# Epidemiology of Diabetes Interventions and Complications Continuing Follow-Up


# PROTOCOL

CORE

**1st Edition November 2005**

**Amended May 2007**
**Amended May 2008**
**Amended March 2009**
**Amended October 2012**
**Amended September 2013**

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## SUMMARY OF PROTOCOL CHANGES

The EDIC protocol represents chapters 1-8 of the EDIC Manual of Operations. The protocol has recently been revised and updated to:

Listed below is a summary of the significant changes made to Chapter 4 of the Protocol; clarifying language that does not change the intent of the original text and grammatical inconsistencies are not included in this summary. Please note that page numbers refer to the "Track Changes" version of the revised Protocol.

### PREFACE

- Listing of activities / decisions updated from 2007 through August 2012 (pages ii-iii)

### CHAPTER 4: INFORMED CONSENT

- Clarifying language added for saved samples at the CBL and the NIDDK Central Repository (page 4-2)
- Informed Consent template:
  1) Study time frame clarified (page 4-3)
  2) Study duration identified as up to June 30, 2017 (page 4-3)
  3) Interim study contact between annual visits was added (page 4-3)
  4) Diabetes supplies as made available by Industry, are offered to participants (page 4)
  5) All previously completed evaluations and collections removed (pages 4-4 and 4-4)
  6) Request for participants to contact EDIC staff if interested in other research (page 4-4)
  7) Inclusion of previously given Social Security # would be kept on file from the previously collected Personal Locator Forms, to be used if needed for future contact (page 4-4)
  8) Separate consent for use of past, current and future stored CBL samples (page 4-4)
  9) Separate consent for use of past, current and future stored NIDDK Central Repository specimens (page 4-5)
  10) Request written correspondence to PI for withdrawing from the study (pages 4-6,4-7)

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# 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 Data Coordinating 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 Study Group.

3. Dissemination of Revisions. After any revisions have been approved, the Data Coordinating Center will be responsible for initial drafts and final editions 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 Diabetes Control and Complications Trial (DCCT) 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 Year 7 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 and measured 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 entered 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), administered with each study ophthalmologic evaluation
    - Quality of Well Being Scale (QWB-SA), to be administered one time
    - The initial 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, with completion in April 2009. Because of the safety issue with respect to the contrast agent, gadolinium, the GFR estimated from serum creatinine was measured locally within 1 – 2 months before the Gadolinium test.

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, the External Advisory Committee (EAC) was renamed the External Evaluation Committee (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 APS will be repeated in EDIC Years 16 & 17.

14. In January 2009, administration of the Food Frequency Recall Questionnaire was discontinued.

15. In fall 2010:

    a. The EEC was renamed the OSMB (Oversight Monitoring Board).

b. Cardiac Autonomic Neuropathy (CAN) testing was repeated during EDIC Years 16-17, based on R-R interval measurement. Rationale: CAN testing serve to measure progression of autonomic neuropathy as a risk factor for CVD.
c. The Authorship policy was updated and revised (Chapter 8)

16. In fall 2011:
    a. The working committees were renamed: Follow-up became the Adherence Monitoring Committee, the Quality Review became the Data Quality Assurance Committee, the Editorial / Analytical Committee became the Publications and Presentations Committee, and the Study Coordinators and Study Group were listed as working committees.
    b. Use of color film was discontinued and the EDIC photographers at all clinical centers were certified for digital photography. This transition was based on an ancillary study that demonstrated equivalence in the quality of photographs and ability to detect the EDIC ophthalmic outcomes. Electronic uploading of digital images via the CORU portal became available at the clinical sites in early 2012.

17. In August 2012:
    a. The four hour renal exam and measurement of albumin excretion rate (AER) was discontinued, and replaced with a random urine collection, preferably in the morning, for calculation of albumin:creatinine ratio (ACR). Annual measurement of serum creatinine did not change.
    b. Annual measurement of cystatin C was suspended, pending future identification of funding. If funding is secured, cystatin C will be measured using annually-collected saved serum samples.
    c. Measurement of ankle and brachial blood pressures for calculation of ankle:brachial index was changed from annual to alternating years, during the renal visit.
    d. The EDIC Protocol and Manual of Operations were reviewed and updated.
    e. The number of clinical sites is reduced from 28 to 27, resulting in the closure of Clinic 22, Albert Einstein College of Medicine. Participants from this center are encouraged to continue participation via transfer to other nearby EDIC clinical centers (Cornell – Clinic 3, Yale – Clinic 22 or University of Pennsylvania – Clinic 2).
    f. Plans initiated to transition from central data entry at the Data Coordinating Center to the clinical centers.

