quest Diagnostics - Stratford	215 E Laurel Rd Suite 102	Stratford	NJ	08084
Quest Diagnostics	1437 Dekalb St	Norristown	PA	19401
Quest Diagnostics - East Greenville	622 Gravel Pike	East Greenville	PA	18041
Quest Diagnostics - S. Broad Street	2219 S Broad St	Philadelphia	PA	19148
Quest Diagnostics - New Britain	40 Hart Street, Building C	New Britain	CT	06052
Quest Diagnostics - Middletown	400 Saybrook Rd	Middletown	CT	06457
Quest Diagnostics - Hammonton PSC	777 White Horse Pike Ste D3	Hammonton	NJ	08037
Quest Diagnostics - KOP	491 Allendale Road Ste300	King Of Prussia	PA	19406
Quest Diagnostics - Collegeville	555 2nd Ave	Collegeville	PA	19426
Quest Diagnostics - Trappe	545 W Main St	Collegeville	PA	19426
Quest Diagnostics - Woodbury	730 N Broad St Suite 125	Woodbury	NJ	08096
Quest Diagnostics	1012 W 9th Avenue 1st Floor	King of Prussia	PA	19406
Quest Diagnostics - Liberty Town Plaza	412 Sicklerville Rd Ste 106	Sicklerville	NJ	08081
Quest Diagnostics - Farmington	399 Farmington Ave	Farmington	CT	06032
Quest Diagnostics - Saugerties	330 Route 212 - Grand Union Plaza	Saugerties	NY	12477
Quest Diagnostics - Old Saybrook	929 Boston Post Road	Old Saybrook	CT	06475
Quest Diagnostics - Havertown	2010 W Chester Pike	Havertown	PA	19083
Quest Diagnostics - Turnersville	188 Fries Mill Rd Bldg. H	Turnersville	NJ	08012
Quest Diagnostics - Newington	955 Main St	Newington	CT	06111
Quest Diagnostics - Essex	7 Wildwood Wildwood Medical Building	Essex	CT	06426
Quest Diagnostics - Sewell	302 Hurffville Crosskeys Rd Suite A-2	Sewell	NJ	08080
Quest Diagnostics - Devon	227 W Lancaster Ave	Devon	PA	19333
Quest Diagnostics - Avon	54 W Avon Rd	Avon	CT	06001
Quest Diagnostics - Gilbertsville	1050 E Philadelphia Ave	Gilbertsville	PA	19525
Quest Diagnostics - Oaks	Oaks Corporate Center 450 Cresson Boulevard, Suite 305	Phoenixville	PA	19460
Quest Diagnostics - Absecon	76 W Jimmie Leeds Rd Ste 403	Galloway	NJ	08205
Quest Diagnostics - West Hartford-Farmington Ave	970 Farmington Ave	West Hartford	CT	06107
Quest Diagnostics - Springfield	1001 Baltimore Pike Suite 9	Springfield	PA	19064
Quest Diagnostics - Wethersfield	465 Silas Deane Highway	Wethersfield	CT	06109
Quest Diagnostics - West Hartford-No Main	345 N Main St	West Hartford	CT	06117

Quest Diagnostics - Pottstown PSC	1569 Medical Dr	Pottstown	PA	19464
Quest Diagnostics - MacDade Blvd	501 W MacDade Boulevard	Folsom	PA	19033
Quest Diagnostics - Paoli PSC	15 Industrial Blvd Ste Suite A-101	Paoli	PA	19301
Quest Diagnostics - Hartford-19 Woodland	19 Woodland Street, Ste 14	Hartford	CT	06105
Quest Diagnostics - Hartford-21 Woodland St.	21 Woodland St	Hartford	CT	06105
Quest Diagnostics - Hartford-Retreat	100 Retreat Avenue	Hartford	CT	06106
Quest Diagnostics - Simsbury	381 Hopmeadow Street	Simsbury	CT	06070
Quest Diagnostics - Glastonbury-N.L. Turnpike	131 New London Turnpike	Glastonbury	CT	06033
Quest Diagnostics - Bloomfield Cottage Grove	701 Cottage Grove Rd Bldg B, Suite 130	Bloomfield	CT	06002
Quest Diagnostics - Glastonbury-Western Blvd	320-B Western blvd	Glastonbury	CT	06033
Quest Diagnostics - East Hartford	477 Connecticut Boulevard, Ste 213	East Hartford	CT	06108
Quest Diagnostics - Marlborough	3-5 E Hampton Rd Unit 8	Marlborough	CT	06447
Quest Diagnostics - Mays Landing	5429 Harding Hwy Suite 102	Mays Landing	NJ	08330

<b>EDIC CLINIC 04 – Henry Ford</b>				
Quest Diagnostics - Dearborn PSC	3735 Monroe St Suite C	Dearborn	MI	48124
Quest Diagnostics - Clawson PSC	555 W 14 Mile Rd Suite B1	Clawson	MI	48017
Quest Diagnostics - Troy Dequindre Rd PSC	38815 Dequindre Rd Suite 102	Troy	MI	48083
Quest Diagnostics - Taylor PSC	12701 Telegraph Rd Suite 104	Taylor	MI	48180
Quest Diagnostics - Livonia Farmington PSC	11583 Farmington Rd	Livonia	MI	48150
Quest Diagnostics - Clinton Township Harper PSC	36535 Harper Ave Suite G	Clinton Township	MI	48035
Quest Diagnostics - Clinton TWP Dalcoma PSC	43475 Dalcoma Dr Suite 135	Clinton Township	MI	48038
Quest Diagnostics - Bloomfield Hills Woodward PSC	43700 Woodward Ave Suite 101	Bloomfield Hills	MI	48302
Quest Diagnostics - Rochester Barclay PSC	135 Barclay Circle Suite 103	Rochester	MI	48307
Quest Diagnostics - Canton PSC	2050 S Haggerty Rd Suite 240	Canton	MI	48188
Quest Diagnostics - Novi PSC	40015 Grand River Road Suite 115	Novi	MI	48375
Quest Diagnostics - Rochester Livernois PSC	455 S Livernois Rd Suite A-14	Rochester	MI	48307
Quest Diagnostics - Waterford Oakland PSC	1255 N Oakland Blvd Suite 135	Waterford	MI	48327
Quest Diagnostics - Clarkston Main PSC	5825 Ortonville Rd Suite 202	Clarkston	MI	48346
Quest Diagnostics - Ypsilanti PSC	2144 Washtenaw Rd	Ypsilanti	MI	48197
Quest Diagnostics - Monroe PSC	743 N Monroe St	Monroe	MI	48162
Quest Diagnostics - Fenton Caroline PSC	234 Caroline Street	Fenton	MI	48430
Quest Diagnostics - Grand Blanc Holly Rd PSC	8447 Holly Rd	Grand Blanc	MI	48439
Quest Diagnostics - Lapeer Davison Rd PSC	3273 Davison Rd Suite 6	Lapeer	MI	48446
Quest Diagnostics - Lapeer Davis Lake Rd PSC	237 Davis Lake Rd	Lapeer	MI	48446
Quest Diagnostics - Grand Blanc Porter PSC	6011 Porter Rd	Grand Blanc	MI	48439
Quest Diagnostics - Davison PSC	1094 S State Rd	Davison	MI	48423
Quest Diagnostics - Burton South Belsay PSC	1096 S Belsay Rd Ste H	Burton	MI	48509
Quest Diagnostics - Burton East Court PSC	4067 East Court St Suite 4	Burton	MI	48509
Quest Diagnostics - Toledo Sunforest PSC	3950 Sunforest Court Suite 100	Toledo	OH	43623
Quest Diagnostics - Flint N Ballenger(Park Plaza)RRLPSC	G1071 N Ballenger Hwy Suite 101	Flint	MI	48504
Quest Diagnostics - Flint Villa Linde Parkway PSC	5080 Villa Linde Parkway Suite 3	Flint	MI	48532
Quest Diagnostics - Mt Morris PSC	11515 N Saginaw St	Mount Morris	MI	48458
Quest Diagnostics - Maumee PSC	1679 Lance Pointe Rd Suite B	Maumee	OH	43537
Quest Diagnostics - Brooklyn PSC	107 Chicago St	Brooklyn	MI	49230
Quest Diagnostics - Jackson PSC	300 W Washington Ave	Jackson	MI	49201
Quest Diagnostics - Frankenmuth PSC	487 N Main St Suite E	Frankenmuth	MI	48734

Quest Diagnostics - Lansing Genesis Park PSC	3955 Patient Care Drive Suite C	Lansing	MI	48910
Quest Diagnostics - Bridgeport PSC	6185 Dixie Hwy Center Suite	Bridgeport	MI	48722
Quest Diagnostics - Saginaw N Michigan Valley PSC	926 N Michigan Ave	Saginaw	MI	48602
Quest Diagnostics - Saginaw North Michigan PSC	1203 N Michigan Ave	Saginaw	MI	48602
Quest Diagnostics - Westlake	24551 Detroit Rd Ste 4	Westlake	OH	44145
Quest Diagnostics - Saginaw Shattuck PSC	3550 Shattuck Rd Suite C	Saginaw	MI	48603
Quest Diagnostics - Saginaw Center RRL/PSC	2062 N Center Rd	Saginaw	MI	48603
Quest Diagnostics - Saginaw Towne Centre PSC	4705 Town Centre Rd Medical Arts Building--Lower Level	Saginaw	MI	48604
Quest Diagnostics - Fairview Park	20455 Lorain Rd Ste T02	Fairview Park	OH	44126
Quest Diagnostics - Grand Ledge PSC	11615 S. Hartel Rd	Grand Ledge	MI	48837
Quest Diagnostics - Bay City Trumbull PSC	714 S Trumbull St Tuscola Professional Building	Bay City	MI	48708
Quest Diagnostics - Middleburg Heights	18660 Bagley Rd, Ste 104	Middleburg Heights	OH	44130
Quest Diagnostics - Bay City Wenona PSC	200 S Wenona St	Bay City	MI	48706
Quest Diagnostics - Bay City Katalin PSC	3720 Katalin Ct	Bay City	MI	48706
Quest Diagnostics - Parma	7441 W Ridgewood Dr Ste 100	Parma	OH	44129

**EDIC CLINIC 05 - Joslin**

Quest Diagnostics - Longwood PSC	319 Longwood Ave	Boston	MA	02115
Quest Diagnostics - Brookline	1101 Beacon St 1st floor	Brookline	MA	02446
Quest Diagnostics - 1180 Beacon Street	1180 Beacon St Ste D	Brookline	MA	02446
Quest Diagnostics - 1BP	1 Brookline Pl Ste 301	Brookline	MA	02445
Quest Diagnostics - Mt. Auburn PSC	575 Mount Auburn St B103	Cambridge	MA	02138
Quest Diagnostics - Melrose	50 Tremont St	Melrose	MA	02176
Quest Diagnostics - Truman Parkway	695 Truman Pkwy Suite 205	Hyde Park	MA	02136
Quest Diagnostics - School St.	21 School St	Quincy	MA	02169
Quest Diagnostics - Crown Colony	500 Congress St Ste 1e	Quincy	MA	02169
Quest Diagnostics - Lynn PSC	225 Boston St	Lynn	MA	01904
Quest Diagnostics - Braintree	340 Wood Rd, Suite 302	Braintree	MA	02184
Quest Diagnostics - Weymouth	73 Pleasant St	S. Weymouth	MA	02190
Quest Diagnostics - Danvers	140 Commonwealth Ave	Danvers	MA	01923
Quest Diagnostics - Cohasset	223 Chief Justice Cushing Hwy	Cohasset	MA	02025
Quest Diagnostics - Norwood	335 Morse St	Norwood	MA	02062
Quest Diagnostics - Cummings Center	900 Cummings Ctr, Suite 126R & 124S Route 62	Beverly	MA	01915
Quest Diagnostics - Hanover	135 Webster St	Hanover	MA	02339
Quest Diagnostics - Rockland	214 Market St	Rockland	MA	02370
Quest Diagnostics - Route 9 West	255 Worcester Road RT. 9 West	Framingham	MA	01701
Quest Diagnostics - Concord St. Framingham	655 Concord St	Framingham	MA	01701

Quest Diagnostics - Walpole	1426 Main Street Suite 3	Walpole	MA	02081
Quest Diagnostics - Billerica	221 Boston Rd, Suite 1	Billerica	MA	01862
Quest Diagnostics - Brockton	225 Quincy Ave	Brockton	MA	02302
Quest Diagnostics - Andover PSC	138 Haverhill St	Andover	MA	01810
Quest Diagnostics - Chelmsford	39 Village Square	Chelmsford	MA	01824
Quest Diagnostics - Foxboro	10 Commercial St	Foxboro	MA	02035
Quest Diagnostics - Pleasant St, N Andover	170 Pleasant St	North Andover	MA	01845
Quest Diagnostics - Branch Street - Methuen	9 Branch St	Methuen	MA	01844
Quest Diagnostics - Merrimack St - Methuen	421 Merrimack St	Methuen	MA	01844
Quest Diagnostics - Wrentham PSC	667 South St Wampum Corner	Wrentham	MA	02093
Quest Diagnostics - Haverhill	161 Summer St	Haverhill	MA	01830
Quest Diagnostics - Salem NH	45 Stiles Rd Ste 102	Salem	NH	03079
Quest Diagnostics - Main Street Nashua	300 Main St	Nashua	NH	03060
Quest Diagnostics - Londonderry	6 Buttrick Rd Ste 200	Londonderry	NH	03053
Quest Diagnostics	333 School St	Pawtucket	RI	02860
Quest Diagnostics - East Ave	407 East Ave	Pawtucket	RI	02860
Quest Diagnostics - Hospital Road	100 Hospital Rd Ste 2b	Leominster	MA	01453
Quest Diagnostics - Memorial Drive	50 Memorial Dr	Leominster	MA	01453
Quest Diagnostics - Derry RRL	6 Tsienneto Road LL102	Derry	NH	03038
Quest Diagnostics - Central St, Worcester	100 Central St	Worcester	MA	01608
Quest Diagnostics - Winthrop St, Worcester	10 Winthrop St	Worcester	MA	01604
Quest Diagnostics - Summit	100 Highland Ave Suite 305	Providence	RI	02906
Quest Diagnostics - Randall	1 Randall Sq	Providence	RI	02904
Quest Diagnostics - Summer St - Fitchburg	76 Summer St	Fitchburg	MA	01420
Quest Diagnostics	1352 Smith St	Providence	RI	02911
Quest Diagnostics - Veterans Memorial	450 Veterans Memorial Parkway Building 8	East Providence	RI	02914
Quest Diagnostics - Plain Street PSC	235 Plain St	Providence	RI	02905
Quest Diagnostics - Fitchburg - Ashby St.	47 Ashby State Rd	Fitchburg	MA	01420
Quest Diagnostics - Johnston	1524 Atwood Ave	Johnston	RI	02919
Quest Diagnostics - Truesdale RRL	1030 President Ave Basement	Fall River	MA	02720
Quest Diagnostics	1681 Cranston St	Cranston	RI	02920
Quest Diagnostics - Wareham	106 Main Street	Wareham	MA	02571
Quest Diagnostics - Reservoir Ave	1145 Reservoir Ave	Cranston	RI	02920
Quest Diagnostics	999 Warwick Ave	Warwick	RI	02888
Quest Diagnostics - Manchester, NH	195 McGregor St. Center Entrance	Manchester	NH	03102
Quest Diagnostics - Portsmouth, NH	200 Griffin Rd Unit 12	Portsmouth	NH	03801
Quest Diagnostics - North Dartmouth	49 State Rd Suite 202	North Dartmouth	MA	02747
Quest Diagnostics	215 Toll Gate Rd Ste 102	Warwick	RI	02886
Quest Diagnostics	300 Toll Gate Rd Ste LI5	Warwick	RI	02886
Quest Diagnostics - North Falmouth PSC	39 Edgerton Dr	North Falmouth	MA	02556
Quest Diagnostics - Dover, NH	750 Central Ave Unit B	Dover	NH	03820
Quest Diagnostics - Bramblebush Park	12 Bramblebush Park	Falmouth	MA	02540
Quest Diagnostics - Aquidneck RRL	50 Memorial Blvd	Newport	RI	02840
Quest Diagnostics - Osterville, MA	23 W Bay Rd	Osterville	MA	02655

Quest Diagnostics - Concord	280 Pleasant St	Concord	NH	03301
Quest Diagnostics - Hyannis	51 Main St	Hyannis	MA	02601
Quest Diagnostics	46 Holley St	Wakefield	RI	02879
Quest Diagnostics - Orleans	229 Cranberry Hwy	Orleans	MA	02653
Quest Diagnostics - Harwich	1421 Orleans Rd, Route 39 Ste 2	Harwich	MA	02645
Quest Diagnostics - Mansfield Center	135d Storrs Rd	Mansfield Center	CT	06250
Quest Diagnostics - Norwich-New London Turnpike	118 New London Turnpike	Norwich	CT	06360
Quest Diagnostics - Norwich-Wawecus	79 Wawecus St	Norwich	CT	06360
Quest Diagnostics - Turners Falls RRL	8 Burnham St	Turners Falls	MA	01376
Quest Diagnostics - Springfield	780 Chestnut St	Springfield	MA	01107
Quest Diagnostics - Enfield	15 Palomba Drive	Enfield	CT	06082
Quest Diagnostics - Vernon	352 Hartford Turnpike	Vernon	CT	06066
Quest Diagnostics - Enfield 54 Hazard Ave	54 Hazard Ave	Enfield	CT	06082
Quest Diagnostics - Florence RRL	190 Nonotuck St	Florence	MA	01062
Quest Diagnostics - Groton-Poheganut	85 Poheganut Drive	Groton	CT	06340
Quest Diagnostics - Groton-Gold Star	495 Gold Star Hwy Ste 220	Groton	CT	06340
Quest Diagnostics - Manchester	555 Main Street	Manchester	CT	06040
Quest Diagnostics - South Windsor	1735 Ellington Rd	South Windsor	CT	06074
Quest Diagnostics - Electric Boat Employees Only	Electric Boat Employees Only	Groton	CT	06340
Quest Diagnostics - New London Bank St	721 Bank Street	New London	CT	06320
Quest Diagnostics - Marlborough	3-5 E Hampton Rd Unit 8	Marlborough	CT	06447
Quest Diagnostics - Windsor Locks	2 Concorde Way, Suite 3A	Windsor Locks	CT	06096
Quest Diagnostics - Windsor	74 Mack Street	Windsor	CT	06095
Quest Diagnostics - Glastonbury-Western Blvd	320-B Western blvd	Glastonbury	CT	06033
Quest Diagnostics - Glastonbury-N.L. Turnpike	131 New London Turnpike	Glastonbury	CT	06033
Quest Diagnostics - East Hartford	477 Connecticut Boulevard, Ste 213	East Hartford	CT	06108
Quest Diagnostics - Hartford-Retreat	100 Retreat Avenue	Hartford	CT	06106
Quest Diagnostics - Wethersfield	465 Silas Deane Highway	Wethersfield	CT	06109
Quest Diagnostics - Bloomfield Cottage Grove	701 Cottage Grove Rd Bldg B, Suite 130	Bloomfield	CT	06002
Quest Diagnostics - Hartford-19 Woodland	19 Woodland Street, Ste 14	Hartford	CT	06105
Quest Diagnostics - Hartford-21 Woodland St.	21 Woodland St	Hartford	CT	06105
Quest Diagnostics - West Hartford-No Main	345 N Main St	West Hartford	CT	06117
Quest Diagnostics - West Hartford-Farmington Ave	970 Farmington Ave	West Hartford	CT	06107
Quest Diagnostics - Simsbury	381 Hopmeadow Street	Simsbury	CT	06070
Quest Diagnostics - Newington	955 Main St	Newington	CT	06111
Quest Diagnostics - Essex	7 Wildwood Wildwood Medical Building	Essex	CT	06426

<b>EDIC CLINIC 06 - MGH</b>				
Quest Diagnostics - Longwood PSC	319 Longwood Ave	Boston	MA	02115
Quest Diagnostics - Brookline	1101 Beacon St 1st floor	Brookline	MA	02446
Quest Diagnostics - 1180 Beacon Street	1180 Beacon St Ste D	Brookline	MA	02446
Quest Diagnostics - 1BP	1 Brookline Pl Ste 301	Brookline	MA	02445
Quest Diagnostics - Mt. Auburn PSC	575 Mount Auburn St B103	Cambridge	MA	02138
Quest Diagnostics - Melrose	50 Tremont St	Melrose	MA	02176
Quest Diagnostics - Truman Parkway	695 Truman Pkwy Suite 205	Hyde Park	MA	02136
Quest Diagnostics - School St.	21 School St	Quincy	MA	02169
Quest Diagnostics - Crown Colony	500 Congress St Ste 1e	Quincy	MA	02169
Quest Diagnostics - Lynn PSC	225 Boston St	Lynn	MA	01904
Quest Diagnostics - Braintree	340 Wood Rd, Suite 302	Braintree	MA	02184
Quest Diagnostics - Weymouth	73 Pleasant St	S. Weymouth	MA	02190
Quest Diagnostics - Danvers	140 Commonwealth Ave	Danvers	MA	01923
Quest Diagnostics - Cohasset	223 Chief Justice Cushing Hwy	Cohasset	MA	02025
Quest Diagnostics - Norwood	335 Morse St	Norwood	MA	02062
Quest Diagnostics - Cummings Center	900 Cummings Ctr, Suite 126R & 124S Route 62	Beverly	MA	01915
Quest Diagnostics - Hanover	135 Webster St	Hanover	MA	02339
Quest Diagnostics - Rockland	214 Market St	Rockland	MA	02370
Quest Diagnostics - Route 9 West	255 Worcester Road RT. 9 West	Framingham	MA	01701
Quest Diagnostics - Concord St. Framingham	655 Concord St	Framingham	MA	01701
Quest Diagnostics - Walpole	1426 Main Street Suite 3	Walpole	MA	02081
Quest Diagnostics - Billerica	221 Boston Rd, Suite 1	Billerica	MA	01862
Quest Diagnostics - Brockton	225 Quincy Ave	Brockton	MA	02302
Quest Diagnostics - Andover PSC	138 Haverhill St	Andover	MA	01810
Quest Diagnostics - Chelmsford	39 Village Square	Chelmsford	MA	01824
Quest Diagnostics - Foxboro	10 Commercial St	Foxboro	MA	02035
Quest Diagnostics - Pleasant St, N Andover	170 Pleasant St	North Andover	MA	01845
Quest Diagnostics - Branch Street - Methuen	9 Branch St	Methuen	MA	01844
Quest Diagnostics - Merrimack St - Methuen	421 Merrimack St	Methuen	MA	01844
Quest Diagnostics - Wrentham PSC	667 South St Wampum Corner	Wrentham	MA	02093
Quest Diagnostics - Haverhill	161 Summer St	Haverhill	MA	01830
Quest Diagnostics - Salem NH	45 Stiles Rd Ste 102	Salem	NH	03079
Quest Diagnostics - Main Street Nashua	300 Main St	Nashua	NH	03060
Quest Diagnostics - Londonderry	6 Buttrick Rd Ste 200	Londonderry	NH	03053
Quest Diagnostics	333 School St	Pawtucket	RI	02860
Quest Diagnostics - East Ave	407 East Ave	Pawtucket	RI	02860
Quest Diagnostics - Hospital Road	100 Hospital Rd Ste 2b	Leominster	MA	01453
Quest Diagnostics - Memorial Drive	50 Memorial Dr	Leominster	MA	01453
Quest Diagnostics - Derry RRL	6 Tsienneto Road LL102	Derry	NH	03038
Quest Diagnostics - Central St, Worcester	100 Central St	Worcester	MA	01608
Quest Diagnostics - Winthrop St, Worcester	10 Winthrop St	Worcester	MA	01604
Quest Diagnostics - Summit	100 Highland Ave Suite 305	Providence	RI	02906
Quest Diagnostics - Randall	1 Randall Sq	Providence	RI	02904