18. In September 2013:
    a. NIDDK Central Repository language was updated to include agreement for use of past, current, and future use of saved samples.
    b. The Central Biochemistry Lab (CBL) language was updated to include agreement for use of past, current, and future use of saved samples.
    c. Language was included in the Informed Consent that allows for interim contact with participants between annual visits to ascertain if interim clinical events have occurred. The frequency of this contact will be need based and likely infrequent.
    d. Other research: participants should notify EDIC study staff when considering participation in other research.
    e. Study withdrawal: study withdrawal requires written notification from the participant to the PI

f. Diabetes supplies: Diabetes supplies, as made available by industry, are offered to participants.
g. Study period: Update the period of study to read “annual visits through June 30, 2017”.
h. Use of personal information: Review contact information and use of personal locator form/SSN.
i. Outdated ancillary studies: Language has been removed related to previously completed studies from the Core Consent (e.g., Cherioarthropathy, SCOUT, ANS, Neurological testing, etc.) If allowed by local IRB policies, placement of ancillary studies as addendums to the Core study can facilitate removal of completed studies over time.

# 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] and by 2007, total costs associated with diabetes and its complications were $174 billion.[71]

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 subjects 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 subjects 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 subjects 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 have been of short (<2 years) duration and have 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 subjects 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 subjects, 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 since participants entered the study in 1983-1989, with over 90% of the surviving cohort participating in the study. This cohort represents the most carefully studied group of type 1 diabetic subjects 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 "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, 1982-1993) and the Epidemiology of Diabetes Interventions and Complications (EDIC, 1994-present) follow-up study have been ongoing for 29 years.[22-25] After a mean follow-up of approximately 25 years, the cohort remains remarkably complete with over 90% of the original cohort participating in the study. 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 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 individuals 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)**

| | Percent Reduction | |
|---|---|---|
| **Complication** | **During DCCT** | ***During EDIC** |
| Retinopathy *(*EDIC results through Year 10)* | | |
| 3-step change | 63 | 72 |
| Proliferative | 47 | 76 |
| Macular edema | 26** | 77 |
| Laser therapy | 51 | 77 |
| Nephropathy *(*EDIC results through Year 8)* | | |
| Microalbuminuria (> 28μg/min) | 39 | 53 |
| Clinical albuminuria (> 208μg/min) | 54 | 82 |
| Neuropathy | 60 | see below+ |

**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

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Methods. The DCCT studied a cohort of 1,441 participants 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 participants 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 participants with T1DM for 1-15 years and mild to moderate nonproliferative retinopathy and a urinary albumin excretion rate <200 mg/day. Participants 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 participants 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 participants 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 at DCCT end) 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 became statistically indistinguishable by the 5th year of EDIC follow-up. (Figure 1.1)

Phase 1 of the EDIC follow-up study spanned 10 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 EDIC year 10 are shown in Table 1.2.