Quest Diagnostics - Summer St - Fitchburg	76 Summer St	Fitchburg	MA	01420
Quest Diagnostics	1352 Smith St	Providence	RI	02911
Quest Diagnostics - Veterans Memorial	450 Veterans Memorial Parkway Building 8	East Providence	RI	02914
Quest Diagnostics - Plain Street PSC	235 Plain St	Providence	RI	02905
Quest Diagnostics - Fitchburg - Ashby St.	47 Ashby State Rd	Fitchburg	MA	01420
Quest Diagnostics - Johnston	1524 Atwood Ave	Johnston	RI	02919
Quest Diagnostics - Truesdale RRL	1030 President Ave Basement	Fall River	MA	02720
Quest Diagnostics	1681 Cranston St	Cranston	RI	02920
Quest Diagnostics - Wareham	106 Main Street	Wareham	MA	02571
Quest Diagnostics - Reservoir Ave	1145 Reservoir Ave	Cranston	RI	02920
Quest Diagnostics	999 Warwick Ave	Warwick	RI	02888
Quest Diagnostics - Manchester, NH	195 McGregor St. Center Entrance	Manchester	NH	03102
Quest Diagnostics - Portsmouth, NH	200 Griffin Rd Unit 12	Portsmouth	NH	03801
Quest Diagnostics - North Dartmouth	49 State Rd Suite 202	North Dartmouth	MA	02747
Quest Diagnostics	215 Toll Gate Rd Ste 102	Warwick	RI	02886
Quest Diagnostics	300 Toll Gate Rd Ste LI5	Warwick	RI	02886
Quest Diagnostics - North Falmouth PSC	39 Edgerton Dr	North Falmouth	MA	02556
Quest Diagnostics - Dover, NH	750 Central Ave Unit B	Dover	NH	03820
Quest Diagnostics - Bramblebush Park	12 Bramblebush Park	Falmouth	MA	02540
Quest Diagnostics - Aquidneck RRL	50 Memorial Blvd	Newport	RI	02840
Quest Diagnostics - Osterville, MA	23 W Bay Rd	Osterville	MA	02655
Quest Diagnostics - Concord	280 Pleasant St	Concord	NH	03301
Quest Diagnostics - Hyannis	51 Main St	Hyannis	MA	02601
Quest Diagnostics	46 Holley St	Wakefield	RI	02879
Quest Diagnostics - Orleans	229 Cranberry Hwy	Orleans	MA	02653
Quest Diagnostics - Harwich	1421 Orleans Rd, Route 39 Ste 2	Harwich	MA	02645
Quest Diagnostics - Mansfield Center	135d Storrs Rd	Mansfield Center	CT	06250
Quest Diagnostics - Norwich-New London Turnpike	118 New London Turnpike	Norwich	CT	06360
Quest Diagnostics - Norwich-Wawecus	79 Wawecus St	Norwich	CT	06360
Quest Diagnostics - Turners Falls RRL	8 Burnham St	Turners Falls	MA	01376
Quest Diagnostics - Springfield	780 Chestnut St	Springfield	MA	01107
Quest Diagnostics - Enfield	15 Palomba Drive	Enfield	CT	06082
Quest Diagnostics - Vernon	352 Hartford Turnpike	Vernon	CT	06066
Quest Diagnostics - Enfield 54 Hazard Ave	54 Hazard Ave	Enfield	CT	06082
Quest Diagnostics - Florence RRL	190 Nonotuck St	Florence	MA	01062
Quest Diagnostics - Groton-Poheganut	85 Poheganut Drive	Groton	CT	06340
Quest Diagnostics - Groton-Gold Star	495 Gold Star Hwy Ste 220	Groton	CT	06340
Quest Diagnostics - Manchester	555 Main Street	Manchester	CT	06040
Quest Diagnostics - South Windsor	1735 Ellington Rd	South Windsor	CT	06074
Quest Diagnostics - Electric Boat Employees Only	Electric Boat Employees Only	Groton	CT	06340
Quest Diagnostics - New London Bank St	721 Bank Street	New London	CT	06320
Quest Diagnostics - Marlborough	3-5 E Hampton Rd Unit 8	Marlborough	CT	06447
Quest Diagnostics - Windsor Locks	2 Concorde Way, Suite 3A	Windsor Locks	CT	06096
Quest Diagnostics - Windsor	74 Mack Street	Windsor	CT	06095
Quest Diagnostics - Glastonbury-Western	320-B Western blvd	Glastonbury	CT	06033

Blvd				
Quest Diagnostics - Glastonbury-N.L. Turnpike	131 New London Turnpike	Glastonbury	CT	06033
Quest Diagnostics - East Hartford	477 Connecticut Boulevard, Ste 213	East Hartford	CT	06108
Quest Diagnostics - Hartford-Retreat	100 Retreat Avenue	Hartford	CT	06106
Quest Diagnostics - Wethersfield	465 Silas Deane Highway	Wethersfield	CT	06109
Quest Diagnostics - Bloomfield Cottage Grove	701 Cottage Grove Rd Bldg B, Suite 130	Bloomfield	CT	06002
Quest Diagnostics - Hartford-19 Woodland	19 Woodland Street, Ste 14	Hartford	CT	06105
Quest Diagnostics - Hartford-21 Woodland St.	21 Woodland St	Hartford	CT	06105
Quest Diagnostics - West Hartford-No Main	345 N Main St	West Hartford	CT	06117
Quest Diagnostics - West Hartford-Farmington Ave	970 Farmington Ave	West Hartford	CT	06107
Quest Diagnostics - Simsbury	381 Hopmeadow Street	Simsbury	CT	06070
Quest Diagnostics - Newington	955 Main St	Newington	CT	06111
Quest Diagnostics - Essex	7 Wildwood Wildwood Medical Building	Essex	CT	06426

**EDIC CLINIC 07 - Mayo**

Quest Diagnostics - River Falls PSC	1687 E Division St	River Falls	WI	54022
Quest Diagnostics - Gallery PSC	17 Exchange St W Ste 218	Saint Paul	MN	55102
Quest Diagnostics - Edina Southdale PSC	6545 France Ave S Bldg Ste200	Edina	MN	55435
Quest Diagnostics - Eau Claire PSC	4330 Golf Ter Ste 202	Eau Claire	WI	54701
Quest Diagnostics - Medical Arts PSC	825 Nicollet Mall Suite 605	Minneapolis	MN	55402
Quest Diagnostics - New Brighton PSC/RRL	600 County Road D W Ste 11	New Brighton	MN	55112

**EDIC CLINIC 08 - MUSC**

Quest Diagnostics - James Island	418 Folly Road Suite	Charleston	SC	29412
Quest Diagnostics - Charleston-West Ashley	1470 Tobias Gadson Blvd Suite 101	Charleston	SC	29407
Quest Diagnostics - Mount Pleasant	913 Bowman Road Suite C	Mt Pleasant	SC	29464
Quest Diagnostics - N Charleston-Trident	2680 Elms Plantation Blvd Suite 103	North Charleston	SC	29406
Quest Diagnostics - Summerville	104 Morgan Lane Place Suite C	Summerville	SC	29485
Quest Diagnostics - Hilton Head -Heritage	460 William Hilton Pkwy	Hilton Head Island	SC	29926
Quest Diagnostics - Bluffton	25 Sherington Dr Ste B	Bluffton	SC	29910
Quest Diagnostics - Savannah	6555 Abercorn St Ste 101	Savannah	GA	31405
Quest Diagnostics - Myrtle Beach	5900 N Kings Hwy Ste F	Myrtle Beach	SC	29577

<b>EDIC CLINIC 09 - IDC</b>				
Quest Diagnostics - Edina Southdale PSC	6545 France Ave S Bldg Ste200	Edina	MN	55435
Quest Diagnostics - Medical Arts PSC	825 Nicollet Mall Suite 605	Minneapolis	MN	55402
Quest Diagnostics - New Brighton PSC/RRL	600 County Road D W Ste 11	New Brighton	MN	55112
Quest Diagnostics - Gallery PSC	17 Exchange St W Ste 218	Saint Paul	MN	55102
Quest Diagnostics - River Falls PSC	1687 E Division St	River Falls	WI	54022
Quest Diagnostics - St Cloud/Logistics	3812 North 8th Street	Saint Cloud	MN	56303

<b>EDIC CLINIC 10 - IOWA</b>				
Quest Diagnostics - Davenport PSC	Note: Quest lab is 52 miles away 3524 Jersey Ridge Rd	From Clinic 10 Davenport	IA	52807

<b>EDIC CLINIC 11- Minnesota</b>				
Quest Diagnostics - Medical Arts PSC	825 Nicollet Mall Suite 605	Minneapolis	MN	55402
Quest Diagnostics - New Brighton PSC/RRL	600 County Road D W Ste 11	New Brighton	MN	55112
Quest Diagnostics - Gallery PSC	17 Exchange St W Ste 218	Saint Paul	MN	55102
Quest Diagnostics - Edina Southdale PSC	6545 France Ave S Bldg Ste200	Edina	MN	55435
Quest Diagnostics - River Falls PSC	1687 E Division St	River Falls	WI	54022
Quest Diagnostics - St Cloud/Logistics	3812 North 8th Street	Saint Cloud	MN	56303
Quest Diagnostics - Eau Claire PSC	4330 Golf Ter Ste 202	Eau Claire	WI	54701

<b>EDIC CLINIC 12 - Missouri</b>				
Quest Diagnostics - Medical Arts PSC	825 Nicollet Mall Suite 605	Minneapolis	MN	55402
Quest Diagnostics - Fairbanks	1919 Lathrop Street Suite 121	Fairbanks	AK	99701
Quest Diagnostics - Louisville - Doctors Office Bldg.	250 E Liberty St. Ste B2	Louisville	KY	40202
Quest Diagnostics - Professional Arts - New Albany	1919 State St Ste 344	New Albany	IN	47150
Quest Diagnostics - Louisville - Bluegrass	1700 Bluegrass Ave, Suite 10	Louisville	KY	40215
Quest Diagnostics - College and Nall	5520 College Blvd Suite 400	Overland park	KS	66211
Quest Diagnostics - Lee's Summit	1741 NE Douglas St Ste 101	Lee's Summit	MO	64088
Quest Diagnostics - North Kansas City	2700 Clay Edwards Dr Ste 350	North Kansas City	MO	64116
Quest Diagnostics - Topeka	1111 SW Gage Blvd Ste 200	Topeka	KS	66604
Quest Diagnostics - Odessa	316 W 40 Hwy Suite C	Odessa	MO	64076
Quest Diagnostics – Exam One Columbia, MO	3600 I 70 Dr SE	Columbia	MO	65201
Quest Diagnostics - Branson	895 State Highway 248 Ste A	Branson	MO	65616
Quest Diagnostics - Joplin-West	3202 Mc Intosh Circle Ste 1 Lower Level	Joplin	MO	64804
Quest Diagnostics - Fairview Heights	317 Salem Pl	Fairview Heights	IL	62208
Quest Diagnostics - Paducah	4793 Village Square Dr Ste A	Paducah	KY	42008
Quest Diagnostics - Rolla	1220 E State Route 72	Rolla	MO	65401
Quest Diagnostics - Decatur	606 W Pershing Rd	Decatur	IL	62526

<b>EDIC CLINIC 13 - Pittsburgh</b>				
Quest Diagnostics - Oakland	3500 5th Avenue Ste G1	Pittsburgh	PA	15213
Quest Diagnostics - Oakland	120 Lytton Ave Ste 100c	Pittsburgh	PA	15213
Quest Diagnostics - Shadyside	5750 Centre Ave Ste 190	Pittsburgh	PA	15206
Quest Diagnostics - Squirrel Hill	4375 Murray Ave	Pittsburgh	PA	15217
Quest Diagnostics - Downtown	625 Stanwix St Street Level	Pittsburgh	PA	15222
Quest Diagnostics - Aspinwall	241-251 Freeport Road Suite 5	Aspinwall	PA	15215
Quest Diagnostics - North Hills	4725 Mcknight Rd Ste 120	Pittsburgh	PA	15237
Quest Diagnostics - Greentree	969 Greentree Rd Primary Care Center, 2nd Floor	Pittsburgh	PA	15220
Quest Diagnostics - Mt. Lebanon	615 Washington Rd Ste 206	Mt Lebanon	PA	15228
Quest Diagnostics - West Mifflin	1907 Lebanon Church Rd, Ste 104	West Mifflin	PA	15122
Quest Diagnostics - Penn Hills	5769 Saltsburg Rd # 2	Verona	PA	15147
Quest Diagnostics - McKeesport	624 Lysle Blvd, Ste 300	Mc Keesport	PA	15132
Quest Diagnostics - Bethel Park	1300 Oxford Dr Ste 1AA	Bethel Park	PA	15102
Quest Diagnostics - Monroeville-Oxford Drive	600 Oxford Dr Ste 110	Monroeville	PA	15146
Quest Diagnostics - Monroeville Center	3824 Northern Pike Ste 650 1 Monroeville Center	Monroeville	PA	15146
Quest Diagnostics - Robinson PSC	5855 Steubenville Pike Ste 101	Mc Kees Rocks	PA	15136
Quest Diagnostics - McCandless	9066 Perry Hwy	Pittsburgh	PA	15237
Quest Diagnostics - White Oak	1976 Lincoln Way	White Oak	PA	15131
Quest Diagnostics - Monroeville	125 Daugherty Dr Ste 420	Monroeville	PA	15146

Quest Diagnostics - Wexford	9000 Brooktree Rd Ste 401	Wexford	PA	15090
Quest Diagnostics - Moon	1600 Coraopolis Heights Rd Ste G	Coraopolis	PA	15108
Quest Diagnostics - New Kensington	2300 Freeport Rd 14 Feldarelli Square	New Kensington	PA	15068
Quest Diagnostics - McMurray	1015 Waterdam Plaza Dr	Mc Murray	PA	15317
Quest Diagnostics - Irwin	9173 Route 30	Irwin	PA	15642
Quest Diagnostics - Monongahela	447 W Main St	Monongahela	PA	15063
Quest Diagnostics - Ambridge	832 Merchant St	Ambridge	PA	15003
Quest Diagnostics - Seven Fields	100 Northpointe Cir Ste 301	Seven Fields	PA	16046
Quest Diagnostics - Cranberry	20826 Route 19	Cranberry Twp	PA	16066
Quest Diagnostics - Monessen	1295 Grand Blvd Ste 101	Monessen	PA	15062
Quest Diagnostics - Washington	396 Locust Street	Washington	PA	15301
Quest Diagnostics - Greensburg	1275 S Main St Ste 104	Greensburg	PA	15601
Quest Diagnostics - Greensburg	518 Pellis Rd	Greensburg	PA	15601
Quest Diagnostics - Beaver	336 College Ave Ste 4	Beaver	PA	15009
Quest Diagnostics - Uniontown	659 Cherry Tree Ln	Uniontown	PA	15401
Quest Diagnostics - Austintown PSC	1570 S Canfield Niles Rd Bldg B	Austintown	OH	44515
Quest Diagnostics - Warren	3915 E Market St Ste 410	Warren	OH	44484
Quest Diagnostics - Altoona	1701 12th Ave Ste C2	Altoona	PA	16601
Quest Diagnostics - Canton PSC	4084 Holiday St NW	N. Canton	OH	44718
Associated Clinical Laboratories - ACL-Meadville PSC	289 North St	Meadville	PA	16335
Quest Diagnostics - Green	1587 Boettler Rd Ste 106	Uniontown	OH	44685
Quest Diagnostics - Akron	676 S Broadway St Ste 100	Akron	OH	44311
Quest Diagnostics - Stow	4465 Darrow Rd	Stow	OH	44224
Quest Diagnostics - Cuyahoga Falls	600 Portage Trl	Cuyahoga Falls	OH	44221
Quest Diagnostics - Chardon	13221 Ravenna Rd Ste 10	Chardon	OH	44024

**EDIC CLINIC 14 – Univ. of Tennessee**

Quest Diagnostics - North Memphis PSC	3980 New Covington Pike. Ste10	Memphis	TN	38128
Quest Diagnostics – Memphis PSC	6685 Quince Rd. Ste 120	Memphis	TN	38119

**EDIC CLINIC 15 – Univ. of Texas**

Quest Diagnostics - Baylor PSC	3600 Gaston Ave Ste 200	Dallas	TX	75246
Quest Diagnostics - DAL - Oak Cliff PSC	221 W Colorado Ste 443	Dallas	TX	75208
Quest Diagnostics - Margo Perot PSC	8160 Walnut Hill Lane, Suite 211A	Dallas	TX	75231
Quest Diagnostics - Presbyterian PSC	8230 Walnut Hill Ln Bldg III Ste 400	Dallas	TX	75231
Quest Diagnostics - Woodhill PSC	8305 Walnut Hill Ln Ste 120	Dallas	TX	75231
Quest Diagnostics - Irving PSC	2001 N Macarthur Blvd Ste 530	Irving	TX	75061
Quest Diagnostics - DAL - Irving PSC	3501 N Macarthur Blvd Ste 310 Bldg III	Irving	TX	75062
Quest Diagnostics - DAL - Forest Lane PSC	11613 N Central Expwy Ste 118	Dallas	TX	75243
Quest Diagnostics - RHD PSC	8 Medical Pkwy Plaza II Ste 305	Dallas	TX	75234
Quest Diagnostics - DAL Casa Linda	1151 N Buckner Blvd Ste 106	Dallas	TX	75218

PSC				
Quest Diagnostics - Richardson PSC	400 N Coit Rd Ste 1920	Richardson	TX	75080
Quest Diagnostics - Mesquite PSC	3501 Towne Crossing Blvd Ste 105	Mesquite	TX	75150
Quest Diagnostics - DAL - Charlton PSC	3430 W Wheatland Rd Ste 224	Dallas	TX	75237
Quest Diagnostics - Garland PSC	777 Walter Reed Blvd Ste 102	Garland	TX	75042
Quest Diagnostics - Coppell PSC	546 E Sandy Lake Rd Ste 120	Coppell	TX	75019
Quest Diagnostics - Plano PSC	4001 W. 15th Street, Suite 400	Plano	TX	75093
Quest Diagnostics - Plano Medical Pavillion PSC	3801 W 15th St Ste 100	Plano	TX	75075
Quest Diagnostics - Carrollton PSC	2008 E Hebron Pkwy Ste 110	Carrollton	TX	75007
Quest Diagnostics - Hospital Parkway PSC	1615 Hospital Pkwy Ste 208	Bedford	TX	76022
Quest Diagnostics - Arlington PSC	903 B Medical Centre Drive	Arlington	TX	76012
Quest Diagnostics - Grapevine PSC	1601 Lancaster Dr Ste 120	Grapevine	TX	76051
Quest Diagnostics - Presbyterian Plano PSC	3600 Communications Parkway, Suite 647	Plano	TX	75093
Quest Diagnostics - Bedford PSC	1305 Airport Freeway, Ste 306	Bedford	TX	76021
Quest Diagnostics - Dal - S Arlington PSC	2625 Matlock Rd Ste 104	Arlington	TX	76015
Quest Diagnostics - Lewisville PSC	500 N Valley Pkwy Ste 110	Lewisville	TX	75067
Quest Diagnostics - Rowlett PSC	9824 Lakeview Pkwy Ste 200	Rowlett	TX	75088
Quest Diagnostics - The Colony PSC	6053 Main Street, Suite 110	The Colony	TX	75056
Quest Diagnostics - Frisco PSC	5575 Warren Pkwy Ste 303	Frisco	TX	75034
Quest Diagnostics - DAL - Allen PSC	400 N Allen Dr Ste 105	Allen	TX	75013
Quest Diagnostics - Mansfield PSC	990 U S Hwy. 287 North, Suite 115	Mansfield	TX	76063
Quest Diagnostics - Fossil Creek PSC	7630 N Beach St Ste 156	Fort Worth	TX	76137
Quest Diagnostics - Midlothian PSC	2220 Bryan PI Ste 108	Midlothian	TX	76065
Quest Diagnostics - Keller PSC	3529 Heritage Trace Parkway Suite 133	Keller	TX	76248
Quest Diagnostics - McKinney PSC	4510 Medical Center Dr Ste 310	Mc Kinney	TX	75069
Quest Diagnostics - Main Street PSC	1350 S Main St Ste 1250	Fort Worth	TX	76104
Quest Diagnostics - DAL - Denton PSC	4851 I-35 Ste 102	Corinth	TX	76210
Quest Diagnostics - 12th Avenue RRL/PSC	1001 12th Avenue, Suite 170	Fort Worth	TX	76104
Quest Diagnostics - UNT PSC	855 Montgomery St Ste 170	Fort Worth	TX	76107
Quest Diagnostics - Lake Worth PSC	4625 Boat Club Road Suite 249	Fort Worth	TX	76135
Quest Diagnostics - DAL - Kaufman PSC	874 W. Hwy 243 Ste 106	Kaufman	TX	75142
Quest Diagnostics - Green Oaks PSC	6855 A Green Oaks Road, Suite 106	Fort Worth	TX	76116
Quest Diagnostics - Oakmont PSC	7555 Oakmont Blvd	Fort Worth	TX	76132
Quest Diagnostics - Azle PSC	124 N. Industrial Blvd.	Azle	TX	76020
Quest Diagnostics - Cleburne PSC	505 N Ridgeway Dr Ste 172	Cleburne	TX	76031
Quest Diagnostics - DAL - Greenville PSC	4101 Wesley St Ste G	Greenville	TX	75401
Quest Diagnostics Weatherford PSC	1105 Sante Fe, Ste 105	Weatherford	TX	76086
Quest Diagnostics - Granbury PSC	805 Hill Blvd Ste 108	Granbury	TX	76048
Quest Diagnostics - DAL - Sherman PSC	1010 La Salle Dr	Sherman	TX	75090
Diagnostic Laboratory of Oklahoma - Marshall County Medical Center	1 Hospital Drive	Madill	OK	73446
Quest Diagnostics - Tyler PSC	822 S. Fleishel Avenue	Tyler	TX	75701