**Figure 1.1**

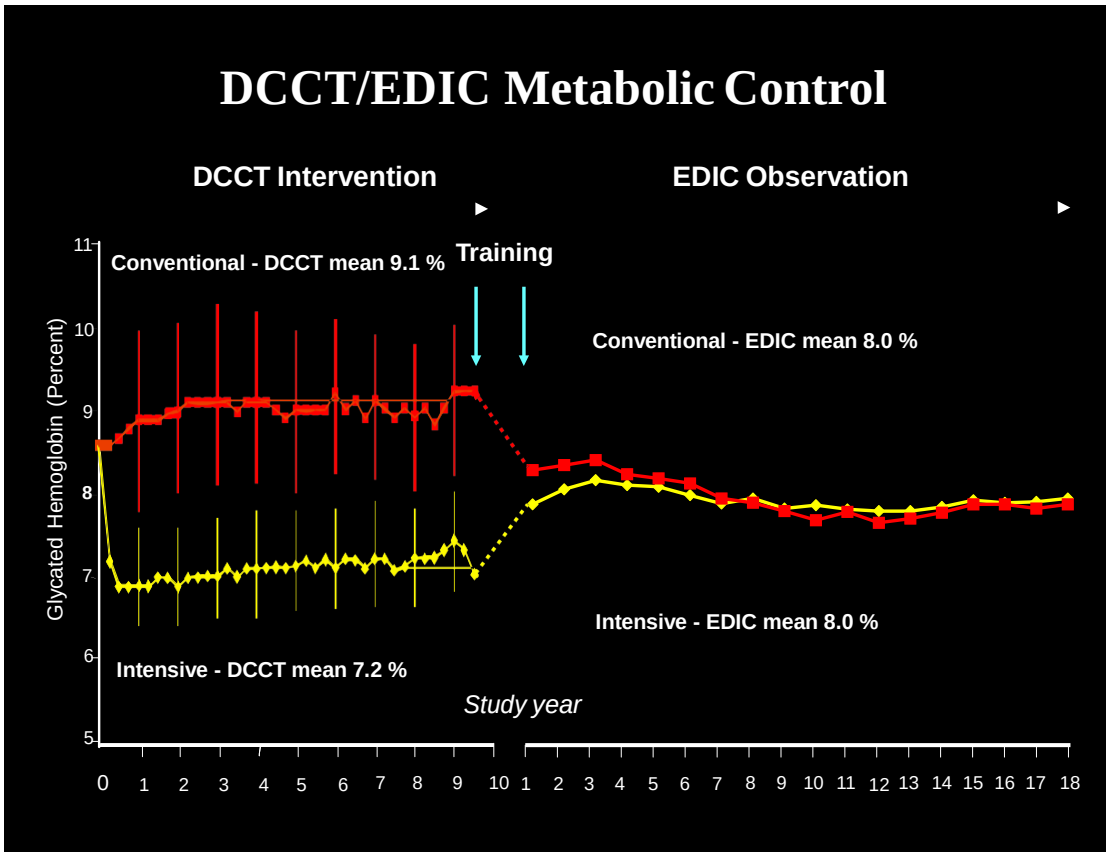


**Figure 1.1: Glycemic Levels during DCCT/EDIC as measured by glycated hemoglobin (HbA1c). Medians with 25th to 75th percentiles shown.**

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

| | Primary Prevention n= 638 | Secondary Intervention n= 638 | All 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[#] or Worse | 7 | 20 | 13 |
| CSME[#] | 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.
[#]NPDR—nonproliferative diabetic retinopathy.
CSME—clinically significant macular edema.
HRC—high risk characteristics.

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Results. In the primary-prevention cohort, intensive therapy during the DCCT 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 "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, three measures of atherosclerosis were employed, ultrasound measurement of carotid intima-media wall thickness (IMT)[28,43], electron beam (or multidetector) computed tomography of the heart to measure coronary artery calcification[29] and cardiac MRI. 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] and IMT was found to be an independent predictor of higher left ventricular mass after adjusting typical cardiovascular risk factors.[72] All three 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. Analysis of the clinical events after a ttotal of 18 years of follow-up has shown differences between the two original treatment groups that support a major benefit of IT on clinical disease as was previously demonstrated for atherosclerosis.[74] 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 reduces CVD events by 58%.

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 in 2001.

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-nine 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 18 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 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, pathogenetic and inflammatory mechanisms that underlie the development and progression of microvascular and neurologic complications? (refer to EDIC Genetic Studies and EDIC CVD protocols)

5. What are the long(er)-term effects of intensive vs. conventional therapy on cardiovascular events?

6. What are the pathophysiologic, pathogenetic and inflammatory mechanisms that underlie the development and progression of cardiovascular disease? (refer to EDIC Genetic Studies and EDIC CVD protocols)

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. New measurement and analytic techniques are included for retinopathy, nephropathy, and neuropathy. 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 1341 living participants (as of the end of EDIC Year 18) 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.

5. To encourage and implement new initiatives, resources permitting, that expand scientific productivity that emanates from the DCCT/EDIC cohort, its data base, and biological samples.

## 2.3 Design

Participants

All DCCT/EDIC participants will be invited to continue followup. The duration of EDIC follow-up has been extended based on competitive funding applications. The most recent 5-year extension is for the period July 1, 2012 through June 30, 2017. An updated consent form will be administered (see Section 4.1 for template).

Recruitment

Although retention of the original DCCT cohort has remained very high during the previous 18 years of EDIC (see Table 2.1), with no appreciable loss to followup, the Study Group will not take continued participation for granted. Any new procedures in the protocol will be explained in detail to participants and informed consent obtained.

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 29 years, this process should be relatively straightforward. Clinic staff, including the PI and Study 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 29 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 participants local care providers. Of note, as of September 2012, approximately 27% 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 5.2 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. When possible, self-administered questionnaires can 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 via interview with the participants by DCCT/EDIC staff. The physical examination is performed by a DCCT/EDIC investigator.[22,44,45]

Questionnaires—The questionnaires, directed at measuring overall health status (SF36) insurance status, and quality-of-life (DQOL) data have been used during DCCT and EDIC and have been described in detail.[44,45] A one-time administration of a questionnaire to measure quality of life – the Quality of Well-Being, CA (QWB-SA) has been completed. Collection of dietary and nutritional data was discontinued in 2009.