Quest Diagnostics - Paris PSC	3306 Lamar Ave Ste B	Paris	TX	75460
Quest Diagnostics - Waco PSC	512 Meadowlake Ctr	Waco	TX	76712
Diagnostic Laboratory of Oklahoma - Ardmore PSC	1007 15th Ave NW	Ardmore	OK	73401

**EDIC CLINIC 16 – Toronto**

Toronto, Ontario, CANADA does not have a Quest Diagnostics Patient Service Center

**EDIC CLINIC 17 – Univ. of Washington**

Quest Diagnostics - Nordstrom Tower PSC	1229 Madison Suite 690	Seattle	WA	98104
Quest Diagnostics - Madison	1101 Madison Street Suite 1210	Seattle	WA	98104
Quest Diagnostics - Med-Dent PSC	509 Olive Way Suite 618	Seattle	WA	98101
Quest Diagnostics - Seattle PSC	1737 Airport Way S Suite 200	Seattle	WA	98134
Quest Diagnostics - Bellevue PSC at Family Med Center	1200 116th Ave NE Suite F	Bellevue	WA	98004
Quest Diagnostics - Totem Lake RRL	12911 120th Avenue NE Suite A 40	Kirkland	WA	98034
Quest Diagnostics - Oakesdale PSC	1412 SW 43rd Street Suite 101	Renton	WA	98057
Quest Diagnostics - Medical Arts Center	4033 Talbot Road South Suite 310	Renton	WA	98055
Quest Diagnostics - Bremerton	2601 Cherry Avenue Suite 206	Bremerton	WA	98310
Quest Diagnostics - Covington	16850 SE 272nd Street Suite 219	Covington	WA	98042
Quest Diagnostics - Capital Square	720 S 320th Street Suite B	Federal Way	WA	98003
Quest Diagnostics - Torquay	34616 11th Place South Suite 2	Federal Way	WA	98003
Quest Diagnostics - Bayview PSC	1302 N I Street	Tacoma	WA	98403
Quest Diagnostics - Gig Harbor	4700 Point Fosdick Drive NW Suite 210	Gig Harbor	WA	98335
Quest Diagnostics - Allenmore	1901 S Union Suite B 3005	Tacoma	WA	98405
Quest Diagnostics - Soundview	3711 Pacific Avenue Suite 201	Tacoma	WA	98418
Quest Diagnostics - Puyallup PSC	1011 E Main Suite 301	Puyallup	WA	98372
Quest Diagnostics - Bridgeport	7424 Bridgeport Way West Suite 202	Lakewood	WA	98499
Quest Diagnostics - Lakewood Village PSC	5920 100th St SW Suite 29	Lakewood	WA	98499
Quest Diagnostics - Lakes PSC	11210 Bridgeport Way SW	Lakewood	WA	98499
Quest Diagnostics - Sunrise PSC	11102 Sunrise Blvd E Suite 105	Puyallup	WA	98374
Quest Diagnostics - Lilly Rd North PSC	703 Lilly Road NE Suite C	Olympia	WA	98506
Quest Diagnostics - Lilly Road PSC	420 Lilly Road NE Suite 101	Olympia	WA	98506
Quest Diagnostics - Shelton	939 Mountain View Drive Suite 110	Shelton	WA	98584
Quest Diagnostics - Olympia PSC	405 Black Hill Lane SW D1	Olympia	WA	98502
Quest Diagnostics - Capitol Medical Center PSC	406 Black Hills Lane SW Suite B	Olympia	WA	98502
Quest Diagnostics - Tumwater PSC	150 W Dennis Street SW	Tumwater	WA	98501
Quest Diagnostics - Parkway	2980 Squalicum Parkway Suite 101	Bellingham	WA	98225
Quest Diagnostics - Aberdeen - CIM	1921 Sumner Ave	Aberdeen	WA	98520

<b>EDIC CLINIC 18 – Western Ontario</b>				
Toronto, Ontario, CANADA does not have a Quest Diagnostics Patient Service Center				

<b>EDIC CLINIC 19 – Vanderbilt</b>				
Quest Diagnostics – Paterson PSC	1916 Patterson St Ste 103	Nashville	TN	37203
Quest Diagnostics – St Thomas LSC	4230 Harding Rd Ste 400	Nashville	TN	37205

<b>EDCI CLINIC 20 – St. Louis</b>				
Quest Diagnostics - West Pine	40 N Kingshighway	Saint Louis	MO	63108
Quest Diagnostics - Lansdowne	6651 Chippewa St	Saint Louis	MO	63109
Quest Diagnostics - Broadway	3946 S Broadway	Saint Louis	MO	63118
Quest Diagnostics - University Club Tower	1034 S Brentwood Blvd Ste 294	Saint Louis	MO	63117
Quest Diagnostics - Cahokia	4041 Mississippi Ave	Cahokia	IL	62206
Quest Diagnostics - Kirkwood	463 S Kirkwood Rd	Kirkwood	MO	63122
Quest Diagnostics - Lemay PSC	3193 Lemay Ferry Rd	Saint Louis	MO	63125
Quest Diagnostics - Sunset Hills	3844 S Lindbergh Blvd	Saint Louis	MO	63127
Quest Diagnostics - Town & Country	2821 N Ballas Rd Ste 120	Saint Louis	MO	63131
Quest Diagnostics - 777 Ballas	777 S New Ballas Rd	Saint Louis	MO	63141
Quest Diagnostics - 522 Ballas	522 N New Ballas Rd Ste 122	Saint Louis	MO	63141
Quest Diagnostics - Florissant	10716 New Halls Ferry Rd	Florissant	MO	63033
Quest Diagnostics - Telegraph	4500 Telegraph Rd Ste 202	Saint Louis	MO	63129
Quest Diagnostics - Walker	12855 N 40 Dr Ste 195	Saint Louis	MO	63141
Quest Diagnostics - Tesson	13131 Tesson Ferry Rd Bldg Ste 210	Saint Louis	MO	63128
Quest Diagnostics - Granite City	2421 Corporate Center	Granite City	IL	62040
Quest Diagnostics - McKelvey	3394 Mckelvey Rd Ste 101	Bridgeton	MO	63044
Quest Diagnostics - Florissant Oaks	85 Floissant Oaks	Florissant	MO	63031
Quest Diagnostics - Arnold	12 Arnold Mall	Arnold	MO	63010
Quest Diagnostics - Belleville	2900 Frank Scott Parkway West Suite 920A	Belleville	IL	62223
Quest Diagnostics - Fairview Heights	317 Salem Pl	Fairview Heights	IL	62208
Quest Diagnostics - Ballwin	15421 Clayton Rd Ste 202	Ballwin	MO	63011
Quest Diagnostics - St. Charles Heritage Landing	2730 S Highway 94 Ste 200	Saint Peters	MO	63303
Quest Diagnostics - Edwardsville PSC	Club Center Shopping Center Suite F	Edwardsville	IL	62025
Quest Diagnostics - Chesterfield	17300 N Outer 40 Ste 104	Chesterfield	MO	63005
Quest Diagnostics - Maryville	2136 Vadalabene Dr Ste A	Maryville	IL	62062
Quest Diagnostics - St Peters	4101 Mexico Rd Ste E	Saint Peters	MO	63376
Quest Diagnostics - Waterloo	509 Hamacher St Ste 201	Waterloo	IL	62298

Quest Diagnostics - Alton	237b E Center Dr	Alton	IL	62002
Quest Diagnostics - Eureka	98 The Legends Pkwy Ste 108	Eureka	MO	63025
Quest Diagnostics - Lake St. Louis	100 Brevco Plz Ste 102	Lake Saint Louis	MO	63367
Quest Diagnostics - Festus	1463 Highway 61 Ste 61	Festus	MO	63028
Quest Diagnostics - Wentzville	1201 Wentzville Pkwy Ste 117	Wentzville	MO	63385
Quest Diagnostics - Washington	2003 Phoenix Center Dr	Washington	MO	63090
Quest Diagnostics - Union	1780 Old Hwy 50 E Ste 103	Union	MO	63084
Quest Diagnostics - Mt. Vernon	1009 S 42nd St Ste 6	Mount Vernon	IL	62864
Quest Diagnostics - Jacksonville	273 N Westgate Ave	Jacksonville	IL	62650
Quest Diagnostics - Springfield	3119 Robbins Rd	Springfield	IL	62704
Quest Diagnostics - Rolla	1220 E State Route 72	Rolla	MO	65401

**EDIC CLINIC 21 - Yale**

Quest Diagnostics - New Haven-Church Street	2 Church St S Ste 115	New Haven	CT	06519
Quest Diagnostics - New Haven-Temple Street	60 Temple Street Temple Medical Building	New Haven	CT	06510
Quest Diagnostics - New Haven-Orchard Street	200 Orchard St	New Haven	CT	06511
Quest Diagnostics - New Haven-Sherman Avenue	136 Sherman Avenue, Suite 02	New Haven	CT	06511
Quest Diagnostics - West Haven-Campbell Avenue	687 Campbell Avenue	West Haven	CT	06516
Quest Diagnostics - West Haven-Main Street	385 Main Street	West Haven	CT	06516
Quest Diagnostics - East Haven	190 Main Street	East Haven	CT	06512
Quest Diagnostics - North Haven	12 Village St Ste 103	North Haven	CT	06473
Quest Diagnostics - Hamden-Whitney Avenue	2200 Whitney Ave Ste 210	Hamden	CT	06518
Quest Diagnostics - Branford-144 North Main St	144 North Main St	Branford	CT	06405
Quest Diagnostics - Hamden-Dixwell	3000 Dixwell Ave	Hamden	CT	06518
Quest Diagnostics - Branford-1008 Main St	1008 Main St	Branford	CT	06405
Quest Diagnostics - Ansonia	158 Main St	Ansonia	CT	06401
Quest Diagnostics - Milford-Noble Ave	88 Noble Ave	Milford	CT	06460
Quest Diagnostics - Derby	299 Seymour Ave	Derby	CT	06418
Quest Diagnostics - Milford-Bridgeport Ave	2044 Bridgeport Avenue	Milford	CT	06460
Quest Diagnostics - Shelton	515 Bridgeport Ave	Shelton	CT	06484
Quest Diagnostics - Wallingford-South Elm Street	15 South Elm Street	Wallingford	CT	06492
Quest Diagnostics - Stratford-Main Street	2890 Main Street	Stratford	CT	06614
Quest Diagnostics - Cheshire	673 S Main St	Cheshire	CT	06410
Quest Diagnostics - Guilford	669 Boston Post Rd	Guilford	CT	06437
Quest Diagnostics - Wallingford-North Main	850 North Main Street Ext	Wallingford	CT	06492
Quest Diagnostics - Bridgeport-1450	1450 Barnum Ave	Bridgeport	CT	06610

Barnum Ave				
Quest Diagnostics - Trumbull-White Plains Rd	888 White Plains Rd	Trumbull	CT	06611
Quest Diagnostics - Stratford-Lordship	555 Lordship Blvd	Stratford	CT	06615
Quest Diagnostics - Trumbull-Technology Dr	115 Technology Dr	Trumbull	CT	06611
Quest Diagnostics - Bridgeport-2660 Main St	2660 Main St	Bridgeport	CT	06606
Quest Diagnostics - Bridgeport-Beechmont	3180 Main St Beechmont Building	Bridgeport	CT	06606
Quest Diagnostics - Prospect	166 Waterbury Rd	Prospect	CT	06712
Quest Diagnostics - Bridgeport-Commerce Park	4695 Main St	Bridgeport	CT	06606
Quest Diagnostics - Madison	11 Woodland Road	Madison	CT	06443
Quest Diagnostics - Waterbury East Main	2457 E Main St	Waterbury	CT	06705
Quest Diagnostics - Trumbull -Park Ave	5520 Park Ave	Trumbull	CT	06611
Quest Diagnostics - Meriden	816 Broad Street, Ste 22	Meriden	CT	06450
Quest Diagnostics - Fairfield-Black Rock	2150 Black Rock Turnpike	Fairfield	CT	06825
Quest Diagnostics - Waterbury-West Main Street	1389 West Main Street, Suite 125	Waterbury	CT	06708
Quest Diagnostics - Waterbury-Westwood Ave	60 Westwood Avenue	Waterbury	CT	06708
Quest Diagnostics - Southbury	385 Main St S	Southbury	CT	06488
Quest Diagnostics - Fairfield-Post Road	1305 Post Rd Ste 101	Fairfield	CT	06824
Quest Diagnostics - Southington	55 Meriden Avenue, Suite 1F	Southington	CT	06489
Quest Diagnostics - Middletown	400 Saybrook Rd	Middletown	CT	06457
Quest Diagnostics - Wading River PSC	6144 Route 25A Building B, Suite 8	Wading River	NY	11792
Quest Diagnostics - Bethel	83b Stony Hill Rd	Bethel	CT	06801
Quest Diagnostics - New Britain	40 Hart Street, Building C	New Britain	CT	06052
Quest Diagnostics - East Setauket PSC	100-10 South Jersey Avenue Heritage Square, Suite 10	East Setauket	NY	11733
Quest Diagnostics - Port Jefferson PSC	1010 Route 112 2nd Floor	Port Jefferson Station	NY	11776
Quest Diagnostics - Thomaston	130 S Main St	Thomaston	CT	06787
Quest Diagnostics - Bristol	935 Farmington Avenue	Bristol	CT	06010
Quest Diagnostics - Danbury-Germantown	7 Germantown Rd	Danbury	CT	06810
Quest Diagnostics - Norwalk-91 East Ave	91 East Ave	Norwalk	CT	06851
Quest Diagnostics - Essex	7 Wildwood Wildwood Medical Building	Essex	CT	06426
Quest Diagnostics - Riverhead PSC	74 Commerce Drive, Suite 2	Riverhead	NY	11901
Quest Diagnostics - Norwalk-148 East Ave	148 East Avenue	Norwalk	CT	06851
Quest Diagnostics - Norwalk Cross St	40 Cross St	Norwalk	CT	06851
Quest Diagnostics - East Setauket PSC	23 Technology Dr. Suite 2	East Setauket	NY	11733
Quest Diagnostics - Old Saybrook	929 Boston Post Road	Old Saybrook	CT	06475
Quest Diagnostics - Selden PSC	235 Boyle Rd	Selden	NY	11784
Quest Diagnostics - Newington	955 Main St	Newington	CT	06111
Quest Diagnostics - Ridgefield	38a Grove St	Ridgefield	CT	06877
Quest Diagnostics - Farmington	399 Farmington Ave	Farmington	CT	06032
Quest Diagnostics - Darien	557 Post Rd	Darien	CT	06820

Quest Diagnostics - Wethersfield	465 Silas Deane Highway	Wethersfield	CT	06109
Quest Diagnostics - New Milford	120 Park Ln	New Milford	CT	06776
Quest Diagnostics - Medford PSC	570 Expressway Dr S Suite1-J	Medford	NY	11763
Quest Diagnostics - Glastonbury-N.L. Turnpike	131 New London Turnpike	Glastonbury	CT	06033
Quest Diagnostics - Smithtown PSC	222 Middle Country Road Suite 107	Smithtown	NY	11787
Quest Diagnostics - West Hartford-Farmington Ave	970 Farmington Ave	West Hartford	CT	06107
Quest Diagnostics - Brookside Drive PSC	9 Brookside Drive	Smithtown	NY	11787
Quest Diagnostics - Marlborough	3-5 E Hampton Rd Unit 8	Marlborough	CT	06447
Quest Diagnostics - Glastonbury-Western Blvd	320-B Western blvd	Glastonbury	CT	06033
Quest Diagnostics - Hartford-Retreat	100 Retreat Avenue	Hartford	CT	06106
Quest Diagnostics - Center Moriches PSC	760-8 Montauk Highway	Center Moriches	NY	11934
Quest Diagnostics - Hartford-19 Woodland	19 Woodland Street, Ste 14	Hartford	CT	06105
Quest Diagnostics - Hartford-21 Woodland St.	21 Woodland St	Hartford	CT	06105
Quest Diagnostics - West Hartford-No Main	345 N Main St	West Hartford	CT	06117
Quest Diagnostics - Stamford-Buxton Farm Rd.	30 Buxton Farm Rd	Stamford	CT	06905
Quest Diagnostics - Torrington	30 Peck Rd	Torrington	CT	06790
Quest Diagnostics - East Hartford	477 Connecticut Boulevard, Ste 213	East Hartford	CT	06108
Quest Diagnostics - East Patchogue PSC	Brookhaven Professional Park 285 Sills Road, Building 8, Suite A	East Patchogue	NY	11772
Quest Diagnostics - Avon	54 W Avon Rd	Avon	CT	06001
Quest Diagnostics - Stamford-Summer Street	1250 Summer St Ste 203	Stamford	CT	06905
Quest Diagnostics - PSC-Brewster	Clock Tower Commons, 601 Route 22	Brewster	NY	10509
Quest Diagnostics - Stamford-Mill River	80 Mill River Street	Stamford	CT	06902
Quest Diagnostics - Hauppauge PSC	490 Wheeler Rd. Suite 190	Hauppauge	NY	11788
Quest Diagnostics - Commack PSC	2171 Jericho Turnpike Suite 102	Commack	NY	11725
Quest Diagnostics - Bloomfield Cottage Grove	701 Cottage Grove Rd Bldg B, Suite 130	Bloomfield	CT	06002
Quest Diagnostics - Huntington PSC	195 E Main St Suite D	Huntington	NY	11743
Quest Diagnostics - Simsbury	381 Hopmeadow Street	Simsbury	CT	06070
Quest Diagnostics - Manchester	555 Main Street	Manchester	CT	06040
Quest Diagnostics - Pulaski Road PSC	180 E Pulaski Rd	Huntington Station	NY	11746
Quest Diagnostics - CARMEL	Barns Office Center - 667 Stoneleigh Ave Bldg N, Suite 115	Carmel	NY	10512
Quest Diagnostics - West Sayville PSC	The Bayview Building 233 Montauk Highway	West Sayville	NY	11796
Quest Diagnostics - Windsor	74 Mack Street	Windsor	CT	06095
Quest Diagnostics - Greenwich-Deerfield Dr	2 1/2 Dearfield Dr	Greenwich	CT	06831
Quest Diagnostics - South Windsor	1735 Ellington Rd	South Windsor	CT	06074
Quest Diagnostics - Mt Kisco	83 South Bedford Road Floor 3	Mt. Kisco	NY	10549

Quest Diagnostics - Bay Shore PSC	8 Saxon Avenue, Suite D	Bay Shore	NY	11706
Quest Diagnostics - Vernon	352 Hartford Turnpike	Vernon	CT	06066
Quest Diagnostics - New London Bank St	721 Bank Street	New London	CT	06320
Quest Diagnostics - Rye Brook	14 Rye Ridge Plz Ste 155	Rye Brook	NY	10573
Quest Diagnostics - Electric Boat Employees Only	Electric Boat Employees Only	Groton	CT	06340
Quest Diagnostics - Windsor Locks	2 Concorde Way, Suite 3A	Windsor Locks	CT	06096
Quest Diagnostics - Syosset PSC	175 Jericho Turnpike Suite 304	Syosset	NY	11791
Quest Diagnostics - Plainview PSC	146A Manetto Hill Rd. Suite 101	Plainview	NY	11803
Quest Diagnostics - Groton-Gold Star	495 Gold Star Hwy Ste 220	Groton	CT	06340
Quest Diagnostics - Norwich-Wawecus	79 Wawecus St	Norwich	CT	06360
Quest Diagnostics - Babylon PSC	400 Montauk Hwy Suite 116	Babylon	NY	11702
Quest Diagnostics - PLEASANTVILLE	174 Marble Ave Ste 1	Pleasantville	NY	10570
Quest Diagnostics - Norwich-New London Turnpike	118 New London Turnpike	Norwich	CT	06360
Quest Diagnostics - Glen Cove PSC	Three Village Square	Glen Cove	NY	11542
Quest Diagnostics - Groton-Poheganut	85 Poheganut Drive	Groton	CT	06340
Quest Diagnostics - Mansfield Center	135d Storrs Rd	Mansfield Center	CT	06250
Quest Diagnostics - Bethpage PSC	4276 Hempstead Tpke	Bethpage	NY	11714
Quest Diagnostics - Seaford PSC	850 Hicksville Road Suite 114	Seaford	NY	11783
Quest Diagnostics - Peekskill	2 Stowe Rd 5th Floor - Suite 15	Peekskill	NY	10566
Quest Diagnostics - Enfield 54 Hazard Ave	54 Hazard Ave	Enfield	CT	06082
Quest Diagnostics - Port Washington PSC	14 Vanderverter Ave Suite 105	Port Washington	NY	11050
Quest Diagnostics - White Plains	280 Dobbs Ferry Rd Sprain Brook Medical Center	White Plains	NY	10607
Quest Diagnostics - Tarrytown	200 South Broadway Suite 102	Tarrytown	NY	10591
Quest Diagnostics - Massapequa Park PSC	Southgate Shopping Center 4900 Merrick Road, 2nd Floor	Massapequa Park	NY	11762
Quest Diagnostics - Roslyn Heights PSC	One Expressway Plaza Suite 116	Roslyn Heights	NY	11577
Quest Diagnostics - Enfield	15 Palomba Drive	Enfield	CT	06082
Quest Diagnostics - New Rochelle	150 Lockwood Ave	New Rochelle	NY	10801
Quest Diagnostics - Mineola PSC	156 First Street Lower Level	Mineola	NY	11501
Quest Diagnostics - Manhasset PSC	1165 Northern Blvd Suite 404	Manhasset	NY	11030
Quest Diagnostics - Fishkill	982 Main St Ste 9	Fishkill	NY	12524
Quest Diagnostics - Garden City PSC	520 Franklin Ave Suite 104	Garden City	NY	11530
Quest Diagnostics - Hempstead PSC	230 Hilton Avenue Room 220	Hempstead	NY	11550
Quest Diagnostics - Mount Vernon	105 Stevens Ave Ste 205	Mount Vernon	NY	10550
Quest Diagnostics - Lake Success PSC	2001 Marcus Ave Suite 98W, Lobby Level	Lake Success	NY	11042
Quest Diagnostics - Great Neck PSC	287 Northern Blvd. Suite 100	Great Neck	NY	11021
Quest Diagnostics - Yonkers	970 N Broadway Ste 205	Yonkers	NY	10701
Quest Diagnostics - Freeport PSC	101 South Bergen Place 2nd Floor	Freeport	NY	11520
Quest Diagnostics - BRONX - WESTCHESTER	3250 Westchester Ave Ste 105	Bronx	NY	10461
Quest Diagnostics - Floral Park PSC	265 Jericho Tpke	Floral Park	NY	11001
Quest Diagnostics - Poughkeepsie-Dutchess Tpke	695 Dutchess Tpke Suite 102	Poughkeepsie	NY	12603
Quest Diagnostics - New City	151 N Main St Unit 307	New City	NY	10956