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] Digital photography replaced film photography in all clinics in 2010. 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. In August, 2012 (year

19) of EDIC, the four hour renal collection for AER (albumin excretion rate) was discontinued, and replaced with a random urine collection for measurement of urinary albumin and creatinine which will be used to calculate albumin creatinine ratio (ACR) and serum creatinine.[70] Serum cystatin-C measurements were added during EDIC years 9-18. Future analysis of cystatin C using stored serum samples will be dependent on receipt of sufficient funding.

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. These evaluations were completed 2005-2007.

Cardiac Autonomic Neuropathy (CAN) testing — Based on R-R interval measurement, CAN testing was repeated to measure progression of autonomic neuropathy and as a risk factor for CVD. This evaluation was completed in 2009-2010.

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 (collected annually through September 2012, and on alternate years thereafter) and EKG, and alternate year fasting lipids (Table 2.1).

**Table 2.1**

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

| Year | Phase | Participants (#) | Retention* (%) |
|---|---|---|---|
| 1983-90 | DCCT | 1441 | 100 |
| 1993 | DCCT end | 1422 | 99 |
| 1994 | EDIC beginning | 1387 | 96 |
| 2004 | End of EDIC Yr 10 | 1357 | 94 |
| 2008 | End of EDIC Yr 15 | 1296 | 95[+] |

*Percent of original DCCT cohort remaining in study. Loss to follow-up includes 7 deaths during DCCT and 67 deaths during EDIC follow-up as of Year 15.
[+]Of the surviving members of the original cohort, 1296 (95%) remained active in EDIC at Year 15.[73]

# 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.

## 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 (metabolic memory) is observed, 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 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 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, 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). 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: In 2011, the definitions and event verification documentation were updated upon the recommendations of the Data Safety and Monitoring Board (DSMB), with guidance from neurology expert(s) to reflect current scientific understanding and diagnostic criteria.

- Definition of TIA – transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction
- CVA – use of this terminology discontinued
- Stroke (formerly known as CVA) – 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); described as either "ischemic" or "hemorrhagic" The neurologic deficit is not known to be secondary to brain trauma, tumor, infection or other non-ischemic cause.
- Event categorization – "confirmed", "unconfirmed" or "no event"
- Duration of event – defined as lasting less than 10 minutes, 10-60 minutes, less than 24 hours, or greater than 24 hours
- See Manual of Operations, Chapter 28

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 $\geq$ 80 mmHg.

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

Albuminuria: urinary albumin excretion, of $\geq$208 $\mu$g/min.

Renal Insufficiency: serum creatinine of $\geq$2 mg/dl, or eGFR of $\leq$ 60 ml/min/1.73m$^2$, or the need for chronic 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, including episodes of coma or seizure, will be ascertained for the 3-month period preceding the annual visits. All accidents will be reviewed with the patient for the possible association with hypoglycemia.

DKA: glycemic 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 participants 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 R2 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 R2[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 albumin excretion rate (AER) obtained from a timed urine collection versus albuminuria as assessed by an albumin/creatinine ratio (ACR) from a random urine collection. This evaluation provided the justification to discontinue the more demanding 4 hour renal collection for AER and replace it with a random collection for urinary albumin and creatinine to calculate ACR. In such cases, the Kappa statistic[58] was 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 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]

# 4. INFORMED CONSENT

## 4.1 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 to document that the participant understands the study and its procedures and agrees to participate in the study activities. The Informed Consent must be signed and maintained in the participant's research records at each EDIC center. The Informed Consent must be signed before any data can be collected on that participant. All informed consent procedures must adhere to local institutional policies. The basic informed consent form for EDIC is presented in Figure 4.1.

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 that 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 that 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 that 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 serum, plasma and urine specimens and associated data to the NIDDK Central Repository. 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**
**INFORMED CONSENT FOR PARTICIPATION IN THE EDIC CONTINUING FOLLOW-UP**
**(Updated 9/9/2013)**

Participant_____ IRB Approval Number

Principal Investigator_____ _____

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

---

**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 to present. Approximately 1,400 volunteers will be asked to participate in the EDIC continuing follow-up in up to 27 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 up to June 30, 2017, 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 administered 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 in the back of the eye, 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. The amount of blood collected each year will be up to 4 tablespoons of blood. Measurements of ankle and arm blood pressures will be performed every other year.

b. You may be contacted by EDIC staff between annual visits to determine if specific diabetes related events may have occurred since your last EDIC visit. If an event has occurred, you may be asked to give your permission for EDIC staff to obtain medical records about that event.

c. 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.

d. 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.

e. 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 subjects 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 DCCT/EDIC centers in North America that may be more convenient for your yearly exams.

f. Throughout your participation in the EDIC study, you are asked to contact study staff before you decide to participate in any other study in order to discuss if that participation may interfere with the objectives of the EDIC study.

g. Each year you will be asked to provide the names and contact information for 1-2 individuals who may be contacted if we are having difficulty reaching you.

h. You have previously given your social security number on the DCCT and EDIC Personal Locator Forms. With your permission, in the event that we have lost contact with you and are not successful in reaching any of the individuals you have previously named as Contacts, we would like to use your social security number to assist in locating you. We would ask public services that assist in locating individuals for your address and contact information or ask state and/or federal agencies to check their survival reports. We will only use these services as a last resort if we are unable to locate you.

i. As part of this study, some of your blood and urine from every visit has been saved at the EDIC Central Biochemistry Laboratory. The EDIC study group, and other researchers who collaborate with us, submit proposals to obtain permission to use these samples. Your name would not have been associated with any of these samples; they would have included only your DCCT/EDIC study number and your initials. Some research with your blood and/or urine may already have been completed, and the information from that research may still be used.

   I understand that some of my stored blood and/or urine may have been released to the EDIC study group and other researchers who collaborate with EDIC for the continued study of type 1 diabetes. I agree that the information gained from this completed research may still be used by the EDIC study group and its collaborators. Please place your initials in the space in front of your response:

   ____Yes ____No

   I agree that my stored blood and urine samples can continue to be used by the EDIC study group and other researchers who collaborate with EDIC for the continued study of type 1 diabetes. Please place your initials in the space in front of your response:

   ____Yes ____No

   I agree that my blood and urine can continue to be collected and saved for use in the future by the EDIC study group and potentially by other researchers who collaborate with EDIC. Please place your initials in the space in front of your response:

   ____Yes ____No

j. In addition and with your permission, we would like to store some of your prior and currently collected samples of blood and urine along with your study data in the NIDDK Central Repository. 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 and your study data available for use in research for the study of Type 1 Diabetes. Sending samples and data to the NIDDK Central Repository may give additional scientists valuable research material that can help them to develop new diagnostic tests, new treatments, and new ways to prevent diseases.

You will not receive any direct benefit or payment for agreeing to have your blood and urine samples and study data sent to the NIDDK Central Repository, but your samples and study data 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.

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 participation is voluntary, and if you choose not to participate, there will be no penalty or loss of benefits to which you are entitled.

I agree that my <u>previously stored</u> blood and urine samples can continue to be used by the NIDDK Central Repository and other researchers for the continued study of type 1 diabetes. Please place your initials in the space in front of your response:

____Yes ____No

I agree that my blood and urine can <u>continue to be collected and stored</u> at the NIDDK repository for use in the future by other researchers. 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. Urine collections have no side effects except the inconvenience of collection.

b. 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.

c. 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.

d. **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.

e. 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 individuals with diabetes in particular. You may be offered diabetes supplies, as available to the study free of charge from industry contributions.

**5. Your participation is voluntary. You may choose not to participate in this research study.** There will be no penalty or loss of benefits to which you are otherwise entitled. Your choice will not at any time affect the commitment of your health care providers to administer. In addition, the investigator may choose to withdraw you from this research study if at any time circumstances arise which warrant doing so.

**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 and data collected from you to be used for research, you can do this by notifying *Name of Principal Investigator* in writing. If you

decide to revoke your authorization, any information already collected about you for this study will continue to be used to the extent that it has been relied on for the study, as necessary to maintain the integrity of the research study or as required by law.

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. **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. **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.**

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

_____ _____

**Participant's Signature** **Date**

**Parent/Guardian or *Legally Authorized Representative's Name and Relationship to Subject:**

_____

**Name** (print)

_____

**Relationship to Subject** (print)

_____ _____

**Signature of Parent/Guardian/Legally Authorized Representative** **Date**

* **Legally Authorized Representative**: In studies conducted in the state of XXXX, the first person on the list below who is reasonably available and competent must sign as the legally authorized representative even if another person on the list is more conveniently available.