Quest Diagnostics - Tappan	111 Route 303 Ste 109	Tappan	NY	10983
Quest Diagnostics - BRONX - WILLIAMSBIDGE	2015 Williamsbridge Rd	Bronx	NY	10461
Quest Diagnostics - Rockville Centre PSC	165 North Village Avenue Suite 103	Rockville Centre	NY	11570
Quest Diagnostics - Queens-Bayside	4401 Francis Lewis Blvd	Bayside	NY	11361
Quest Diagnostics - Nanuet	420 Nanuet Mall S Unit 307	Nanuet	NY	10954
Quest Diagnostics - Pomona	978 Route 45 Ste 202	Pomona	NY	10970
Quest Diagnostics - Bronx-Arthur Avenue	2385 Arthur Ave Suites 201 & 202	Bronx	NY	10458
Quest Diagnostics - Springfield	780 Chestnut St	Springfield	MA	01107
Quest Diagnostics - Poughkeepsie - South Avenue	205 South Ave Ste 203	Poughkeepsie	NY	12601
Quest Diagnostics - Newburgh	347 Fullerton Ave	Newburgh	NY	12550
Quest Diagnostics - Queens - Flushing	41-61 Kissena Blvd Ste 25	Flushing	NY	11355
Quest Diagnostics - EMERSON	452 Old Hook Rd Suite 1A	Emerson	NJ	07630
Quest Diagnostics - Englewood Cliffs	464 Hudson Ter	Englewood Cliffs	NJ	07632
Quest Diagnostics - QUEENS - JAMAICA	12614 Merrick Blvd	Jamaica	NY	11434
Quest Diagnostics - NYC-West 168th Street	607 W 168th St	New York	NY	10032
Quest Diagnostics - Queens-Forest Hills	7010 Austin St	Forest Hills	NY	11375
Quest Diagnostics - ENGLEWOOD	25 Rockwood Pl Ste 1	Englewood	NJ	07631
Quest Diagnostics - Hyde Park	7 Pine Woods Rd Suite #6	Hyde Park	NY	12538
Quest Diagnostics - Queens-Jackson Heights	75-35 31st Ave	Jackson Heights	NY	11372
Quest Diagnostics - Cedarhurst PSC	222 Rockaway Tpke, Suite 5	Cedarhurst	NY	11516
Quest Diagnostics - Queens-Astoria	27-47 Crescent Street	Astoria	NY	11102
Quest Diagnostics - Teaneck	179 Cedar Ln Suite E	Teaneck	NJ	07666
Quest Diagnostics - QUEENS - MIDDLE VILLAGE	7121 Eliot Ave	Middle Village	NY	11379
Quest Diagnostics - Paramus	275-277 Forest Ave	Paramus	NJ	07652
Quest Diagnostics - NYC-1651 3rd Avenue	1651 3rd Ave Fl 2	New York	NY	10128
Quest Diagnostics - Suffern	Indian Rock Shopping Center Route 59 & Hemion Road	Suffern	NY	10901
Quest Diagnostics - NYC - 115 E. 86th Street	115 E 86th St	New York	NY	10028
Quest Diagnostics - NYC - 66 E 86TH ST	66 E 86th St	New York	NY	10028
Quest Diagnostics - Hackensack	385 Prospect Ave	Hackensack	NJ	07601
Quest Diagnostics - NYC - WEST 86TH ST	2 W 86th St Apt 1a	New York	NY	10024
Quest Diagnostics - Queens-Howard Beach	Lindenwood Village Shopping Center 82-29 153rd Avenue	Howard Beach	NY	11414
Quest Diagnostics - NYC - EAST 76TH ST	65 E 76th St	New York	NY	10021
Quest Diagnostics - NYC - E 67TH ST	235 E 67th St Rm 201	New York	NY	10021
Quest Diagnostics - Ramsey	500 N Franklin Tpke Fl 2	Ramsey	NJ	07446
Quest Diagnostics - NYC - EAST 61ST STREET	115 E 61st St	New York	NY	10021
Quest Diagnostics - NYC - 115 E 57TH ST	115 E 57th St Ste 1530	New York	NY	10022
Quest Diagnostics - Ridgewood	127 Union St	Ridgewood	NJ	07450
Quest Diagnostics - PSC- West 58th	330 West 58th Street Suite 203	New York	NY	10019

Street				
Quest Diagnostics - BROOKLYN - GREENPOINT	147 Greenpoint Ave First Floor	Brooklyn	NY	11222
Quest Diagnostics - FAIRLAWN	33-00 Broadway Suite 305	Fair Lawn	NJ	07410
Quest Diagnostics - NYC - EAST 36TH STREET	137 E 36th St	New York	NY	10016
Quest Diagnostics - New Paltz	Cherry Hill Plaza 246 Main Street, Suite 202	New Paltz	NY	12561
Quest Diagnostics - NYC - 247 3RD AVENUE	247 Third Ave Rm 303	New York	NY	10010
Quest Diagnostics - West New York	4914-4922 Kennedy Blvd. Suite 206	West New York	NJ	07093
Quest Diagnostics - New York Seventh Avenue	275 Seventh Avenue Between 25th & 26th Streets	New York	NY	10001
Quest Diagnostics - NYC - WEST 16TH ST	269 West 16th Street Lower Level	New York	NY	10011
Quest Diagnostics - NYC - West 14th Street	314 West 14th St. Lower Level	New York	NY	10014
Quest Diagnostics - NYC - GREENWICH AVE	119 Greenwich Ave # 5	New York	NY	10014
Quest Diagnostics - NYC - MOTT ST	41 Mott St Fl 4	New York	NY	10013
Quest Diagnostics - Red Hook	7385 S Broadway 2nd Floor	Red Hook	NY	12571
Quest Diagnostics - BROOKLYN - RALPH AVENUE	2035 Ralph Ave Ste B1	Brooklyn	NY	11234
Quest Diagnostics - BROOKLYN - PIERREPONT	146 Pierrepont St	Brooklyn	NY	11201
Quest Diagnostics - Rutherford	17 Sylvan St	Rutherford	NJ	07070
Quest Diagnostics - BROOKLYN HEIGHTS	120 Atlantic Ave	Brooklyn	NY	11201
Quest Diagnostics - North Haledon	535 High Mountain Rd	North Haledon	NJ	07508
Quest Diagnostics - BROOKLYN - PARK SLOPE	348 13th St Suite 102	Brooklyn	NY	11215
Quest Diagnostics - Brooklyn Newkirk Avenue	1416 Newkirk Ave	Brooklyn	NY	11226
Quest Diagnostics - Jersey City	600 Pavonia Ave	Jersey City	NJ	07306
Quest Diagnostics - Kingston - Grand Street	5 Grand St	Kingston	NY	12401
Quest Diagnostics - Wayne	401 Hamburg Tpke Ste 203	Wayne	NJ	07470
Quest Diagnostics - BROOKLYN - EAST 14TH ST	1660 E 14th St Ste LL2	Brooklyn	NY	11229
Quest Diagnostics - PSC-Brooklyn- 48th Street	949 48th St	Brooklyn	NY	11219
Quest Diagnostics - Brooklyn - Boro Park	5102 13th Ave	Brooklyn	NY	11219
Quest Diagnostics - Clifton	881 Allwood Rd, Suite 103	Clifton	NJ	07012
Quest Diagnostics - Kingston-Washington Avenue	380 Washington Ave Suite A	Kingston	NY	12401
Quest Diagnostics - Florence RRL	190 Nonotuck St	Florence	MA	01062
Quest Diagnostics - Totowa	500 Union Blvd	Totowa	NJ	07512
Quest Diagnostics - BROOKLYN-BENSONHURST	15 Bay 29th St Room 2B	Brooklyn	NY	11214
Quest Diagnostics - BROOKLYN - BAYRIDGE	7601 4th Ave	Brooklyn	NY	11209

Quest Diagnostics - Kearny	206 Bergen Ave Suite A5	Kearny	NJ	07032
Quest Diagnostics - Goshen	30 Hatfield Ln	Goshen	NY	10924
Quest Diagnostics - MONTCLAIR	49 Claremont Avenue	Montclair	NJ	07042
Quest Diagnostics - Newark	24 Commerce St Fl 4	Newark	NJ	07102
Quest Diagnostics - Saugerties	330 Route 212 - Grand Union Plaza	Saugerties	NY	12477
Quest Diagnostics	46 Holley St	Wakefield	RI	02879
Quest Diagnostics - STATEN ISLAND - 81 RANDALL	81 Randall Ave	Staten Island	NY	10301
Quest Diagnostics - PSC-Bayonne	686-692 Broadway, 3rd Floor	Bayonne	NJ	07002
Quest Diagnostics - STATEN ISLAND - 1361 HYLAN	1361 Hylan Blvd	Staten Island	NY	10305
Quest Diagnostics - BUTLER	1395 Route 23S Unit C-1	Butler	NJ	07405
Quest Diagnostics - Staten Island-Todt Hill Road	78 Todt Hill Rd Ste 109	Staten Island	NY	10314
Quest Diagnostics - STATEN ISLAND - WILLOWBROOK	651 Willowbrook Road Suite 101	Staten Island	NY	10314
Quest Diagnostics - STATEN ISLAND - 2627A HYLAN	2627a Hylan Blvd	Staten Island	NY	10306
Quest Diagnostics - West Orange	769 Northfield Ave Ste LI3	West Orange	NJ	07052
Quest Diagnostics - Livingston	349 E Northfield Rd Ste 203	Livingston	NJ	07039
Quest Diagnostics - STATEN ISLAND - 3311 HYLAN	3311 Hylan Blvd	Staten Island	NY	10306
Quest Diagnostics	300 Toll Gate Rd Ste LI5	Warwick	RI	02886
Quest Diagnostics	215 Toll Gate Rd Ste 102	Warwick	RI	02886
Quest Diagnostics - Roselle	711 E 1st Ave Store #17	Roselle	NJ	07203
Quest Diagnostics - UNION-CHESTNUT	440 Chestnut St Unit 102	Union	NJ	07083
Quest Diagnostics - UNION-MORRIS	2333 Morris Ave Ste A-121	Union	NJ	07083
Quest Diagnostics - STATEN ISLAND - RICHMOND AVEN	3733 Richmond Ave	Staten Island	NY	10312
Quest Diagnostics - Johnston	1524 Atwood Ave	Johnston	RI	02919
Quest Diagnostics - Staten Island 4855 Hylan Blvd	4855 Hylan Blvd	Staten Island	NY	10312
Quest Diagnostics	1681 Cranston St	Cranston	RI	02920
Quest Diagnostics - Reservoir Ave	1145 Reservoir Ave	Cranston	RI	02920
Quest Diagnostics - Parsippany	50 Cherry Hill Rd Ste 103	Parsippany	NJ	07054
Quest Diagnostics	999 Warwick Ave	Warwick	RI	02888
Quest Diagnostics	1352 Smith St	Providence	RI	02911
Quest Diagnostics - Denville	Main Street (Route 53) and Luger Road	Denville	NJ	07834
Quest Diagnostics - Aquidneck RRL	50 Memorial Blvd	Newport	RI	02840
Quest Diagnostics - Westfield	189 Elm St Lower Level	Westfield	NJ	07090
Quest Diagnostics - Staten Island - Tottenville	7001 Amboy Road, Store A-4 Tottenville Square Shopping Center	Staten Island	NY	10307
Quest Diagnostics - Plain Street PSC	235 Plain St	Providence	RI	02905
Quest Diagnostics - PSC-Cedar Knolls	8 Saddle Rd Suite 204	Cedar Knolls	NJ	07927
Quest Diagnostics - Randall	1 Randall Sq	Providence	RI	02904
Quest Diagnostics - Morristown	101 Madison Ave Ste 101	Morristown	NJ	07960
Quest Diagnostics - Veterans Memorial	450 Veterans Memorial Parkway Building 8	East Providence	RI	02914
Quest Diagnostics - Winthrop St, Worcester	10 Winthrop St	Worcester	MA	01604

Quest Diagnostics - Red Bank	240 Maple Ave	Red Bank	NJ	07701
Quest Diagnostics - LITTLE SILVER	200 White Rd Ste 104 Little Silver Commons	Little Silver	NJ	07739
Quest Diagnostics - Summit	100 Highland Ave Suite 305	Providence	RI	02906
Quest Diagnostics - HAZLET	1 Bethany Rd Building 5, Suite 67	Hazlet	NJ	07730
Quest Diagnostics - Central St, Worcester	100 Central St	Worcester	MA	01608
Quest Diagnostics - East Ave	407 East Ave	Pawtucket	RI	02860
Quest Diagnostics - HOLMDEL	704 N Beers St	Holmdel	NJ	07733
Quest Diagnostics - Edison-James Street	102 James St Suite 201	Edison	NJ	08820
Quest Diagnostics	333 School St	Pawtucket	RI	02860
Quest Diagnostics - Turners Falls RRL	8 Burnham St	Turners Falls	MA	01376
Quest Diagnostics - Edison - Amboy Avenue	1199 Amboy Ave # Storea-4	Edison	NJ	08837
Quest Diagnostics - Randolph	477 Route 10 East Suite 203	Randolph	NJ	07801
Quest Diagnostics - South Plainfield	904 Oak Tree Ave Ste K	South Plainfield	NJ	07080
Quest Diagnostics - Oakhurst	1900 Highway 35, Suite 101 Ocean Park Cente	Oakhurst	NJ	07755
Quest Diagnostics - Neptune	1809 Corlies Ave Floor 2	Neptune	NJ	07753
Quest Diagnostics - Warren	37 Mountain Blvd Suite #5	Warren	NJ	07059
Quest Diagnostics - PSC-Bernardsville	1 Anderson Rd Ste 101	Bernardsville	NJ	07924
Quest Diagnostics - New Brunswick	77 Church Street	New Brunswick	NJ	08901
Quest Diagnostics - EAST BRUNSWICK	1020 Route 18 Unit 007 - Route 18 Shopping Center	East Brunswick	NJ	08816
Quest Diagnostics - Wrentham PSC	667 South St Wampum Corner	Wrentham	MA	02093
Quest Diagnostics - Truesdale RRL	1030 President Ave Basement	Fall River	MA	02720
Quest Diagnostics - MANALAPAN	46-50 Franklin Lane, Suite 202	Manalapan	NJ	07726
Quest Diagnostics - PSC-BOUND BROOK	601 West Union Ave.	Bound Brook	NJ	08805

<b>EDIC CLINIC 22 – Albert Eienstein</b>				
Quest Diagnostics - Mount Vernon	105 Stevens Ave Ste 205	Mount Vernon	NY	10550
Quest Diagnostics - NYC-West 168th Street	607 W 168th St	New York	NY	10032
Quest Diagnostics - New Rochelle	150 Lockwood Ave	New Rochelle	NY	10801
Quest Diagnostics - Englewood Cliffs	464 Hudson Ter	Englewood Cliffs	NJ	07632
Quest Diagnostics - Queens - Flushing	41-61 Kissena Blvd Ste 25	Flushing	NY	11355
Quest Diagnostics - Queens-Jackson Heights	75-35 31st Ave	Jackson Heights	NY	11372
Quest Diagnostics - Queens-Astoria	27-47 Crescent Street	Astoria	NY	11102
Quest Diagnostics - Queens-Bayside	4401 Francis Lewis Blvd	Bayside	NY	11361
Quest Diagnostics - NYC-1651 3rd Avenue	1651 3rd Ave Fl 2	New York	NY	10128
Quest Diagnostics - NYC - 115 E. 86th Street	115 E 86th St	New York	NY	10028
Quest Diagnostics - NYC - 66 E 86TH ST	66 E 86th St	New York	NY	10028
Quest Diagnostics - ENGLEWOOD	25 Rockwood Pl Ste 1	Englewood	NJ	07631
Quest Diagnostics - Great Neck PSC	287 Northern Blvd. Suite 100	Great Neck	NY	11021
Quest Diagnostics - NYC - WEST 86TH	2 W 86th St Apt 1a	New York	NY	10024

ST				
Quest Diagnostics - NYC - EAST 76TH ST	65 E 76th St	New York	NY	10021
Quest Diagnostics - NYC - E 67TH ST	235 E 67th St Rm 201	New York	NY	10021
Quest Diagnostics - Manhasset PSC	1165 Northern Blvd Suite 404	Manhasset	NY	11030
Quest Diagnostics - Port Washington PSC	14 Vanderventer Ave Suite 105	Port Washington	NY	11050
Quest Diagnostics - Queens-Forest Hills	7010 Austin St	Forest Hills	NY	11375
Quest Diagnostics - NYC - EAST 61ST STREET	115 E 61st St	New York	NY	10021
Quest Diagnostics - Yonkers	970 N Broadway Ste 205	Yonkers	NY	10701
Quest Diagnostics - NYC - 115 E 57TH ST	115 E 57th St Ste 1530	New York	NY	10022
Quest Diagnostics - QUEENS - MIDDLE VILLAGE	7121 Eliot Ave	Middle Village	NY	11379
Quest Diagnostics - PSC- West 58th Street	330 West 58th Street Suite 203	New York	NY	10019
Quest Diagnostics - Teaneck	179 Cedar Ln Suite E	Teaneck	NJ	07666
Quest Diagnostics - Lake Success PSC	2001 Marcus Ave Suite 98W, Lobby Level	Lake Success	NY	11042
Quest Diagnostics - NYC - EAST 36TH STREET	137 E 36th St	New York	NY	10016
Quest Diagnostics - BROOKLYN - GREENPOINT	147 Greenpoint Ave First Floor	Brooklyn	NY	11222
Quest Diagnostics - West New York	4914-4922 Kennedy Blvd. Suite 206	West New York	NJ	07093
Quest Diagnostics - NYC - 247 3RD AVENUE	247 Third Ave Rm 303	New York	NY	10010
Quest Diagnostics - New York Seventh Avenue	275 Seventh Avenue Between 25th & 26th Streets	New York	NY	10001
Quest Diagnostics - Floral Park PSC	265 Jericho Tpke	Floral Park	NY	11001
Quest Diagnostics - NYC - WEST 16TH ST	269 West 16th Street Lower Level	New York	NY	10011
Quest Diagnostics - NYC - West 14th Street	314 West 14th St. Lower Level	New York	NY	10014
Quest Diagnostics - NYC - GREENWICH AVE	119 Greenwich Ave # 5	New York	NY	10014
Quest Diagnostics - Glen Cove PSC	Three Village Square	Glen Cove	NY	11542
Quest Diagnostics - Roslyn Heights PSC	One Expressway Plaza Suite 116	Roslyn Heights	NY	11577
Quest Diagnostics - Hackensack	385 Prospect Ave	Hackensack	NJ	07601
Quest Diagnostics - QUEENS - JAMAICA	12614 Merrick Blvd	Jamaica	NY	11434
Quest Diagnostics - NYC - MOTT ST	41 Mott St Fl 4	New York	NY	10013
Quest Diagnostics - EMERSON	452 Old Hook Rd Suite 1A	Emerson	NJ	07630
Quest Diagnostics - Queens-Howard Beach	Lindenwood Village Shopping Center 82-29 153rd Avenue	Howard Beach	NY	11414
Quest Diagnostics - Paramus	275-277 Forest Ave	Paramus	NJ	07652
Quest Diagnostics - White Plains	280 Dobbs Ferry Rd Sprain Brook Medical Center	White Plains	NY	10607
Quest Diagnostics - Mineola PSC	156 First Street Lower Level	Mineola	NY	11501
Quest Diagnostics - Tappan	111 Route 303 Ste 109	Tappan	NY	10983
Quest Diagnostics - BROOKLYN - PIERREPONT	146 Pierrepont St	Brooklyn	NY	11201

Quest Diagnostics - BROOKLYN HEIGHTS	120 Atlantic Ave	Brooklyn	NY	11201
Quest Diagnostics - Rye Brook	14 Rye Ridge Plz Ste 155	Rye Brook	NY	10573
Quest Diagnostics - Rutherford	17 Sylvan St	Rutherford	NJ	07070
Quest Diagnostics - Jersey City	600 Pavonia Ave	Jersey City	NJ	07306
Quest Diagnostics - Garden City PSC	520 Franklin Ave Suite 104	Garden City	NY	11530
Quest Diagnostics - Hempstead PSC	230 Hilton Avenue Room 220	Hempstead	NY	11550
Quest Diagnostics - BROOKLYN - PARK SLOPE	348 13th St Suite 102	Brooklyn	NY	11215
Quest Diagnostics - FAIRLAWN	33-00 Broadway Suite 305	Fair Lawn	NJ	07410
Quest Diagnostics - BROOKLYN - RALPH AVENUE	2035 Ralph Ave Ste B1	Brooklyn	NY	11234
Quest Diagnostics - Tarrytown	200 South Broadway Suite 102	Tarrytown	NY	10591
Quest Diagnostics - Brooklyn Newkirk Avenue	1416 Newkirk Ave	Brooklyn	NY	11226
Quest Diagnostics - PSC-Brooklyn- 48th Street	949 48th St	Brooklyn	NY	11219
Quest Diagnostics - Rockville Centre PSC	165 North Village Avenue Suite 103	Rockville Centre	NY	11570
Quest Diagnostics - Brooklyn - Boro Park	5102 13th Ave	Brooklyn	NY	11219
Quest Diagnostics - Cedarhurst PSC	222 Rockaway Tpke, Suite 5	Cedarhurst	NY	11516
Quest Diagnostics - Greenwich-Deerfield Dr	2 1/2 Dearfield Dr	Greenwich	CT	06831
Quest Diagnostics - Ridgewood	127 Union St	Ridgewood	NJ	07450
Quest Diagnostics - Kearny	206 Bergen Ave Suite A5	Kearny	NJ	07032
Quest Diagnostics - Clifton	881 Allwood Rd, Suite 103	Clifton	NJ	07012
Quest Diagnostics - BROOKLYN - EAST 14TH ST	1660 E 14th St Ste LL2	Brooklyn	NY	11229
Quest Diagnostics - BROOKLYN - BAYRIDGE	7601 4th Ave	Brooklyn	NY	11209
Quest Diagnostics - Syosset PSC	175 Jericho Turnpike Suite 304	Syosset	NY	11791
Quest Diagnostics - BROOKLYN-BENSONHURST	15 Bay 29th St Room 2B	Brooklyn	NY	11214
Quest Diagnostics - Newark	24 Commerce St Fl 4	Newark	NJ	07102
Quest Diagnostics - Freeport PSC	101 South Bergen Place 2nd Floor	Freeport	NY	11520
Quest Diagnostics - MONTCLAIR	49 Claremont Avenue	Montclair	NJ	07042
Quest Diagnostics - Nanuet	420 Nanuet Mall S Unit 307	Nanuet	NY	10954
Quest Diagnostics - North Haledon	535 High Mountain Rd	North Haledon	NJ	07508
Quest Diagnostics - PLEASANTVILLE	174 Marble Ave Ste 1	Pleasantville	NY	10570
Quest Diagnostics - STATEN ISLAND - 81 RANDALL	81 Randall Ave	Staten Island	NY	10301
Quest Diagnostics - PSC-Bayonne	686-692 Broadway, 3rd Floor	Bayonne	NJ	07002
Quest Diagnostics - Plainview PSC	146A Manetto Hill Rd. Suite 101	Plainview	NY	11803
Quest Diagnostics - Totowa	500 Union Blvd	Totowa	NJ	07512
Quest Diagnostics - Wayne	401 Hamburg Tpke Ste 203	Wayne	NJ	07470
Quest Diagnostics - Bethpage PSC	4276 Hempstead Tpke	Bethpage	NY	11714
Quest Diagnostics - Seaford PSC	850 Hicksville Road Suite 114	Seaford	NY	11783
Quest Diagnostics - Stamford-Mill River	80 Mill River Street	Stamford	CT	06902
Quest Diagnostics - STATEN ISLAND - 1361 HYLAN	1361 Hylan Blvd	Staten Island	NY	10305
Quest Diagnostics - Staten Island-Todt Hill Road	78 Todt Hill Rd Ste 109	Staten Island	NY	10314

Quest Diagnostics - Stamford-Summer Street	1250 Summer St Ste 203	Stamford	CT	06905
Quest Diagnostics - Ramsey	500 N Franklin Tpke Fl 2	Ramsey	NJ	07446
Quest Diagnostics - New City	151 N Main St Unit 307	New City	NY	10956
Quest Diagnostics - STATEN ISLAND - WILLOWBROOK	651 Willowbrook Road Suite 101	Staten Island	NY	10314
Quest Diagnostics - Huntington PSC	195 E Main St Suite D	Huntington	NY	11743
Quest Diagnostics - Pulaski Road PSC	180 E Pulaski Rd	Huntington Station	NY	11746
Quest Diagnostics - STATEN ISLAND - 2627A HYLAN	2627a Hylan Blvd	Staten Island	NY	10306
Quest Diagnostics - Suffern	Indian Rock Shopping Center Route 59 & Hemion Road	Suffern	NY	10901
Quest Diagnostics - Pomona	978 Route 45 Ste 202	Pomona	NY	10970
Quest Diagnostics - Massapequa Park PSC	Southgate Shopping Center 4900 Merrick Road, 2nd Floor	Massapequa Park	NY	11762
Quest Diagnostics - Stamford-Buxton Farm Rd.	30 Buxton Farm Rd	Stamford	CT	06905
Quest Diagnostics - West Orange	769 Northfield Ave Ste LI3	West Orange	NJ	07052
Quest Diagnostics - Roselle	711 E 1st Ave Store #17	Roselle	NJ	07203
Quest Diagnostics - Livingston	349 E Northfield Rd Ste 203	Livingston	NJ	07039
Quest Diagnostics - STATEN ISLAND - 3311 HYLAN	3311 Hylan Blvd	Staten Island	NY	10306
Quest Diagnostics - UNION-CHESTNUT	440 Chestnut St Unit 102	Union	NJ	07083
Quest Diagnostics - Mt Kisco	83 South Bedford Road Floor 3	Mt. Kisco	NY	10549
Quest Diagnostics - UNION-MORRIS	2333 Morris Ave Ste A-121	Union	NJ	07083
Quest Diagnostics - Darien	557 Post Rd	Darien	CT	06820
Quest Diagnostics - STATEN ISLAND - RICHMOND AVEN	3733 Richmond Ave	Staten Island	NY	10312
Quest Diagnostics - Staten Island 4855 Hylan Blvd	4855 Hylan Blvd	Staten Island	NY	10312
Quest Diagnostics - BUTLER	1395 Route 23S Unit C-1	Butler	NJ	07405
Quest Diagnostics - Babylon PSC	400 Montauk Hwy Suite 116	Babylon	NY	11702
Quest Diagnostics - Commack PSC	2171 Jericho Turnpike Suite 102	Commack	NY	11725
Quest Diagnostics - Norwalk Cross St	40 Cross St	Norwalk	CT	06851
Quest Diagnostics - Norwalk-148 East Ave	148 East Avenue	Norwalk	CT	06851
Quest Diagnostics - Norwalk-91 East Ave	91 East Ave	Norwalk	CT	06851
Quest Diagnostics - Westfield	189 Elm St Lower Level	Westfield	NJ	07090
Quest Diagnostics - Staten Island - Tottenville	7001 Amboy Road, Store A-4 Tottenville Square Shopping Center	Staten Island	NY	10307
Quest Diagnostics - Peekskill	2 Stowe Rd 5th Floor - Suite 15	Peekskill	NY	10566
Quest Diagnostics - Parsippany	50 Cherry Hill Rd Ste 103	Parsippany	NJ	07054
Quest Diagnostics - PSC-Cedar Knolls	8 Saddle Rd Suite 204	Cedar Knolls	NJ	07927
Quest Diagnostics - Morristown	101 Madison Ave Ste 101	Morristown	NJ	07960
Quest Diagnostics - Hauppauge PSC	490 Wheeler Rd. Suite 190	Hauppauge	NY	11788
Quest Diagnostics - Edison-James Street	102 James St Suite 201	Edison	NJ	08820
Quest Diagnostics - Bay Shore PSC	8 Saxon Avenue, Suite D	Bay Shore	NY	11706
Quest Diagnostics - Denville	Main Street (Route 53) and Luger Road	Denville	NJ	07834
Quest Diagnostics - Brookside Drive PSC	9 Brookside Drive	Smithtown	NY	11787

Quest Diagnostics - Edison - Amboy Avenue	1199 Amboy Ave # Storea-4	Edison	NJ	08837
Quest Diagnostics - South Plainfield	904 Oak Tree Ave Ste K	South Plainfield	NJ	07080
Quest Diagnostics - Smithtown PSC	222 Middle Country Road Suite 107	Smithtown	NY	11787
Quest Diagnostics - HAZLET	1 Bethany Rd Building 5, Suite 67	Hazlet	NJ	07730
Quest Diagnostics - Ridgefield	38a Grove St	Ridgefield	CT	06877
Quest Diagnostics - HOLMDEL	704 N Beers St	Holmdel	NJ	07733
Quest Diagnostics - Red Bank	240 Maple Ave	Red Bank	NJ	07701
Quest Diagnostics - LITTLE SILVER	200 White Rd Ste 104 Little Silver Commons	Little Silver	NJ	07739
Quest Diagnostics - Fairfield-Post Road	1305 Post Rd Ste 101	Fairfield	CT	06824
Quest Diagnostics - Warren	37 Mountain Blvd Suite #5	Warren	NJ	07059
Quest Diagnostics - Randolph	477 Route 10 East Suite 203	Randolph	NJ	07801
Quest Diagnostics - CARMEL	Barns Office Center - 667 Stoneleigh Ave Bldg N, Suite 115	Carmel	NY	10512
Quest Diagnostics - Fairfield-Black Rock	2150 Black Rock Turnpike	Fairfield	CT	06825
Quest Diagnostics - PSC-Bernardsville	1 Anderson Rd Ste 101	Bernardsville	NJ	07924
Quest Diagnostics - East Setauket PSC	100-10 South Jersey Avenue Heritage Square, Suite 10	East Setauket	NY	11733
Quest Diagnostics - New Brunswick	77 Church Street	New Brunswick	NJ	08901
Quest Diagnostics - PSC-Brewster	Clock Tower Commons, 601 Route 22	Brewster	NY	10509
Quest Diagnostics - East Setauket PSC	23 Technology Dr. Suite 2	East Setauket	NY	11733
Quest Diagnostics - West Sayville PSC	The Bayview Building 233 Montauk Highway	West Sayville	NY	11796
Quest Diagnostics - EAST BRUNSWICK	1020 Route 18 Unit 007 - Route 18 Shopping Center	East Brunswick	NJ	08816
Quest Diagnostics - Trumbull -Park Ave	5520 Park Ave	Trumbull	CT	06611
Quest Diagnostics - Oakhurst	1900 Highway 35, Suite 101 Ocean Park Cente	Oakhurst	NJ	07755
Quest Diagnostics - Bridgeport-2660 Main St	2660 Main St	Bridgeport	CT	06606
Quest Diagnostics - Bridgeport-Beechmont	3180 Main St Beechmont Building	Bridgeport	CT	06606
Quest Diagnostics - Selden PSC	235 Boyle Rd	Selden	NY	11784
Quest Diagnostics - PSC-BOUND BROOK	601 West Union Ave.	Bound Brook	NJ	08805
Quest Diagnostics - Bridgeport-Commerce Park	4695 Main St	Bridgeport	CT	06606
Quest Diagnostics - Port Jefferson PSC	1010 Route 112 2nd Floor	Port Jefferson Station	NY	11776
Quest Diagnostics - Stratford-Lordship	555 Lordship Blvd	Stratford	CT	06615
Quest Diagnostics - Somerset	49 Veronica Ave Ste 203	Somerset	NJ	08873
Quest Diagnostics - Bridgeport-1450 Barnum Ave	1450 Barnum Ave	Bridgeport	CT	06610
Quest Diagnostics - MANALAPAN	46-50 Franklin Lane, Suite 202	Manalapan	NJ	07726
Quest Diagnostics - Trumbull-White Plains Rd	888 White Plains Rd	Trumbull	CT	06611
Quest Diagnostics - Danbury-Germantown	7 Germantown Rd	Danbury	CT	06810
Quest Diagnostics - Stratford-Main Street	2890 Main Street	Stratford	CT	06614

Quest Diagnostics - Trumbull-Technology Dr	115 Technology Dr	Trumbull	CT	06611
Quest Diagnostics - Neptune	1809 Corlies Ave Floor 2	Neptune	NJ	07753
Quest Diagnostics - Goshen	30 Hatfield Ln	Goshen	NY	10924
Quest Diagnostics - Medford PSC	570 Expressway Dr S Suite1-J	Medford	NY	11763
Quest Diagnostics - Bethel	83b Stony Hill Rd	Bethel	CT	06801
Quest Diagnostics - East Patchogue PSC	Brookhaven Professional Park 285 Sills Road, Building 8, Suite A	East Patchogue	NY	11772
Quest Diagnostics - Jamesburg	333 Forsgate Dr Ste 203	Jamesburg	NJ	08831
Quest Diagnostics - Newburgh	347 Fullerton Ave	Newburgh	NY	12550
Quest Diagnostics - Fishkill	982 Main St Ste 9	Fishkill	NY	12524
Quest Diagnostics - FREEHOLD	260 Mounts Corner Drive	Freehold	NJ	07728
Quest Diagnostics - Milford-Bridgeport Ave	2044 Bridgeport Avenue	Milford	CT	06460
Quest Diagnostics - Milford-Noble Ave	88 Noble Ave	Milford	CT	06460
Quest Diagnostics - Shelton	515 Bridgeport Ave	Shelton	CT	06484
Quest Diagnostics - Howell	400 Candlewood Commons, Bldg. 4	Howell	NJ	07731
Quest Diagnostics - Hackettstown	137 Mountain Ave Ste 2	Hackettstown	NJ	07840
Quest Diagnostics - Derby	299 Seymour Ave	Derby	CT	06418
Quest Diagnostics - Ansonia	158 Main St	Ansonia	CT	06401
Quest Diagnostics - Wading River PSC	6144 Route 25A Building B, Suite 8	Wading River	NY	11792
Quest Diagnostics - Princeton	601 Ewing St Suite C-22	Princeton	NJ	08540
Quest Diagnostics - Southbury	385 Main St S	Southbury	CT	06488
Quest Diagnostics - Center Moriches PSC	760-8 Montauk Highway	Center Moriches	NY	11934
Quest Diagnostics - PSC-BRICK	1608 Route 88 Ste 114	Brick	NJ	08724
Quest Diagnostics - West Haven-Main Street	385 Main Street	West Haven	CT	06516
Quest Diagnostics - West Haven-Campbell Avenue	687 Campbell Avenue	West Haven	CT	06516
Quest Diagnostics - New Milford	120 Park Ln	New Milford	CT	06776
Quest Diagnostics - New Haven-Orchard Street	200 Orchard St	New Haven	CT	06511
Quest Diagnostics - New Haven-Sherman Avenue	136 Sherman Avenue, Suite 02	New Haven	CT	06511
Quest Diagnostics - New Haven-Church Street	2 Church St S Ste 115	New Haven	CT	06519
Quest Diagnostics - New Haven-Temple Street	60 Temple Street Temple Medical Building	New Haven	CT	06510
Quest Diagnostics - FLEMINGTON	309 WALTER E. FORAN BLVD. TOWNE CENTRE	FLEMINGTON	NJ	08822
Quest Diagnostics - Poughkeepsie - South Avenue	205 South Ave Ste 203	Poughkeepsie	NY	12601
Quest Diagnostics - East Haven	190 Main Street	East Haven	CT	06512

**EDIC CLINIC 23 – Northwestern**

Quest Diagnostics - Gold Coast PSC	680 N Lake Shore Dr Ste 907	Chicago	IL	60611
Quest Diagnostics - Chicago Loop PSC	111 N Wabash Ave Ste 1514	Chicago	IL	60602
Quest Diagnostics - Sheridan PSC	2800 N Sheridan Rd Ste G1	Chicago	IL	60657

Quest Diagnostics - Halsted PSC	3000 N. Halsted Suite 604	Chicago	IL	60657
Quest Diagnostics - Western Ave PSC	1431 N. Western Avenue Ste 502	Chicago	IL	60622
Quest Diagnostics - Parkway Plaza PSC	4126 N Milwaukee Ave	Chicago	IL	60641
Quest Diagnostics - Peterson PSC	4747 W Peterson Ave Ste 402	Chicago	IL	60646
Quest Diagnostics - Oak Park PSC	610 S Maple Ave Ste 5800	Oak Park	IL	60304
Quest Diagnostics - Berwyn PSC	7222 W. Cermak Rd. Suite 718	North Riverside	IL	60546
Quest Diagnostics - Greenwood PSC	8751 S Greenwood Ave Ste 106	Chicago	IL	60619
Quest Diagnostics - Evanston PSC	2500 Ridge Ave Ste 211	Evanston	IL	60201
Quest Diagnostics - Skokie PSC	4709 W. Golf Suite 806	Skokie	IL	60076
Quest Diagnostics - Rotunda PSC	4340 W 95th St	Oak Lawn	IL	60453
Quest Diagnostics - Oak Lawn PSC	10838 S Cicero Ave	Oak Lawn	IL	60453
Quest Diagnostics - Park Ridge PSC	1600 Dempster St Ste 218	Park Ridge	IL	60068
Quest Diagnostics - The Glen PSC	2591 Compass Rd Ste 110	Glenview	IL	60026
Quest Diagnostics - Hinsdale PSC	40 S Clay St	Hinsdale	IL	60521
Quest Diagnostics - Elmhurst PSC	533 W North Ave Ste 100	Elmhurst	IL	60126
Quest Diagnostics - Glenview PSC	3633 W Lake Ave Ste 201 (2nd floor)	Glenview	IL	60025
Quest Diagnostics - Palos Heights PSC	7800 W College Dr Room 1-W	Palos Heights	IL	60463
Quest Diagnostics - Harvey PSC	15900 Carol Ave	Harvey	IL	60426
Quest Diagnostics - Chicago	1355 Mittel Blvd	Wood Dale	IL	60191
Quest Diagnostics - Lombard PSC	2340 S Highland Ave Ste 330	Lombard	IL	60148
Quest Diagnostics - Downers Grove/Westmont PSC	1113 Fairview Ave	Westmont	IL	60559
Quest Diagnostics - Calumet City Logistics/PSC	1595 Valencia Ct	Calumet City	IL	60409
Quest Diagnostics - Arlington Hgts. East	1300 E Central Rd Ste B - Lower Level	Arlington Hts	IL	60005
Quest Diagnostics - Orland Park PSC	14475 John Humphrey Dr Ste 100	Orland Park	IL	60462
Quest Diagnostics - Tinley Park (S. Oak Park) PSC	16532 S. Oak Park Ave	Tinley Park	IL	60477
Quest Diagnostics - Arlington Heights PSC	1614 W Central Rd Ste 209	Arlington Heights	IL	60005
Quest Diagnostics - Glendale Hgts PSC	303 E Army Trail Rd Ste 111	Bloomington	IL	60108
Quest Diagnostics - Woodridge PSC	7530 Woodward Ave	Woodridge	IL	60517
Quest Diagnostics - Bannockburn PSC	2151 N. Waukegan Rd. Ste. 170	Bannockburn	IL	60015
Quest Diagnostics - Flossmoor PSC	19150 South Kedzie Avenue Suite 101	Flossmoor	IL	60422
Quest Diagnostics - Munster PSC	9126 Columbia Ave	Munster	IN	46321
Quest Diagnostics - Arlington Heights North	1051 W Rand Rd	Arlington Heights	IL	60004
Quest Diagnostics - Tinley Park (S. LaGrange) PSC	18210 S. LaGrange Park Rd. Ste 203	Tinley Park	IL	60477
Quest Diagnostics - Bloomington PSC	471 W Army Trail Rd Ste 101	Bloomington	IL	60108
Quest Diagnostics - Bolingbrook PSC	484 W Boughton Rd	Bolingbrook	IL	60440
Quest Diagnostics - Hobson PSC	1220 Hobson Rd Ste 220	Naperville	IL	60540
Quest Diagnostics - Lake Forest PSC	900 N Westmoreland Rd Ste 123	Lake Forest	IL	60045
Quest Diagnostics - Naperville PSC	640 S Washington St Ste 140	Naperville	IL	60540
Quest Diagnostics - Hoffman Estates PSC	2500 W Higgins Rd Ste 460	Hoffman Estates	IL	60169
Quest Diagnostics - Vernon Hills PSC	870 W End Ct Ste 207	Vernon Hills	IL	60061

Quest Diagnostics - Naperville 95th St. PSC	1012 W. 95th St. Ste. 4	Naperville	IL	60563
Quest Diagnostics - Aurora PSC	4255 Westbrook Dr Ste 203	Aurora	IL	60504
Quest Diagnostics - Aurora Eola PSC	2972 Indian Trail Rd	Aurora	IL	60504
Quest Diagnostics - Portage PSC	6375 US Highway 6	Portage	IN	46368
Quest Diagnostics - Merrillville PSC	9001 Broadway	Merrillville	IN	46410
Quest Diagnostics - Smith Barrington PSC	27401 W. Highway 22	Barrington	IL	60010
Quest Diagnostics - Gurnee PSC	15 Tower Court S-170	Gurnee	IL	60031
Quest Diagnostics - Elgin PSC	373 Summit St Ste 105	Elgin	IL	60120
Quest Diagnostics - Aurora Ogden PSC	2088 Ogden Ave Ste 240	Aurora	IL	60504
Quest Diagnostics - Aurora Copley PSC	2020 Ogden Ave Suite 400	Aurora	IL	60504
Quest Diagnostics - Plainfield PSC	15905 S Frederick St	Plainfield	IL	60586
Quest Diagnostics - Prairie Crossing PSC	1475 E Belvidere Rd Suite 213	Grayslake	IL	60030
Quest Diagnostics - Batavia PSC	1180 W Wilson St	Batavia	IL	60510
Quest Diagnostics - Joliet PSC	310 Hammes Ave Ste 102	Joliet	IL	60435
Quest Diagnostics - St. Charles PSC	640 S Randall Rd	St Charles	IL	60174
Quest Diagnostics - Valparaiso PSC	401 Wall St Suite I	Valparaiso	IN	46383
Quest Diagnostics - Crystal Lake PSC	260 E Congress Pkwy Ste E	Crystal Lake	IL	60014
Quest Diagnostics - McHenry PSC	4119 Shamrock Ln	McHenry	IL	60050
Quest Diagnostics - Yorkville PSC	507 W Kendall Dr Ste 12	Yorkville	IL	60560
Quest Diagnostics - Kankakee PSC	175 E Bethel Dr	Bourbonnais	IL	60914
Quest Diagnostics - St Joseph PSC	2820 Niles Rd Suite A	Saint Joseph	MI	49085
Quest Diagnostics - Belvidere PSC	303 Andrews Dr	Belvidere	IL	61008
Quest Diagnostics - Layton PSC	555 W Layton Ave Ste 400	Milwaukee	WI	53207
Quest Diagnostics - Rockford PSC	5701 Strathmoor Dr Ste 5	Rockford	IL	61107
Quest Diagnostics - Mayfair PSC	2600 N Mayfair Rd Suite 890	Wauwatosa	WI	53226

### EDIC CLINIC 24 – San Diego

Quest Diagnostics - San Diego - Frost	7910 Frost St Ste 180	San Diego	CA	92123
Quest Diagnostics - San Diego - Berger	3131 Berger Ave Ste 100	San Diego	CA	92123
Quest Diagnostics - San Diego - 4th	4060 4th Ave Ste 125	San Diego	CA	92103
Quest Diagnostics - San Diego - Park	4067 Park Blvd	San Diego	CA	92103
Quest Diagnostics - San Diego - 3rd	3260 3rd Ave	San Diego	CA	92103
Quest Diagnostics - San Diego - Alvarado	6367 Alvarado Ct. Ste 205	San Diego	CA	92120
Quest Diagnostics - Encinitas - Santa Fe	351 Santa Fe Dr Ste 110	Encinitas	CA	92024
Quest Diagnostics - Encinitas - El Camino Real	477 N El Camino Real Ste B201	Encinitas	CA	92024
Quest Diagnostics - Poway - Pomerado	15725 Pomerado Rd Suite 210	Poway	CA	92064
Quest Diagnostics - La Mesa- Grossmont Center	5565 Grossmont Center Dr Building 3 Suite 463	La Mesa	CA	91942
Quest Diagnostics - La Mesa - Fletcher	8881 Fletcher Pkwy Suite 285	La Mesa	CA	91942
Quest Diagnostics - La Mesa - Garfield	5125 Garfield St	La Mesa	CA	91941
Quest Diagnostics - National City - 8th	2340 E 8th St Suite F	National City	CA	91950
Quest Diagnostics - El Cajon - Main	1685 E Main St Ste 103	El Cajon	CA	92021