1. The designated proxy (such as a Durable Power of Attorney for Health Care)
2. Court-appointed guardian
3. Spouse (does not include "Common-law" spouse)
4. Adult child
5. Parent
6. Adult sibling

**Statement of Person Who Obtained Consent**

**I have discussed the above points with the subject or, where appropriate, with the subject's legally authorized representative. It is my opinion that the subject understands the risks, benefits, and procedures involved with participation in this research study.**

_____ _____

**Signature of Person Who Obtained Consent** **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, maximize efficiency and minimize costs.

A standardized follow-up history and physical examination will be scheduled yearly for each participant. 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 Participant Interactions in the Course of Outcome Determinations

Although official recording and interpretation of outcome measurements are carried out in the central units, in the process of data collection certain local EDIC staff will see outcome data before it is transmitted centrally. Examples include visual acuity testing, fundus photographs, etc. If in the process of data collection a staff member is asked for information by a participant, he/she should respond based on clinical knowledge and expertise and remind the participant that all data collected is sent to a central source for analysis and interpretation. The participant should be informed that outcome data will be examined at central units and results will be transmitted to the EDIC center by the Data Coordinating Center.

Personal research data will not be communicated to the participant until results have been analyzed and reported by the EDIC central units except in situations where the local results suggest a safety issue for the participant. In this circumstance, local center EDIC staff are expected to act expeditiously to protect participant safety and well-being.

After a participant's data have been analyzed centrally and the results have been returned to the Data Coordinating Center, all data will be made available to the participant, 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 participant and his/her physician, if requested by the participant.

## 5.3 Elements of the EDIC Annual Visit

### 5.3.1 General

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

### 5.3.2 Ophthalmologic

A. The standardized history will occur annually.

B. 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 Ophthalmolgic 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. In 2010, film media was replaced by digital images. Electronic submission of completed fundus images to the Fundus Photograph Reading Center (FPRC) was made available 2011.

### 5.3.3 Renal

A. Renal examination will be performed every 2 years on alternate years from the lipid assessments.

B. Effective August 2012, the four hour renal exam was replaced with a random collection, preferably collected in the morning, to measure urinary albumin and creatinine. Annual collection of serum creatinine will continue. Urine and serum will be sent to the Central Biochemistry Laboratory for the following:

   i. Measurement and calculation of albumin creatinine ratio (ACR)
   ii. Measurement of serum creatinine and calculation of eGFR

C. Effective August, 2012 annual collection and measurement of cystatin C was discontinued; pending receipt of funding, future evaluation of cystatin C using annual saved serum samples may be performed.

### 5.3.4 Neurologic

A. The Michigan Neuropathy Screening Instrument (MNSI), which includes a participant questionnaire and physical examination, is performed annually.

B. The Quantitative sensory test, Cardiac Autonomic Neuropathy Testing, and Neuro Quality of Life questionnaire were done in Years 13 and 14 (2005-2007).

C. The neurological history and examination, nerve conduction studies and autonomic nervous system testing performed during the DCCT were repeated during EDIC in years 13 or 14 (2005-2007) to evaluate the development and progression of distal symmetrical peripheral neuropathy and autonomic neuropathy in the EDIC.

D. During years 13 or 14, inconjunction with the testing referenced in 5.3.4.C, participants underwent quantitative sensory testing (QST) and completed two questionnaires: a neurology symptom-specific quality of life questionnaire (NeuroQOL) and the autonomic symptom questionnaire (Autonomic Symptom Profile – ASP).

E. Autonomic nervous system testing and the ASP were repeated in Years 16 & 17 (2009-2010).

### 5.3.5 Cardiovascular

A. 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). A serum creatinine will be measured from this collection. Saved serum and plasma specimens will also be aliquoted, frozen and forwarded to the CBL for central storage.

B. Resting electrocardiograms performed yearly and coded at the Central ECG Reading Unit.

C. Ankle-brachial blood pressure will be measured every year. In 2012, the frequency of this measurement was changed to every 2 years, with completion to

occur at the renal visit.

D. In EDIC year 14 and 15 (2007-2009), the Cardiac MRI with gadolinium was performed and read at the Central MRI Reading Unit. Gadolinium, an MRI contrast agent, was used to help identify presence of scaring of the heart. If a participant was excluded from the gadolinium part of the MRI protocol they may have been eligible for the MRI if they met the criteria for that portion of the exam.