Quest Diagnostics - Chula Vista - 4th	480 4th Ave Ste 101	Chula Vista	CA	91910
Quest Diagnostics - Escondido - Valley Pkwy	488 E Valley Pkwy #215	Escondido	CA	92025
Quest Diagnostics - Chula Vista - 3rd	855 3rd Ave Ste 2250	Chula Vista	CA	91911
Quest Diagnostics - Escondido - Grand	629 E Grand Ave	Escondido	CA	92025
Quest Diagnostics - Chula Vista - 765 Medical Center	765 Medical Center Ct. Suite 204	Chula Vista	CA	91911
Quest Diagnostics - Chula Vista - 754 Medical Center	754 Medical Center Ct Ste 103	Chula Vista	CA	91911
Quest Diagnostics - Chula Vista - Kuhn	841 Kuhn Dr Ste 101	Chula Vista	CA	91914
Quest Diagnostics - Vista - Thunder	145 Thunder Dr	Vista	CA	92083
Quest Diagnostics - Vista - Vista	2023 W Vista Way Ste D	Vista	CA	92083
Quest Diagnostics - Oceanside - Waring	3231 Waring Ct Ste A	Oceanside	CA	92056
Quest Diagnostics - Temecula - Rancho California	29645 Rancho California Rd Ste 117	Temecula	CA	92591
Quest Diagnostics - Temecula - Jefferson	27699 Jefferson Ave Ste 109	Temecula	CA	92590
Quest Diagnostics - San Clemente - Camino De Los Mares	675 Camino De Los Mares Ste 220	San Clemente	CA	92673
Quest Diagnostics - Murrieta - Hancock	25405 Hancock Ave Ste 217	Murrieta	CA	92562
Quest Diagnostics - Dana Point - Monarch Bay Plaza	3 Monarch Bay Plz Ste 108	Dana Point	CA	92629
Quest Diagnostics - Wildomar - Inland Valley	36243 Inland Valley Dr Ste 260	Wildomar	CA	92595
Quest Diagnostics - Mission Viejo - 26732 Crown Valley	26732 Crown Valley Pkwy Ste 521	Mission Viejo	CA	92691
Quest Diagnostics - Mission Viejo - 26800 Crown Valley	26800 Crown Valley Pkwy Ste 480	Mission Viejo	CA	92691
Quest Diagnostics - Elsinore-Casino Dr.	31712 Casino Dr Ste 7b	Lake Elsinore	CA	92530
Quest Diagnostics - Menifee - Haun	29798 Haun Rd Ste 201	Sun City	CA	92586
Quest Diagnostics - Laguna Hills - Calle De La Plata	24022 Calle De La Plata Ste 475	Laguna Hills	CA	92653
Quest Diagnostics - Laguna Woods - Paseo De Valencia	24167 Paseo De Valencia	Laguna Woods	CA	92637
Quest Diagnostics - Rancho Santa Margarita - Santa Marg	29873 Santa Margarita Pkwy Ste 102	Rancho Santa Margarita	CA	92688
Quest Diagnostics - Newport Beach - Avocado	1401 Avocado Ave Ste 103	Newport Beach	CA	92660
Quest Diagnostics - Hemet - Latham	1000 E Latham Ave Ste D	Hemet	CA	92543
Quest Diagnostics - Hemet - Devonshire	1011 E Devonshire Ave Ste 103	Hemet	CA	92543
Quest Diagnostics - Irvine - 4950 Barranca	4950 Barranca Pkwy Ste 101	Irvine	CA	92604
Quest Diagnostics - Irvine - 4050 Barranca	4050 Barranca Pkwy Ste 120	Irvine	CA	92604
Quest Diagnostics - Newport Beach - Placentia	355 Placentia Ave Ste 204	Newport Beach	CA	92663
Quest Diagnostics - Costa Mesa - Baker	1190 Baker St Ste 104	Costa Mesa	CA	92626
Quest Diagnostics - Tustin - Irvine	1095 Irvine Blvd Bldg B	Tustin	CA	92780
Quest Diagnostics - Huntington Beach-19582 Beach	19582 Beach Blvd Ste 217	Huntington Beach	CA	92648
Quest Diagnostics - Santa Ana - Tustin	801 N Tustin Ave Ste 407	Santa Ana	CA	92705
Quest Diagnostics - Fountain Valley -	9900 Talbert Ave # 303	Fountain Valley	CA	92708

Talbert				
Quest Diagnostics - Fountain Valley - Warner	11180 Warner Ave Ste 159	Fountain Valley	CA	92708
Quest Diagnostics - Huntington Beach - Main	18800 Main St Ste 111	Huntington Beach	CA	92648
Quest Diagnostics - Santa Ana - Bush	1800 N Bush St Ste 101	Santa Ana	CA	92706
Quest Diagnostics - Huntington Beach - 17742 Beach	17742 Beach Blvd Ste 227	Huntington Beach	CA	92647
Quest Diagnostics - Corona - Fullerton	1820 Fullerton Ave Ste 100	Corona	CA	92881
Quest Diagnostics - Orange - 705 La Veta	705 W La Veta Ave Ste 102	Orange	CA	92868
Quest Diagnostics - Orange - 1201 W. La Veta	1201 W La Veta Ave Ste 103	Orange	CA	92868
Quest Diagnostics - Orange - 1140 La Veta	1140 W La Veta Ave Ste 570	Orange	CA	92868
Quest Diagnostics - Orange - Stewart	1310 W Stewart Dr Ste 304	Orange	CA	92868
Quest Diagnostics - Corona - 9th	118 W 9th St	Corona	CA	92882
Quest Diagnostics - Orange - Main	230 S Main St Ste 220	Orange	CA	92868
Quest Diagnostics - Westminster - Bolsa	9081 Bolsa Ave Ste 109	Westminster	CA	92683
Quest Diagnostics - Garden Grove - Garden Grove	12665 Garden Grove Blvd Ste 114	Garden Grove	CA	92843
Quest Diagnostics - Anaheim Hills - Anaheim Hills	500 S Anaheim Hills Rd Ste 238	Anaheim	CA	92807
Quest Diagnostics - Moreno Valley - Day	6485 Day St Ste 102	Riverside	CA	92507
Quest Diagnostics - Moreno Valley - Heacock	12712 Heacock St Ste 2	Moreno Valley	CA	92553
Quest Diagnostics - Riverside - 9041 Magnolia	9041 Magnolia Ave Ste 205	Riverside	CA	92503
Quest Diagnostics - Palm Desert - Highway 111	74065 Highway 111	Palm Desert	CA	92260
Quest Diagnostics - Beaumont - Highland Springs	701 Highland Springs Ave Ste 2	Beaumont	CA	92223
Quest Diagnostics - Riverside - 6926 Brockton	6926 Brockton Ave Ste 2	Riverside	CA	92506
Quest Diagnostics - Palm Springs - Tachevah	555 E Tachevah Dr Ste 102w	Palm Springs	CA	92262
Quest Diagnostics - Riverside - 4646 Brockton	4646 Brockton Ave Ste 102	Riverside	CA	92506
Quest Diagnostics - Anaheim - La Palma	1120 W La Palma Ave Ste 11	Anaheim	CA	92801
Quest Diagnostics - Anaheim - Romneya	1801 W Romneya Dr Ste 206	Anaheim	CA	92801
Quest Diagnostics - Rancho Mirage - Bob Hope	36101 Bob Hope Dr Ste E6	Rancho Mirage	CA	92270
Quest Diagnostics - Los Alamitos - Katella	3771 Katella Ave Ste 300	Los Alamitos	CA	90720
Quest Diagnostics - Los Alamitos - Cherry	10861 Cherry St Ste 201	Los Alamitos	CA	90720
Quest Diagnostics - Bermuda Dunes - Washington	41800 Washington St # 108	Bermuda Dunes	CA	92203
Quest Diagnostics - Indio - Dr. Carreon	81715 Dr Carreon Blvd Ste A4	Indio	CA	92201
Quest Diagnostics - Fullerton - Valencia Mesa	100 E Valencia Mesa Dr Ste 104	Fullerton	CA	92835
Quest Diagnostics - La Palma - Walker	7872 Walker St # 109	La Palma	CA	90623
Quest Diagnostics - Fullerton - Harbor	2720 N Harbor Blvd Ste 120	Fullerton	CA	92835
Quest Diagnostics - LONG BEACH-	1045 S. Atlantic Avenue Suite 507	Long Beach	CA	90813

Atlantic-1045				
Quest Diagnostics - Redlands - Terracina	245 Terracina Blvd Ste 104b	Redlands	CA	92373
Quest Diagnostics - LONG BEACH-Woodruff Avenue	3816 Woodruff Avenue Suite 306	Long Beach	CA	90808
Quest Diagnostics - Yucaipa - Yucaipa	34675 Yucaipa Blvd # 100	Yucaipa	CA	92399
Quest Diagnostics - LONG BEACH-Atlantic-2865	2865 Atlantic Avenue Suite 213	Long Beach	CA	90806
Quest Diagnostics - Chino - Roswell	13768 Roswell Suite 220	Chino	CA	91710
Quest Diagnostics - SAN PEDRO	1294 W. 6th Street Suite 206	San Pedro	CA	90732
Quest Diagnostics - WHITTIER-Painter	8135 S. Painter Avenue Suite 104	Whittier	CA	90602
Quest Diagnostics - Chino - Walnut	5475 Walnut Ave	Chino	CA	91710
Quest Diagnostics - BELLFLOWER	10230 Artesia Blvd Suite 307	Bellflower	CA	90706
Quest Diagnostics - LAKEWOOD-South Street	3650 E. South Street Suite 105	Lakewood	CA	90712
Quest Diagnostics - LONG BEACH-Downey Avenue	5830 Downey Ave	Long Beach	CA	90805
Quest Diagnostics - WHITTIER-Whittier Blvd	15141 Whittier Blvd Suite 125	Whittier	CA	90603
Quest Diagnostics - HACIENDA HEIGHTS	1850 S. Azusa Avenue Suite 110	Hacienda Heights	CA	91745
Quest Diagnostics - Diamond Bar - Diamond Bar	750 N Diamond Bar Blvd Ste 110	Diamond Bar	CA	91765
Quest Diagnostics - PARAMOUNT	14906 Paramount Blvd.	Paramount	CA	90723
Quest Diagnostics - TORRANCE-Skypark	3333 Skypark Drive Suite 320	Torrance	CA	90505
Quest Diagnostics - San Bernardino - Waterman	2150 N Waterman Ave Ste 100b	San Bernardino	CA	92404
Quest Diagnostics - DOWNEY-Brookshire	11525 Brookshire Avenue Suite 103	Downey	CA	90241
Quest Diagnostics - Pomona - Artesia	160 E Artesia St Ste 110a	Pomona	CA	91767
Quest Diagnostics - Upland - San Bernardino	1060 San Bernardino Rd	Upland	CA	91786
Quest Diagnostics - Rancho Cucamonga - Grove	8283 Grove Ave Ste 204	Rancho Cucamonga	CA	91730
Quest Diagnostics - TORRANCE-Madison	23441 Madison Street Suite 300	Torrance	CA	90505
Quest Diagnostics - TORRANCE-Lomita Blvd.	3500 Lomita Blvd. Suite 104	Torrance	CA	90505
Quest Diagnostics - Upland - Mountain	575 N Mountain Ave Ste A	Upland	CA	91786
Quest Diagnostics - DOWNEY-Paramount	10800 South Paramount Blvd Suite 103	Downey	CA	90241
Quest Diagnostics - El Centro - Pepper Dr.	1550 Pepper Dr Ste A	El Centro	CA	92243
Quest Diagnostics - El Centro - S. Imperial Ave.	1745 S Imperial Ave Ste 110	El Centro	CA	92243
Quest Diagnostics - SAN DIMAS-Via Verde	1125 Via Verde Rd. Suite B	San Dimas	CA	91773
Quest Diagnostics - REDONDO BEACH-South Prospect	1970 S Prospect Avenue Suite 5	Redondo Beach	CA	90277
Quest Diagnostics - LYNWOOD	3737 Martin Luther King Jr. Blvd. Suite 333	Lynwood	CA	90262
Quest Diagnostics - TORRANCE-	4201 Torrance Blvd. Suite 570	Torrance	CA	90503

Torrance Blvd.				
Quest Diagnostics - Brawley - W. Legion Rd.	751 W Legion Rd	Brawley	CA	92227
Quest Diagnostics - Rancho Cucamonga - Lemon	10399 Lemon Ave Suite 104 Suite 104	Rancho Cucamonga	CA	91737
Quest Diagnostics - WEST COVINA-Sunset Avenue	1135 S. Sunset Ave. Suite 403	West Covina	CA	91790
Quest Diagnostics - SAN DIMAS-West Covina 1330	1330 W. Covina Blvd. Suite 204A	San Dimas	CA	91773
Quest Diagnostics - SAN DIMAS-West Covina 1334	1334 W Covina Blvd Suite 208	San Dimas	CA	91773
Quest Diagnostics - COVINA-Rowland	420 West Rowland Street Lower Level	Covina	CA	91723
Quest Diagnostics - WEST COVINA-Merced Avenue	1535 W Merced Avenue Suite 306	West Covina	CA	91790
Quest Diagnostics - REDONDO BEACH-North Prospect	520 N. Prospect Ave. Suite 207	Redondo Beach	CA	90277
Quest Diagnostics - COVINA-Badillo	546 West Badillo Street Suite A	Covina	CA	91723
Quest Diagnostics - MONTEBELLO	111 W Beverly Blvd Suite 217	Montebello	CA	90640
Quest Diagnostics - GLENDORA-Grand	210 S. Grand Avenue Suite 323	Glendora	CA	91741
Quest Diagnostics - Calexico - East Third	408 East Third Ste Suite E	Calexico	CA	92231
Quest Diagnostics - HAWTHORNE	4477 W. 118 th St. Suite 204	Hawthorne	CA	90250
Quest Diagnostics - ALHAMBRA	1 West Hellman Avenue Suite 6	Alhambra	CA	91803
Quest Diagnostics - INGLEWOOD	323 N. Prairie Avenue Suite 308	Inglewood	CA	90301
Quest Diagnostics - SAN GABRIEL	416 W. Las Tunas Dr., Ste 103 Suite 103	San Gabriel	CA	91776
Quest Diagnostics - EAST LOS ANGELES	1632 E. Cesar Chavez Ave.	Los Angeles	CA	90033
Quest Diagnostics - ARCADIA-West Duarte	612 W Duarte Road Suite 104	Arcadia	CA	91007
Quest Diagnostics - LOS ANGELES-East 3rd Street	420 E. 3rd Street Suite 802	Los Angeles	CA	90013
Quest Diagnostics - LOS ANGELES-Grand Avenue	1414 S. Grand Avenue Suite 180	Los Angeles	CA	90015
Quest Diagnostics - ARCADIA-West Huntington	301 W Huntington Drive Suite 413	Arcadia	CA	91007
Quest Diagnostics - LOS ANGELES-Wilshire 1127	1127 Wilshire Blvd Suite 202	Los Angeles	CA	90017
Quest Diagnostics - LOS ANGELES-Beverly Blvd.	2105 Beverly Blvd. Suite 105	Los Angeles	CA	90057
Quest Diagnostics - PASADENA-Bellefontaine	50 Bellefontaine Street Suite 102	Pasadena	CA	91105
Quest Diagnostics - PASADENA-Congress	10 Congress Street Suite 101	Pasadena	CA	91105
Quest Diagnostics - PASADENA-Green Street	1060 E. Green Street Suite 207	Pasadena	CA	91106

<b>EDIC CLINIC 25 - Maryland</b>				
Quest Diagnostics - Garwyn Medical	2300 Garrison Blvd Ste 206	Baltimore	MD	21216
Quest Diagnostics - Wilkens Ave. PSC	4660 Wilkens Ave SUITE 201	Baltimore	MD	21229
Quest Diagnostics - Catonsville: Maiden Choice	724 Maiden Choice Ln Ste 101	Catonsville	MD	21228
Quest Diagnostics - Frederick Villa	5411 Old Frederick Rd Ste 9	Baltimore	MD	21229
Quest Diagnostics - Dundalk	7544 Holabird Ave	Baltimore	MD	21222
Quest Diagnostics - Harford Road PSC	8035 Harford Road Suite B	Baltimore	MD	21234
Quest Diagnostics - Crain Hwy PSC	1412 N. Crain Hwy Suite 3A	Glen Burnie	MD	21061
Quest Diagnostics - Naylor's Court PSC	4000 Old Court Rd Suite 102	Pikesville	MD	21208
Quest Diagnostics - Lutherville	1205 York Rd Ste 15a	Lutherville	MD	21093
Quest Diagnostics - Seven Square Park PSC	9110 Philadelphia Rd Ste 212	Baltimore	MD	21237
Quest Diagnostics - Randallstown/ Old Court	5400 Old Court Rd Ste 102	Randallstown	MD	21133
Quest Diagnostics - Whitemarsh	8114 Sandpiper Cir Ste 115	Nottingham	MD	21236
Quest Diagnostics - Cross Roads PSC #2	23 Cross Roads Suite 120	Owings Mills	MD	21117
Quest Diagnostics - Owings Mills: Crossroads Drive	21 Crossroads Drive Bldg B -Suite 245	Owings Mills	MD	21117
Quest Diagnostics - Hospital Drive PSC	200 Hospital Dr Ste 103	Glen Burnie	MD	21061
Quest Diagnostics - Oakwood PSC	7845 Oakwood Rd Ste 304	Glen Burnie	MD	21061
Quest Diagnostics - Ellicott City	9055 Chevrolet Dr Ste 101	Ellicott City	MD	21043
Quest Diagnostics - Columbia Medical Center	11055 Little Patuxent Pkwy SUITE 202	Columbia	MD	21044
Quest Diagnostics - Columbia Medical Arts	11085 Little Patuxent Pkwy suite LL 010	Columbia	MD	21044
Quest Diagnostics - Main Street PSC	750 Main St Suite 306	Reisterstown	MD	21136
Quest Diagnostics - Waugh Chapel	2401 Brandermill Blvd	Gambrills	MD	21054
Quest Diagnostics - Eldersburg	6190 Georgetown Blvd Ste 101	Eldersburg	MD	21784
Quest Diagnostics - Crofton	1667 Crofton Ctr Ste 4	Crofton	MD	21114
Quest Diagnostics - Laurel	14201 Laurel Park Dr Ste Suite 107	Laurel	MD	20707
Quest Diagnostics - Old Emmorton Commons	2227 Old Emmorton Rd	Bel Air	MD	21015
Quest Diagnostics - Bel Air: MacPhail Rd	620 W MacPhail Rd Ste 103	Bel Air	MD	21014
Quest Diagnostics - Bestgate PSC	820 Bestgate Rd	Annapolis	MD	21401
Quest Diagnostics - Bel Air: North Ave	4 C North Ave Suite 405	Bel Air	MD	21014
Quest Diagnostics - Bowie: Omni Professional Bldg	4000 Mitchellville Rd Ste A112	Bowie	MD	20716
Quest Diagnostics - Bowie Health Campus	14999 Health Center Dr Ste 201	Bowie	MD	20716
Quest Diagnostics - College Park	6201 Greenbelt Rd Ste M3	College Park	MD	20740
Quest Diagnostics - Westminster Washington Heights	222 Washington Road	Westminster	MD	21157
Quest Diagnostics - Lockwood PSC	10801 Lockwood Dr Ste 130	Silver Spring	MD	20901
Quest Diagnostics - Silver Spring: Four Corners	344 University Blvd W Ste 212	Silver Spring	MD	20901
Quest Diagnostics - Aberdeen PSC	219 W Bel Air Ave Ste 3	Aberdeen	MD	21001
Quest Diagnostics - Takoma Park PSC	7610 Carroll Ave Suite 205	Takoma Park	MD	20912
Quest Diagnostics - Willco Psc	6000 Executive Blvd	Rockville	MD	20852
Quest Diagnostics - Montgomery Village	19271 Montgomery Village Avenue	Montgomery	MD	20886

PSC	Suite H-3			
Quest Diagnostics - Rockville: Shady Grove	15225 Shady Grove Rd Ste 207	Rockville	MD	20850
Quest Diagnostics - Rockville Medical Center Dr	9707 Medical Center Dr Ste 120	Rockville	MD	20850
Quest Diagnostics - Chevy Chase PSC	5454 Wisconsin Ave Ste 1335	Chevy Chase	MD	20815
Quest Diagnostics - Germantown	20528 Boland Farm Rd Ste 205	Germantown	MD	20876
Quest Diagnostics - 19th Street (DC)	1145 19th St, NW Suite 701	Washington	DC	20036
Quest Diagnostics - FoxHall	3301 New Mexico Ave NW Ste 303	Washington	DC	20016
Quest Diagnostics - K St (DC)	2141 K St NW Ste 508	Washington	DC	20037
Quest Diagnostics - M Street PSC	2440 M St NW Ste 414	Washington	DC	20037
Quest Diagnostics - Arlington-Ballston PSC	3833 Fairfax Dr Ste 330	Arlington	VA	22203
Quest Diagnostics - McLean	1515 Chain Bridge Rd Ste G16	Mc Lean	VA	22101
Quest Diagnostics - Clinton	9131 Piscataway Rd Ste 180	Clinton	MD	20735
Quest Diagnostics - Carlin Springs PSC	611 S Carlin Springs Road Suite 103	Arlington	VA	22204
Quest Diagnostics - Hanover	1157 Eichelberger St Suite 3A	Hanover	PA	17331
Quest Diagnostics - Frederick Opossumtown Pike	1560 Opossumtown Pike Ste A-22	Frederick	MD	21702
Quest Diagnostics - Frederick Toll House	915 Toll House Ave Ste 203	Frederick	MD	21701
Quest Diagnostics - Prosperity Plaza	3020 Hamaker Ct Ste 506	Fairfax	VA	22031
Quest Diagnostics - Prosperity Medical Center	8501 Arlington Blvd Ste 120	Fairfax	VA	22031
Quest Diagnostics - Woodburn	3289 Woodburn Rd Ste 90	Annandale	VA	22003
Quest Diagnostics - Fuller Court	6162 Fuller Ct	Alexandria	VA	22310
Quest Diagnostics - Sterling	2 Pidgeon Hill Dr Suite 120	Sterling	VA	20165
Quest Diagnostics - Herndon	106 Elden St Ste 18b	Herndon	VA	20170
Quest Diagnostics - York PSC	1748 6th Ave	York	PA	17403
Quest Diagnostics - York Crossings	York Crossings 2189 York Crossing Drive	York	PA	17408
Quest Diagnostics - Lansdowne PSC	19415 Deerfield Ave Ste 115-b	Leesburg	VA	20176
Quest Diagnostics - Fairfax Main Street	10721 Main St Ste 2100	Fairfax	VA	22030
Quest Diagnostics - Ashburn PSC	21785 Filigree Court, Suite 204	Ashburn	VA	20147
Quest Diagnostics - Middletown PSC	Ketley Professional Plaza - 114 Sandhill Drive Suite 202	Middletown	DE	19709
Quest Diagnostics - Waldorf: Cambridge Prof Bldg	3460 Old Washington Rd Ste 104	Waldorf	MD	20602
Quest Diagnostics	300 Biddle Avenue Suite 202	Newark	DE	19702
Quest Diagnostics - Glasgow PSC	2600 Glasgow Ave Ste 100	Newark	DE	19702
Quest Diagnostics - Catoctin PSC	211 S King St Suite C	Leesburg	VA	20175
Quest Diagnostics - West Grove PSC	1101 Baltimore Pike, Suite 209	West Grove	PA	19390
Quest Diagnostics - Lorton PSC	8988 Lorton Station Blvd Ste 203	Lorton	VA	22079
Quest Diagnostics - Newark Main St	249 E Main Street	Newark	DE	19711
Quest Diagnostics - Lancaster PSC	215 Granite Run Dr	Lancaster	PA	17601
Quest Diagnostics - LaPlata PSC	105 Centennial Street Bldg 3 Unit C	La Plata	MD	20646
Quest Diagnostics - Hor-Omega PSC	A98 100 Omega Drive	Newark	DE	19713
Quest Diagnostics - Woodbridge PSC at Opitz Crossing	2080 Daniel Stuart Sq	Woodbridge	VA	22191
Quest Diagnostics - Stoney Batter	5311 Limestone Rd Suite 202	Wilmington	DE	19808