### 5.3.6. Health Care

A. The Health Status and Diabetes Quality of Life questionnaires will be completed every two years. In EDIC years 13 and 14 (2006-2007), these forms were not completed because other Quality of Life questionnaires were used.

B. The QWB-SA will be filled out by the entire cohort once.(completed) C. The Healthcare Delivery questionnaire will be completed annually.

### 5.3.7 Dietary

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

### 5.3.8 Blood Glucose Control

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

## 5.4 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 participant and if necessary the participant's personal physician.

## 5.5 Missed Visits

The importance of the visit schedule will be stressed to both the participant 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 Adherence Monitoring Committee will develop incentive programs and other activities to promote high adherence to the data collection schedules.

## 5.6 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 participant 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 participant is willing and able to undergo them.

## 5.7 Participant Transfer

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

When a participant 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 participant will be approached about a possible transfer to the new center. Alternate visit completion and data collection strategies can be discussed with the participant if travel to any EDIC center is not feasible or the participant is unwilling to travel. Regular direct communication between the center and the participant should be maintained by telephone, letter, newsletter, and other adherence techniques.

## 5.8 Temporary Inactive Status

Transfer to inactive status is defined as a temporary or permanent moratorium on participant 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 Coordinator, any manner of participation in the study would be directly injurious to the participant'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. Participant withdraws consent for continuing participation in the study.

## 5.9 Lost to Follow-Up

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

## 5.10 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 during and 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 participants and getting their consent that the specimens can be sent to a central repository. If a participant declines continued sharing of his/her saved samples or data with the NIDDK Central Repositories, the clinic will notify the Data Coordinating Center who will in turn notify the CBL. See Section 8.9.

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

| EXAMINATIONS (Outcomes) | Year 19 | Year 20 | Year 21 | Year 22 | Year 23 |
|---|---|---|---|---|---|
| **CARDIOVASCULAR (CABG, Angioplasty, MI, Angina, CHF, Stroke, TIA, Foot ulcer, Amputation)** | | | | | |
| Standardized History and Physical Exam | X | X | X | X | X |
| Electrocardiogram | X | X | X | X | X |
| Ankle/Brachial Index by Doppler ***(Year 20: every other year, with renal visit)*** | X | X | X | X | X |
| **LIPOPROTEIN LEVELS (Hypercholesterolemia, Hypertriglyceridemia)** *(alternate years from albuminuria assessments)* | | | | | |
| Total Cholesterol | Scheduling of evaluations is a function of randomization date, alternate years | | | | |
| HDL Cholesterol | | | | | |
| Triglycerides | | | | | |
| Calculated LDL | | | | | |
| **NEPHROPATHIC (Renal Failure, Transplant, Dialysis, Elevated Serum Creatinine)** | | | | | |
| Standardized History and Physical Exam | X | X | X | X | X |
| Urinary albumin and creatinine ***(** alternate years, opposite lipid evaluations)*** | ** | ** | ** | ** | ** |
| Serum Creatinine | X | X | X | X | X |
| **NEUROPATHY** | | | | | |
| Michigan Neuropathy Screening Instrument | X | X | X | X | X |
| 10 gm Filament Examination | | | | | |
| **RETINOPATHIC (Photocoagulation, Vitrectomy, Blindness, Vitreous Hemorrhage)** | | | | | |
| Standardized History | Every 4 years | | | | |
| Ophthalmological Exam | | | | | |
| Visual Acuity | | | | | |
| Fundus Photographs | | | | | |
| NEI-VFQ-25 | | | | | |
| **HYPOGLYCEMIA (Accidental Mortality/Morbidity)** | | | | | |
| Standardized History | X | X | X | X | X |
| **METABOLIC (DKA, Chronic Glycemia)** | | | | | |
| Standardized History | X | X | X | X | X |
| HbA1c | X | X | X | X | X |
| **PSYCHOLOGICAL** | | | | | |
| Quality of Life Questionnaire | Alternate years, with lipid evaluations | | | | |
| Health Status Questionnaire | | | | | |
| **HEALTH CARE DELIVERY** | | | | | |
| Standardized Questionnaire | X | X | X | X | X |