Quest Diagnostics - Manassas PSC- Canterbury	8685 Sudley Rd	Manassas	VA	20110
Quest Diagnostics - Waynesboro Mall	626 E Main St	Waynesboro	PA	17268
Quest Diagnostics - Dover PSC	1102 South Dupont Highway	Dover	DE	19901
Quest Diagnostics - Millcreek PSC	4512 Kirkwood Hwy Ste 100	Wilmington	DE	19808
Quest Diagnostics - New Castle	525 E Basin Rd	New Castle	DE	19720
Quest Diagnostics - Pennsville PSC	181 N Broadway	Pennsville	NJ	08070
Quest Diagnostics - Trolley Square PSC	Delaware Ave & Clayton St Trolley Square, Suites 3b-4b	Wilmington	DE	19806
Quest Diagnostics - Ephrata PSC	112 N Reading Rd	Ephrata	PA	17522
Quest Diagnostics - Camp Hill	3401 Hartzdale Dr	Camp Hill	PA	17011
Quest Diagnostics - Thorndale	3508 Lincoln Hwy	Thorndale	PA	19372
Quest Diagnostics - Milford	975 N Dupont Hwy	Milford	DE	19963
Quest Diagnostics - Foulk Road PSC	1403 Foulk Rd Ste 103	Wilmington	DE	19803
Quest Diagnostics - Carlisle BMC	850 Walnut Bottom Rd	Carlisle	PA	17013
Quest Diagnostics - Silverside PSC	2700 Silverside Rd Ste 1b	Wilmington	DE	19810
Quest Diagnostics - Carlisle PSC	40 Brookwood Ave	Carlisle	PA	17013
Quest Diagnostics - Harrisburg PSC	4824 Londonderry Rd	Harrisburg	PA	17109
Quest Diagnostics - Downingtown	308 E Lancaster Ave	Downingtown	PA	19335
Quest Diagnostics - Chambersburg	144 S 8th St	Chambersburg	PA	17201
Quest Diagnostics - Seaford PSC	808 Middleford Rd	Seaford	DE	19973
Quest Diagnostics - Concordville PSC	736 Baltimore Pike Suite 9	Concordville	PA	19331
Quest Diagnostics - West Chester	600 E Marshall St	West Chester	PA	19380
Quest Diagnostics - Linglestown PSC	2021 Linglestown Rd	Harrisburg	PA	17110
Quest Diagnostics - Lebanon	Rt 422 West	Lebanon	PA	17042
Quest Diagnostics - Exton	80 W Welsh Pool Rd Ste 102	Exton	PA	19341
Quest Diagnostics - Bridgeton PSC	216 Laurel Heights Dr	Bridgeton	NJ	08302
Quest Diagnostics - Myerstown	725 E Lincoln Ave	Myerstown	PA	17067
Quest Diagnostics - Shillington Shopping Center	520 E Lancaster Ave	Shillington	PA	19607
Quest Diagnostics - Paoli PSC	15 Industrial Blvd Ste Suite A-101	Paoli	PA	19301
Quest Diagnostics - MacDade Blvd	501 W MacDade Boulevard	Folsom	PA	19033
Quest Diagnostics - Birdsboro	321 N Furnace St	Birdsboro	PA	19508
Quest Diagnostics - Berkshire	Berkshire Mall 1665 State Hill Road	Wyomissing	PA	19610
Quest Diagnostics - Springfield	1001 Baltimore Pike Suite 9	Springfield	PA	19064
Quest Diagnostics - Exeter	4400 Perkiomen Ave	Reading	PA	19606
Quest Diagnostics - Fredericksburg	603a Jefferson Davis Hwy	Fredericksburg	VA	22401
Quest Diagnostics - Devon	227 W Lancaster Ave	Devon	PA	19333
Quest Diagnostics - Oaks	Oaks Corporate Center 450 Cresson Boulevard, Suite 305	Phoenixville	PA	19460
Quest Diagnostics - Havertown	2010 W Chester Pike	Havertown	PA	19083
Quest Diagnostics - Fairgrounds Square Mall	3050 N 5th Street Hwy	Reading	PA	19605
Quest Diagnostics - Pottstown PSC	1569 Medical Dr	Pottstown	PA	19464
Quest Diagnostics - Salisbury	712 E Main St	Salisbury	MD	21804
Quest Diagnostics - Millville PSC	1601 N 2nd St Street Unit C-9	Millville	NJ	08332
Quest Diagnostics	2848 S Delsea Dr Suite 2-C	Vineland	NJ	08360
Quest Diagnostics	1012 W 9th Avenue 1st Floor	King of Prussia	PA	19406
Quest Diagnostics - Chancellor PSC	12008 Kilarney Dr	Fredericksburg	VA	22407
Quest Diagnostics - Milford Street PSC	106 Milford St Ste 604	Salisbury	MD	21804

Quest Diagnostics - KOP	491 Allendale Road Ste300	King Of Prussia	PA	19406
Quest Diagnostics - Spotsylvania PSC	10530 Spotsylvania Ave Ste 101	Fredericksburg	VA	22408
Quest Diagnostics - Lewes PSC	1526 Savannah Rd	Lewes	DE	19958
Quest Diagnostics - Collegeville	555 2nd Ave	Collegeville	PA	19426
Quest Diagnostics - Woodbury	730 N Broad St Suite 125	Woodbury	NJ	08096
Quest Diagnostics - Trappe	545 W Main St	Collegeville	PA	19426
Quest Diagnostics - S. Broad Street	2219 S Broad St	Philadelphia	PA	19148
Quest Diagnostics - Sewell	302 Hurffville Crosskeys Rd Suite A-2	Sewell	NJ	08080
Quest Diagnostics - Vineland	3071 E Chestnut Ave Suite A-3	Vineland	NJ	08360
Quest Diagnostics - Gilbertsville	1050 E Philadelphia Ave	Gilbertsville	PA	19525
Quest Diagnostics - Turnersville	188 Fries Mill Rd Bldg. H	Turnersville	NJ	08012
Quest Diagnostics	1437 Dekalb St	Norristown	PA	19401
Quest Diagnostics - Bala Cynwyd	4190 City Avenue - Ste. 416	Philadelphia	PA	19131
Quest Diagnostics - Norristown PSC	720--730 E Johnson Highway	Norristown	PA	19401
Quest Diagnostics - North Broad Street	227 N. Broad St	Philadelphia	PA	19107
Quest Diagnostics - Walnut St PSC	828 Walnut St	Philadelphia	PA	19107
Quest Diagnostics - Roxborough	525 Jamestown St	Philadelphia	PA	19128
Quest Diagnostics - Liberty Town Plaza	412 Sicklerville Rd Ste 106	Sicklerville	NJ	08081
Quest Diagnostics - Haddon Heights	515 Grove Street Suite 1 A	Haddon Heights	NJ	08035
Quest Diagnostics	Cooper River Plaza West 6981 North Park Drive Suite 203	Pennsauken	NJ	08109
Quest Diagnostics - Germantown	2 Penn Blvd Suite 205	Philadelphia	PA	19144
Quest Diagnostics - Flourtown	1107 Bethlehem Pike	Flourtown	PA	19031
Quest Diagnostics - Hamburg	400-B South 4th Street	Hamburg	PA	19526
Quest Diagnostics - Stratford	215 E Laurel Rd Suite 102	Stratford	NJ	08084
Quest Diagnostics - Haddonfield PSC	807 Haddon Ave	Haddonfield	NJ	08033
Quest Diagnostics - Harleysville	484 Harleysville Pike	Harleysville	PA	19438
Quest Diagnostics - Rio Grande PSC	1500 Delsea Drive (Rt 47)	Rio Grande	NJ	08242
Quest Diagnostics - Camden County UDS	1101 White Horse Rd	Voorhees	NJ	08043
Quest Diagnostics - Lansdale	1050 S Broad St	Lansdale	PA	19446
Quest Diagnostics - Juniata	4501 Castor Ave	Philadelphia	PA	19124
Quest Diagnostics - Voorhees	1010 Haddonfield Berlin Rd Suite 400	Voorhees	NJ	08043
Quest Diagnostics - Millville	200 Atlantic Ave Suite A	Millville	DE	19967
Quest Diagnostics - Cherry Hill PSC	1040 Kings Hwy Suite 102	Cherry Hill	NJ	08034
Quest Diagnostics - Roosevelt Plaza	6555 Roosevelt Blvd.	Philadelphia	PA	19149
Quest Diagnostics - Cottman Avenue PSC	700 Cottman Ave	Philadelphia	PA	19111
Quest Diagnostics - Maple Shade	19 W Main St	Maple Shade	NJ	08052
Quest Diagnostics - East Greenville	622 Gravel Pike	East Greenville	PA	18041
Quest Diagnostics - Pottsville	1851 W End Ave	Pottsville	PA	17901
Quest Diagnostics - Abington PSC	1419 Old York Rd	Abington	PA	19001
Quest Diagnostics - Hidden Meadow	2131 N Broad St	Lansdale	PA	19446
Quest Diagnostics - Frankford Avenue	7526 Frankford Ave	Philadelphia	PA	19136
Quest Diagnostics - Hammonton PSC	777 White Horse Pike Ste D3	Hammonton	NJ	08037
Quest Diagnostics - Souderton Square	708 Route 113	Souderton	PA	18964
Quest Diagnostics - Horsham	200 Lakeside Dr Ste 230	Horsham	PA	19044
Quest Diagnostics - Moorestown	502 Pleasant Valley Ave	Moorestown	NJ	08057
Quest Diagnostics - Marlton	4 Eves Dr # A	Marlton	NJ	08053

Quest Diagnostics - Welsh Road	2417 Welsh Rd	Philadelphia	PA	19114
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**EDIC CLINIC 26 – New Mexico**

Quest Diagnostics - Albuquerque PSC	7510 Montgomery Blvd NE Suite 105	Albuquerque	NM	87109
Quest Diagnostics - Santa Fe PSC	465 Saint Michaels Dr Suite 111	Santa Fe	NM	87505
Quest Diagnostics - Los Alamos PSC	159 Central Park Sq	Los Alamos	NM	87544

**EDIC CLINIC 27 - Florida**

Quest Diagnostics - Tampa USF Medical	12901 Bruce B Downs Blvd	Tampa	FL	33612
Quest Diagnostics - Tampa University Plaza	13562 University Plaza #301	Tampa	FL	33613
Quest Diagnostics - Lutz	15511 N Florida Ave Suites 501 & 503	Tampa	FL	33613
Quest Diagnostics - Tampa- Dale Mabry	14831 N Dale Mabry Hwy	Tampa	FL	33618
Quest Diagnostics - Tampa Habana	4710 N Habana Ave Ste 102	Tampa	FL	33614
Quest Diagnostics - Tampa Armenia	4150 N Armenia Ave Ste 101	Tampa	FL	33607
Quest Diagnostics - Tampa South Swann	2919 W Swann Ave Ste 403	Tampa	FL	33609
Quest Diagnostics - Valrico	1946 State Road 60 East	Valrico	FL	33594
Quest Diagnostics - Palm Harbor East Lake	3488 E Lake Rd Suite 203	Palm Harbor	FL	34685
Quest Diagnostics - Brandon Bloomingdale	Bloomingdale Shopping Center, Unit #159 159 E. Bloomingdale Avenue	Brandon	FL	33511
Quest Diagnostics - Palm Harbor	31846 Us Highway 19 N	Palm Harbor	FL	34684
Quest Diagnostics - Plant City	1409 Thonotosassa Rd	Plant City	FL	33566
Quest Diagnostics - Tarpon Springs	1081 S Pinellas Ave Suite E4 & 5	Tarpon Springs	FL	34689
Quest Diagnostics - New Port Richey-Trinity	8823 River Crossing Blvd	New Port Richey	FL	34655
Quest Diagnostics - Clearwater	1219 Cleveland St	Clearwater	FL	33755
Quest Diagnostics - Zephyrhills	6719 Gall Blvd. Suite 203	Zephyrhills	FL	33541
Quest Diagnostics - New Port Richey	Bank of America Professional Center 6014 U.S. Highway 19, suite 402	New Port Richey	FL	34652
Quest Diagnostics - St. Petersburg Northside	6006 49th St N Suite 300	St Petersburg	FL	33709
Quest Diagnostics - Largo	1601 W Bay Dr	Largo	FL	33770
Quest Diagnostics - St. Petersburg	2299 9th Ave N Ste 1b	St Petersburg	FL	33713
Quest Diagnostics - St. Petersburg Pediatric	600 8th Street South Suite A	St. Petersburg	FL	33701
Quest Diagnostics - Seminole	7161 Seminole Boulevard Store #6	Seminole	FL	33772
Quest Diagnostics - Bayonet Point	7515 State Road 52 Suite 103	Bayonet Point	FL	34667
Quest Diagnostics - Ruskin Sun City Center	3814 State Road 674	Ruskin	FL	33573
Quest Diagnostics - Hudson	7414 Community Ct	Hudson	FL	34667
Quest Diagnostics - South Pasadena	6800 Gulfport Blvd S Ste 115	South	FL	33707

		Pasadena		
Quest Diagnostics - Lakeland North	3131 Lakeland Hills Blvd Ste 4	Lakeland	FL	33805
Quest Diagnostics - Lakeland South	1925 E Edgewood Dr Suite 103	Lakeland	FL	33803
Quest Diagnostics - Springhill Landover	3041 Landover Blvd.	Spring Hill	FL	34606
Quest Diagnostics - Brooksville	7007 Nightwalker Rd	Brooksville	FL	34613
Quest Diagnostics - Bradenton	701 Manatee Avenue West Suite 102	Bradenton	FL	34205
Quest Diagnostics - Bradenton Med Arts	2010 59th St W Ste 5800	Bradenton	FL	34209
Quest Diagnostics - Davenport	2217 North Blvd W Suite A	Davenport	FL	33837
Quest Diagnostics - Sarasota University	8451 Shade Avenue, Suite 106	Sarasota	FL	34243
Quest Diagnostics - Lake Wales	2035 State Road 60 E	Lake Wales	FL	33898
Quest Diagnostics - Wachula	465 Carlton St	Wauchula	FL	33873
Quest Diagnostics - Sarasota Bahia Vista	2650 Bahia Vista St Suite 205	Sarasota	FL	34239
Quest Diagnostics - Sarasota Floyd	1901 Floyd St Ste 303	Sarasota	FL	34239
Quest Diagnostics - Sarasota Cattleman	3501 Cattleman Rd	Sarasota	FL	34232
Quest Diagnostics - Clermont	245 Citrus Tower Blvd Suite 203	Clermont	FL	34711
Quest Diagnostics - Inverness	210 S. Apopka Ave	Inverness	FL	34452
Quest Diagnostics - Crystal River	6199 W Gulf To Lake Hwy	Crystal River	FL	34429
Quest Diagnostics - Kissimmee Oak	413 W Oak St	Kissimmee	FL	34741
Quest Diagnostics - Orlando-Sandlake Commons	9350 Turkey Lake Road Suite 200	Orlando	FL	32819
Quest Diagnostics - Orlando Hunters Creek	14050 Town Loop Ctr Blvd W. Suite 201	Orlando	FL	32837
Quest Diagnostics - Ocoee	10131 W. Colonial Dr., Bld. C Suite 8	Ocoee	FL	34761
Quest Diagnostics - Orlando Commerce Center	7520 Commerce Center Dr	Orlando	FL	32819
Quest Diagnostics - Kissimmee East	2238 E Irlo Bronson Hwy	Kissimmee	FL	34744
Quest Diagnostics - Leesburg 11th Street	101 S 11th St Ste 2	Leesburg	FL	34748
Quest Diagnostics - Leesburg Dixie	801 E Dixie Ave Suite 105a	Leesburg	FL	34748
Quest Diagnostics - Sebring	6801 Us Highway 27 N Ste C2	Sebring	FL	33870
Quest Diagnostics - Orlando-Metro West	1603 S Hiawasse Rd Suite 120	Orlando	FL	32835
Quest Diagnostics - St. Cloud	2900 17th Street Suite A	St. Cloud	FL	34769
Quest Diagnostics - Orlando Lucerne Terrace	1700 Lucerne Ter	Orlando	FL	32806
Quest Diagnostics - Venice	333 S. Tamiami Trail Suite 171	Venice	FL	34285
Quest Diagnostics - Lady Lake	121 Lagrande Blvd Ste C	Lady Lake	FL	32159
Quest Diagnostics - Eustis Prevatt	2130 Prevatt St Suite B	Eustis	FL	32726
Quest Diagnostics - Orlando Semoran	5575 S Semoran Blvd Suite 501	Orlando	FL	32822
Quest Diagnostics - Orlando North Mills	1900 N Mills Ave Suite 102	Orlando	FL	32803
Quest Diagnostics - Orlando Par	324 E Par Ave Ste 100	Orlando	FL	32804
Quest Diagnostics - Summerfield	17820 Se 109 Avenue Suite 106A	Summerfield	FL	34491
Quest Diagnostics - Eustis North Bay	720 N Bay St Ste 10	Eustis	FL	32726
Quest Diagnostics - Maitland	541 E Horatio Ave	Maitland	FL	32751
Quest Diagnostics - Winter Park	2111 Glenwood Drive Suite 103	Winter Park	FL	32792
Quest Diagnostics - Longwood	1060 West Sr 434 Suite 100	Longwood	FL	32750
Quest Diagnostics - Ocala State Road 200	8602 SW State Road 200 103rd Street Plaza, Suite J	Ocala	FL	34481
Quest Diagnostics - Orlando Alafaya	2000 N Alafaya Trl Suite 100	Orlando	FL	32826
Quest Diagnostics - Port Charlotte	2484 Caring Way Unit E	Port Charlotte	FL	33952

Quest Diagnostics - Lake Mary	2500 W. Lake Mary Blvd.,suite 210	Lake Mary	FL	32746
Quest Diagnostics - Oviedo	1950 W Sr 426 Ste 108	Oviedo	FL	32765
Quest Diagnostics - Englewood	Merchants Crossing Shopping Ctr 1500 Placida Road, Unit F1	Englewood	FL	34223
Quest Diagnostics - Charlotte Harbor	4161 Tamiami Trl	Charlotte Harbor	FL	33952
Quest Diagnostics - Ocala 3rd Court	2910 SE 3rd Ct Ste B	Ocala	FL	34471
Quest Diagnostics - Ocala Churchill	303 SE 17th St Suite 101a	Ocala	FL	34471
Quest Diagnostics - Orange City	830 Commed Blvd Suite B	Orange City	FL	32763
Quest Diagnostics - Deland	750 W Plymouth Ave Ste B	Deland	FL	32720
Quest Diagnostics - Melbourne Sun Tree	335 Pineda Ct Suite 105	Melbourne	FL	32940
Quest Diagnostics - Titusville	500 N Washington Ave Ste 109	Titusville	FL	32796
Quest Diagnostics - Merritt Island	190 Fortenberry Rd	Merritt Island	FL	32952
Quest Diagnostics - Melbourne Elizabeth	1515 Elizabeth Street	Melbourne	FL	32901

### EDIC CLINIC 41 - Michigan

Quest Diagnostics - Ypsilanti PSC	2144 Washtenaw Rd	Ypsilanti	MI	48197
Quest Diagnostics - Canton PSC	2050 S Haggerty Rd Suite 240	Canton	MI	48188
Quest Diagnostics - Livonia Farmington PSC	11583 Farmington Rd	Livonia	MI	48150
Quest Diagnostics - Novi PSC	40015 Grand River Road Suite 115	Novi	MI	48375
Quest Diagnostics - Taylor PSC	12701 Telegraph Rd Suite 104	Taylor	MI	48180
Quest Diagnostics - Dearborn PSC	3735 Monroe St Suite C	Dearborn	MI	48124
Quest Diagnostics - Allen Park	7445 Allen Rd Suite 150	Allen Park	MI	48101
Quest Diagnostics - Brooklyn PSC	107 Chicago St	Brooklyn	MI	49230
Quest Diagnostics - Waterford Oakland PSC	1255 N Oakland Blvd Suite 135	Waterford	MI	48327
Quest Diagnostics - Monroe PSC	743 N Monroe St	Monroe	MI	48162
Quest Diagnostics - Southfield Advance PSC	23077 Greenfield Rd Suite 472	Southfield	MI	48075
Quest Diagnostics - Bloomfield Hills Woodward PSC	43700 Woodward Ave Suite 101	Bloomfield Hills	MI	48302
Quest Diagnostics - Clarkston Main PSC	5825 Ortonville Rd Suite 202	Clarkston	MI	48346
Quest Diagnostics - Clawson PSC	555 W 14 Mile Rd Suite B1	Clawson	MI	48017
Quest Diagnostics - Fenton Caroline PSC	234 Caroline Street	Fenton	MI	48430
Quest Diagnostics - Jackson PSC	300 W Washington Ave	Jackson	MI	49201
Quest Diagnostics - Troy Dequindre Rd PSC	38815 Dequindre Rd Suite 102	Troy	MI	48083
Quest Diagnostics - Rochester Barclay PSC	135 Barclay Circle Suite 103	Rochester	MI	48307
Quest Diagnostics - Rochester Livernois PSC	455 S Livernois Rd Suite A-14	Rochester	MI	48307
Quest Diagnostics - Toledo Sunforest PSC	3950 Sunforest Court Suite 100	Toledo	OH	43623
Quest Diagnostics - Grand Blanc Holly Rd PSC	8447 Holly Rd	Grand Blanc	MI	48439
Quest Diagnostics - Eastpointe Kelly PSC	22850 Kelly Rd	Eastpointe	MI	48021
Quest Diagnostics - Grand Blanc Porter	6011 Porter Rd	Grand Blanc	MI	48439

PSC				
Quest Diagnostics - Clinton TWP Dalcama PSC	43475 Dalcama Dr Suite 135	Clinton Township	MI	48038
Quest Diagnostics - Maumee PSC	1679 Lance Pointe Rd Suite B	Maumee	OH	43537
Quest Diagnostics - Lansing Genesis Park PSC	3955 Patient Care Drive Suite C	Lansing	MI	48910
Quest Diagnostics - Clinton Township Harper PSC	36535 Harper Ave Suite G	Clinton Township	MI	48035
Quest Diagnostics - Flint Villa Linde Parkway PSC	5080 Villa Linde Parkway Suite 3	Flint	MI	48532
Quest Diagnostics - Flint N Ballenger(Park Plaza)RRLPSC	G1071 N Ballenger Hwy Suite 101	Flint	MI	48504
Quest Diagnostics - Burton East Court PSC	4067 East Court St Suite 4	Burton	MI	48509
Quest Diagnostics - Burton South Belsay PSC	1096 S Belsay Rd Ste H	Burton	MI	48509
Quest Diagnostics - Davison PSC	1094 S State Rd	Davison	MI	48423
Quest Diagnostics - Lapeer Davison Rd PSC	3273 Davison Rd Suite 6	Lapeer	MI	48446
Quest Diagnostics - Mt Morris PSC	11515 N Saginaw St	Mount Morris	MI	48458
Quest Diagnostics - Lapeer Davis Lake Rd PSC	237 Davis Lake Rd	Lapeer	MI	48446
Quest Diagnostics - Grand Ledge PSC	11615 S. Hartel Rd	Grand Ledge	MI	48837
Quest Diagnostics - Frankenmuth PSC	487 N Main St Suite E	Frankenmuth	MI	48734
Quest Diagnostics - Bridgeport PSC	6185 Dixie Hwy Center Suite	Bridgeport	MI	48722
Quest Diagnostics - Saginaw N Michigan Valley PSC	926 N Michigan Ave	Saginaw	MI	48602
Quest Diagnostics - Saginaw North Michigan PSC	1203 N Michigan Ave	Saginaw	MI	48602
Quest Diagnostics - Saginaw Center RRL/PSC	2062 N Center Rd	Saginaw	MI	48603
Quest Diagnostics - Saginaw Shattuck PSC	3550 Shattuck Rd Suite C	Saginaw	MI	48603
Quest Diagnostics - Saginaw Towne Centre PSC	4705 Town Centre Rd Medical Arts Building--Lower Level	Saginaw	MI	48604
Quest Diagnostics - Bay City Trumbull PSC	714 S Trumbull St Tuscola Professional Building	Bay City	MI	48708
Quest Diagnostics - Bay City Wenona PSC	200 S Wenona St	Bay City	MI	48706
Quest Diagnostics - Bay City Katalin PSC	3720 Katalin Ct	Bay City	MI	48706
Quest Diagnostics - Kalamazoo Gull Rd PSC	5555 Gull Rd Suite 203	Kalamazoo	MI	49048
Quest Diagnostics - Midland PSC	111 E Wackerly St Suite C	Midland	MI	48642

## Appendix B

### Informed Consent for Participation in the Cardiac MRI in EDIC Continuing Follow-Up

*(To be modified to meet local IRB Requirements)*

*The purpose of this document is to provide your site with some guidelines for submission of your site-specific consent form. You may choose to utilize a portion of this consent form language for inclusion in an existing consent form or you may choose to utilize the entire document for submission of a separate consent form. This language should only be considered a guideline.*

.....

#### RESEARCH PARTICIPANT INFORMED CONSENT AND PRIVACY AUTHORIZATION FORM

**Protocol Title:** Epidemiology of Diabetes Interventions and Complications Cardiac Magnetic Resonance Imaging (MRI) Study (EDIC CMRI)

**Application No.:**

**Principal Investigator:**

**Date:**

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#### **A. PURPOSE AND BACKGROUND:**

*The purpose of Epidemiology of Diabetes Interventions and Complications (EDIC) is to examine the long-term effects of conventional vs. intensive diabetes treatment received during the DCCT on the development and progression of eye, kidney, nerve, and large blood vessel complications in diabetes. The EDIC study also examines factors, such as blood glucose control, blood pressure, cholesterol levels, smoking and medication use that may be associated with the risk for development and progression of diabetes complications.*

*Because you are a participant in the EDIC study, you are being asked to have a test called a Cardiac Magnetic Resonance Imaging (CMRI) study. People with type 1 diabetes may have greater risk for heart disease, blood vessel disease (arteriosclerosis, sometimes called "hardening of the arteries") and "silent" heart attacks (that is, heart damage that occurs without any of the typical symptoms such as chest pain, arm pain, or chest pressure). The CMRI study in EDIC will provide information about the frequency and severity of these types of problems in people with type 1 diabetes.*

*The EDIC CMRI study is being done in collaboration with the Johns Hopkins University Magnetic Resonance Imaging Reading Center, (JHU MRI RC). If you agree to participate in this study, you will have a CMRI here at the [Local EDIC CMRI Center] and the study itself will be sent to the JHU MRI RC for analysis. The JHU MRI RC will work closely with the EDIC study staff to analyze the information from all participants at all EDIC sites.*

This consent form explains the CMRI study and your part in the study. Please read it carefully and take as much time as you need. Please ask questions at any time about anything you do not understand.

#### **B. VOLUNTARY:**

Your participation in the EDIC CMRI study is voluntary. While you are in this CMRI study, the study team will tell you any new information that could affect whether you want to stay in the study. You may refuse to participate or even withdraw from the study at anytime. If you leave the EDIC CMRI study before it is finished, there will be no penalty to you and you will not lose any benefits to which you are otherwise entitled. If you choose not to participate in this study, it will not affect your participation in any other aspects of EDIC.

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## Informed Consent for Participation in the Cardiac MRI in EDIC Continuing Follow-Up

### C. STUDY PROCEDURES:

The EDIC CMRI study will be done one time during EDIC years 14-15. This study uses magnetic resonance imaging (MRI) to make detailed images of your heart. Before having the CMRI done, you'll be asked to complete a questionnaire to make sure that you are able to safely enter the MRI area. This questionnaire is given to all people having CMRI performed at [the local EDIC CMRI Center]. If you have a history of any metal in your head, eyes, or body; if you have a pacemaker, implanted defibrillator, or other electrical device; or if you are pregnant, you cannot have CMRI performed. Not taking part in the EDIC CMRI will not affect your participation in other parts of the EDIC study. If you are a woman, you will be tested for pregnancy with a urine test.

#### Serum Creatinine measurement of Glomerular Filtration (GFR):

Serum Creatinine measurement of Glomerular Filtration Rate (GFR): A small blood specimen for serum creatinine and calculated GFR will need to be obtained prior to the Gadolinium scan. (5 ml, or less than a teaspoon of blood, will need to be drawn in a lab either at the University of Iowa on the day of test, or locally 1-2 months before the visit). GFR is estimated from serum creatinine using an equation that varies if the participant is a woman, non-Caucasian, and older. Therefore, if you are on dialysis or had a kidney transplant or ever had a GFR < 60 during DCCT or EDIC you will not complete the Gadolinium portion of this test. However, you may still participate in the remaining portions of the CMRI study. Also note that

The GFR will be estimated from a Serum Creatinine that is measured locally within 1 - 2 months before the Gadolinium test. Your Serum Creatinine will either be drawn on the day of your EDIC visit and sent to the University of Iowa Hospitals & Clinics laboratory, or you may choose to use a lab identified for you by the EDIC staff ahead of time, on a separate visit, which may be closer to where you live.

MRI Examination: The effects of magnetic fields in a CMRI scanner have been extensively studied, and there are no known significant risks with an MRI exam. However, you may not participate in this study if you have a pacemaker, an implanted defibrillator or certain other implanted electronic or metallic devices. It is important for you to advise the EDIC MRI staff if you have had brain surgery for a cerebral aneurysm, or if you have implanted medical or metallic devices, shrapnel, or other metal, such as metal in your eye.

If you use an insulin pump or continuous glucose pens you will be asked to remove these devices during the CMRI scanning procedure. The study coordinator will work with you to minimize any impact this may have on your diabetes control.

The CMRI scanner is a long, narrow tube, and even though ends of the tube are open, you may be bothered by feeling confined (claustrophobia). If this is significant to you, please notify the CMRI staff. You may end your participation in this study at any time by telling the CMRI staff.

If you are able to have CMRI testing, you will be asked to lie on a padded table. A device called an imaging coil will be placed on your body in the area where the images will be taken. The coil is necessary to help the MRI machine take pictures. The table on which you are lying will be moved to the center of a CMRI magnet, which looks like a long narrow tube.

When CMRI pictures are taken it is normal for the CMRI machine to make loud banging and clicking noises. You will be asked to wear earplugs or earphones for your comfort during the test.

Contrast Agent (Gadolinium) Gadolinium is used routinely for CMRI exams to help identify the presence of scarring of the heart. You will be given a contrast agent call Gadolinium. This will be given as an injection through a vein in your arm. The Gadolinium contrast agent is used to make any cardiac scarring that is present easier to identify. Cardiac scarring occurs following heart attacks, and so this test will be useful especially for identifying "silent" heart attacks.

Insertion of the needle may cause minor pain, bruising, and/or infection at the injection site. The Gadolinium itself does not cause pain but you may feel discomfort, tingling, or warmth in the lips, a metallic taste in the mouth, tingling in the arm, nausea, or headache. These symptoms occur in less than 1% (less than 1 in 100) of people and go away quickly. Very rarely allergic reactions to Gadolinium have occurred, but the risk of severe allergic reaction is less than one in 300,000. There will be emergency personnel and equipment on hand for your safety. A physician will be

## Informed Consent for Participation in the Cardiac MRI in EDIC Continuing Follow-Up

available during the procedure to administer any necessary care if side effects do occur, and to determine when or if the injection of the contrast agent should be stopped.

Please notify the EDIC staff and CMRI technologist if you are allergic to gadolinium, if you have experienced any of these effects, or if other symptoms concern you.

\*Special Note\* - In June 2006, the FDA released a public advisory regarding contrast agents containing gadolinium. They are investigating a potential relationship between gadolinium and the development of Nephrogenic Systemic Fibrosis/Nephrogenic Fibrosing Dermopathy (NSF/NFD) in patients with renal failure. The clinical picture of NSF/NFD involves the skin with hardening and plaque formation, flexion contractures of the joints, the liver, lungs kidneys and heart. There have been a few fatalities. Gadolinium is excreted by the kidney so people with chronic renal insufficiency have greater degrees of exposure through longer retention times.

GFR is estimated from serum creatinine using an equation that varies if the participant is a woman, non-Caucasian, and older. Therefore, if you are on dialysis or had a kidney transplant or have a GFR result < 60 within 1-2 months of the CMRI study, you will not complete the Gadolinium portion of this test. However, you may still participate in the remaining portions of the CMRI study.

During the exam, the CMRI staff will be able to see and hear you. In addition, you will be able to hear the CMRI staff. The CMRI staff will be talking to you throughout your CMRI exam, and may give you simple instructions, such as holding your breath or repositioning a stance. You will generally be requested to lie perfectly still through out the exam. In most cases, the CMRI procedure can be completed within 1 to 2 hours.

The results of the CMRI exam will be made available to you and your own physician (s) or health care professional after they have been analyzed. The results will be added to the other data that have been collected in DCCT and EDIC.

### **What might interfere with the completion of your CMRI test?**

We may take you out of the study early or reschedule your study if you are unable to tolerate the CMRI examination for whatever reason or if the equipment malfunctions.

### **Inclusion and Exclusion Criteria [amend according to local CMRI inclusion/exclusion criteria].**

Inclusion Criteria: Anyone who is a participant in the EDIC study may take part in the EDIC CMRI study UNLESS any of the CMRI exclusion criteria listed below are present.

Exclusion Criteria: [amend to include any local exclusion criteria not listed]

You cannot take part in the EDIC CMRI study if;

- You are pregnant.
- You have a history of any metal in your head or eyes.
- You have a pacemaker, an implanted defibrillator, or certain other implanted electronic or metallic devices.

You cannot take part in the Gadolinium test if;

- You are on dialysis, had a kidney transplant, or ever had a GFR < 60.
- You have had an allergic reaction to Gadolinium in the past.

**For safety purposes, it is critical that the estimated GFR be from a serum creatinine measured locally within 1 – 2 months before the Gadolinium test. The locally determined serum creatinine must be sent to the Data Coordinating Center where the GFR will be calculated and sent to the study coordinator who will complete the screening process.**

### **D. RISKS AND/OR DISCOMFORT:**

Time Commitment:

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Participation in this CMRI study will involve a commitment of up to several hours. The study coordinator will work with you and the local CMRI staff to help find a time that best fits your schedule. If possible, the study will be done on the same day that you come to the EDIC center for your other yearly tests.

### Informed Consent for Participation in the Cardiac MRI in EDIC Continuing Follow-Up

You will ordinarily not be paid for travel expenses to the clinic conducting the examinations. You will not be paid for time lost from work. You will also not be provided with free medical care for any diabetes complications discovered during yearly visits. You will, however, be counseled as to what care would be appropriate and where and how to obtain it.

#### Risk of Loss of Privacy:

Your CMRI study will be identified using your EDIC study identification number, and not by information, that personally identifies you. Information that could link your EDIC study identification number to your personal identity will not be

given to anyone outside of the EDIC study and will not be available to the staff at the JHU MRI RC or other third parties unless they have a legal right to view that information. Information about you collected for the EDIC study, including results from your CMRI are sent to the EDIC Data Coordinating Center at The Biostatistics Center of The George Washington University for statistical analysis. Research records will be kept in restricted areas at **(EDIC Clinic)**. Please review section G of this document for further details about the confidentiality of research information collected about you.

WHAT SHOULD YOU DO IF YOU ARE INJURED OR ILL AS A RESULT OF BEING IN THIS CMRI STUDY?

Call **(EDIC Clinic PI, SC) at (EDIC Clinic PI and SC Phone #)**, if you have an urgent medical problem or if you think you injured or ill because of your participation in this study.

Medical care at **(EDIC Clinic)** is open to you as it is to all sick or injured people. **(EDIC Clinic)** does not have a program to pay you if you are hurt or have other bad results from being in the study. The costs for any treatment or hospital care would be charged to you and/or your insurance company.

#### **E. BENEFITS:**

Because you have diabetes, you may benefit from the tests being conducted in this study because they may identify problems that would benefit from early detection and treatment. The results of the CMRI exam will be made available to you, and if you choose, to your personal health care professional, once they have been analyzed. The information gathered during this study will also continue to be of great benefit to society at large and other patients with diabetes in particular.

#### **F. COST/PAYMENT:**

All of the tests conducted in this CMRI study will be performed at no cost to you or to your insurance carrier. However, if any of the tests performed for CMRI reveal a condition that may require additional testing or evaluation, you or your insurance carrier will be responsible for those charges. You, or your insurance company, will still be responsible for the costs associated with any procedures that were ordered by your health care professional as part of your routine care.

**Will you be paid if you join this study?**

You will not be paid if you participate in this study.

#### **G. CONFIDENTIALITY:**

**How will your privacy be protected?**

**(EDIC Clinic)** has rules to protect information about you. Federal and state laws also protect your privacy. This part of the consent form tells you what information about you may be collected in this study and who might see or use it.

## Informed Consent for Participation in the Cardiac MRI in EDIC Continuing Follow-Up

Generally, only people on the EDIC research team will know that you are in the study and will see your information. However, there are a few exceptions that are listed later in this section of the consent form. Unless you give permission or the board that reviews research studies approves it, no one else will be able to see or use your information.

The people working on the study will collect information about you. This includes things learned from the tests described in this consent form. They may collect other information including your name, address, date of birth, and other details.

Sometimes other people at **(EDIC Clinic)** may see or give out your information. These include people who review the research studies, their staff, lawyers, or other **(EDIC Clinic)** staff.

People outside of **(EDIC Clinic)** may need to see your information for this study. Examples include government groups, safety monitors, other hospitals in the study, and organizations that sponsor the study.

We cannot do this study without your permission to use and give out your information. You do not have to give us this permission. If you choose to not provide your permission, you may not be able to participate in CMRI study.

We will use and share your information only as described in this consent form and in our Notice of Privacy Practices. However, people outside **(EDIC Clinic)** who receive your information also will be asked to not share your information.

We try to make sure that everyone who needs to see your information keeps it confidential – but we cannot guarantee this.

The use of your information has no time limit. You can cancel your permission to use and disclose your information at any time by calling the **(EDIC Clinic)** IRB at \_\_\_\_\_ or by sending a letter to:

### **(EDIC Clinic) IRB Address**

Your cancellation would not affect information already collected in this study.

### **Will the study require any of your other health care providers to share your health information with the researchers of this study?**

By participating in this study, you are providing researchers involved with this study permission to access your medical records. If you do not want researchers involved in this study to have access to your medical records, you should not participate in this study.

*What is the Institutional Review Board (IRB) and how does it protect you?*

The **(EDIC Clinic)** IRB is made up of:

- Doctors
- Nurses
- Ethicists
- Non-scientists
- People from the local community.

The IRB reviews human research studies. It protects the rights and welfare of the people taking part in those studies. You may contact the IRB if you have questions about your rights as a participant or if you think you have not been treated fairly. The IRB office number is **(EDIC Clinic IRB phone #)**. You may also call this number for other concerns or questions about the research.

### **H. CONTACT INFORMATION:**

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2 WHAT ARE THE ORGANIZATIONS THAT ARE PART OF (EDIC CLINIC)?  
(EDIC Clinic) includes the following:

**Informed Consent for Participation in the Cardiac MRI in EDIC Continuing Follow-Up**

- The (EDIC Clinic) University
- The (EDIC Clinic) Hospital
- Etc...

**What do you do if you have questions about the study?**

Call the principal investigator, (EDIC Clinic PI) or study coordinator (EDIC Clinic SC) at (EDIC Clinic SC Phone #). If you cannot reach the principal investigator study coordinator or wish to talk to someone else, you may call the IRB office at (EDIC Clinic IRB Phone #)

**I. RECORD OF INFORMATION PROVIDED:**

**What does your signature on this consent form mean?**

Your signature on this consent form means that:

- you understand the information given to you in this form
- you accept the information contained in this form
- you agree to participate in the EDIC CMRI study

You will not give up any legal rights by signing this consent form.

**WE WILL GIVE YOU A COPY OF THIS SIGNED AND DATED CONSENT FORM**

NOT VALID WITHOUT THE IRB  
STAMP OF CERTIFICATION

*Do not sign after the expiration date of: \_\_\_\_\_*

\_\_\_\_\_  
Signature of Participant

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature of Person Obtaining Consent

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature of Witness to Consent Procedures (optional unless IRB or Sponsor required)

\_\_\_\_\_  
Date

**NOTE: A COPY OF THE SIGNED, DATED CONSENT FORM MUST BE KEPT BY THE PRINCIPAL INVESTIGATOR; A COPY MUST BE GIVEN TO THE PARTICIPANT; AND IF APPROPRIATE A COPY OF THE CONSENT FORM MUST BE PLACED IN THE PARTICIPANT'S MEDICAL RECORD**

Revised 1/15/2008

## 32. ANCILLARY STUDIES

An ancillary study is defined as research or data collection involving EDIC study participants or specimens, using any technique, medication, procedure, questionnaire, or observation other than those set forth in the EDIC Protocol. (Refer to Chapter 8.5) Ancillary studies will be evaluated with careful consideration of their potential impact on the objectives and performance of the EDIC.

Ancillary studies that complement the objectives and enhance the value of the EDIC Core protocol, while serving to augment and promote the continued interest of both participants and investigators are encouraged. No ancillary study will:

- 1) Cause a deviation from the Core Protocol
- 2) Confound interpretation of the study results
- 3) Adversely affect participant cooperation
- 4) Jeopardize the public image of the study
- 5) Create a significant diversion of the study resources locally or centrally
- 6) Negatively influence the cooperative spirit of the collaborating investigators
- 7) Compromise the scientific integrity of the study

Numerous ancillary studies (completed and to be completed) have been implemented within the EDIC study. These studies are listed in the Table 32.1. Some of the studies listed in Table 32.1 have been included in the EDIC Manual of Operations (refer to the Table of Contents). For all of the Ancillary Studies, operational issues and further information about the study protocol, informed consent process, data collection methods, local and central operations and other information pertaining to the ancillary study can be found on the secure EDIC website (Home Page → Projects → Current or Historic → Project name).

**TABLE 32.1 - EDIC ANCILLARY STUDIES**

Study/Project Name and Description	Data Collection Period
<b>DCCT Family Study</b> - Study of familial clustering and correlation of severity of eye & kidney disease in first degree relatives of the DCCT proband	1992
<b>Lipoprotein Collections (Brunzell)</b> - Study of natural history of changes in lipoprotein distribution and LDL composition to predict atherosclerosis and premature death	1993-2006
<b>Marker &amp; Mechanisms of Vascular Disease in Diabetes (MMVD)</b> - Collaborative study to determine why people with diabetes have increased incidence of heart and blood vessel disease	1993-2006
<b>Carotid Ultrasounds</b> - Study of diabetes effects on carotid arteries (intimal thickening) in large blood vessels	1993, 1996, 2005
<b>Coronary Calcium (EBCT)</b> - Study of effects of diabetes and atherosclerosis in the coronary arteries and large blood vessels	2001
<b>EDIC Genetic Family</b> - Study of first degree relatives to determine the associated genes for the development of diabetes and its complications	2001-2004
<b>URO EDIC I</b> - Study of the prevalence and severity of bladder dysfunction, sexual dysfunction and UTI's in T1DM	2002-2003
<b>Neurocognitive</b> – Evaluate the impact of diabetes control in T1DM on learning skills, memory, problem-solving, and mental efficiency	2004-2006
<b>Neurology</b> (exam; nerve conduction; ANS) - Study of diabetes control in T1DM on nerve damage to both the peripheral and autonomic nervous systems	2005-2007
<b>ANS 2</b> - ANS testing only	2009 -
<b>Cardiac MRI</b> - Evaluation of the heart and its blood vessels for problems related to both structure and function in T1DM.	2007-2009
<b>Fundus Methods</b> - Comparison / validation study employing both standard film and digital images	2007-2009
<b>Retention Survey</b> – Study to understand participant reasons for continued participation in a long term epidemiological study	2008-20010
<b>Epigenetics</b> – Case/Control study of select subset of subjects to determine if “metabolic memory” is related to expression/repression of certain genes in the development of eye / kidney complications in T1DM	2009-
<b>SCOUT</b> – Evaluate use of non-fluorescence device to assess the risk of diabetes related complications	2009- 2010

**TABLE 32.1 - EDIC ANCILLARY STUDIES** *(continued)*

Study/Project Name and Description	Data Collection Period
<b>DCCT/EDIC Collaborations - Collaborations with Cleveland Clinic and CVD Biomarkers</b>	2010 -
<b>URO-EDIC II</b> - Examine the relationships between diabetes and bladder and sexual health in both men and women, and assess the differences in PSA/testosterone in males at year 10/11 compared to year 17/18.	2010-
<b>Cheiroarthropathy</b> – Determine prevalence cheiroarthropathy, identify risk factors, and determine association with other diabetes complications	2011 -
<b>C-Peptide Pilot</b> – Determine the likelihood of measurable amounts of stimulated C-peptide in selected subjects (n=60) in the DCCT/EDIC cohort	2011 -
Haptoglobin Markers – Collaboration with A. Levy on saved specimens	2011 -