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

| Evaluation | Content/Method | Frequency |
|---|---|---|
| Standardized history | | Annual |
| Standardized physical exam | | Annual |
| Current Medications | | Annual |
| Questionnaires | Health Insurance | Annual |
| | Health Status Questionnaire | Alternate years* |
| | Diabetes QOL | Alternate years |
| Retinopathy | 7-field stereoscopic Fundus photography | Quadrennial |
| | Fundus exam, Visual Acuity, and IOP | Quadrennial |
| | NEI-VFQ-25[&] | Quadrennial |
| Nephropathy | Urinary albumin and creatinine | Alternate years |
| | | Alternate years |
| | Serum creatinine[▽] | Annual |
| Neuropathy | Michigan Neuropathy Screening Instrument | Annual |
| Cardiovascular disease | Ankle:brachial BP | Alternate years, with renal visit |
| | 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.
[&] NEI-VFQ-25 is a quality of life measure specific to eye disease.
[▽] Serum creatinine measured annually, with lipid and renal collections
IOP—intraocular pressure.
Quadrennial—randomization anniversary multiplied by 4, i.e., 16, 20, 24, 28, 32, 36, etc.

NOTE: 7-Day Dietary Recall (discontinued 2009); QWB SA (completed); Quantitative Sensory testing and Neuro QOL (completed years 13-14); Autonomic Nervous System testing (completed years 13-14 and 16-17); 4-hour renal for AER and replaced by random collection for urinary albumin and creatinine for use in calculating albumin creatinine ratio [ACR] (August 2012); annual measurement of cystatin C was discontinued with future analysis using saved serum samples pending funding (August 2012)

**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 |

# 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 carried out by the Data Coordinating Center in collaboration with the Data Quality Assurance Committee to assess the precision and accuracy of all measurements made by the Central Biochemistry Laboratory (CBL), Central Ophthalmologic Reading Unit (CORU), and the Central ECG Reading Unit. The Adherence Monitoring Committee works with the Clinic Coordinating Center to monitor clinic performance with regard to subject retention and adherence to the protocol and Manual of Operations. 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) Data Quality Assurance Committee

   i) History and physical data; doppler measurements

   ii) Central Biochemistry Laboratory

   iii) Central Ophthalmologic Reading Unit

   iv) Central ECG Reading Unit

b) Adherence Monitoring Committee

   i) Clinical Centers and patient retention

   ii) Adherence to the outcome schedule

## 6.3 Performance Monitoring

### 6.3.1 Clinical Centers

Clinical centers are able to monitor their performance compared to other sites utilizing reports posted on the clinic's private page of the EDIC website. The Adherence Monitoring Committee will monitor all aspects of clinical center performance regularly. The Adherence Monitoring Committee meets quarterly by conference call to monitor adherence to follow-up schedules and standardization of study procedures and to evaluate the timeliness and 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 Data Quality Assurance Committee and the Executive Committee will review these reports every 3-4 months.

### 6.3.2 Central Units

#### 6.3.2.1 Central Biochemistry Laboratory

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 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 databases at the Data Coordinating Center. 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 corrections made to the database as indicated.

#### 6.3.2.2 Central Ophthalmologic Reading Unit

A 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.

#### 6.3.2.3 Central ECG Reading Unit

A 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 clinical site is contacted to determine possible causes and proper procedures are reviewed.

### 6.3.3 Data Forms

The Data 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 form 002 (Medical History and Physical Exam). 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 Data Quality Assurance Committee and then considered by the Executive Committee and/or Study Group. 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 Oversight Monitoring Board (OSMB).

# 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

### 7.2.1 Study Group

The Study Group is the representative body of all study staff. It is comprised of a Chair (or Co-Chairs), the Principal Investigator and Study Coordinator from each of the clinical centers, one representative from the NIDDK Clinical Studies Program Office, one representative from the Data Coordinating Center and one representative from the Clinical Coordinating Center. The Study Group 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.

### 7.2.2 National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK)

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/she 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 study Chair / Co-Chairs and members of the Observational Study Monitoring Board (OSMB).

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 Study Group and an ex-officio member of each of the working committees.

### 7.2.3 External Evaluation Committee (EEC) / Observational Study Monitoring Board (OSMB)

The External Evaluation Committee (EEC), which was appointed by and reported to NIDDK, was replaced in 2010 by an Observational Study Monitoring Board (OSMB).

(Oversight Monitoring Board). The OSMB is appointed by the Director, NIDDK and consists 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. The OSMB is comprised of individuals who are independent of the conduct of the study, and it is chaired by an individual selected by the Director, NIDDK who is also independent of the operational aspects of the study. The OSBM may be augmented with ad hoc members as necessary. The OSMB 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 OSMB 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 the OSMB will include the following:

1. If the Study Group believes that an objective of the study has been reached, the OSMB 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 study, including quality control procedures and performance of clinical centers, Data and Clinical Coordinating Centers, and central units.
3. Review of study data to ensure the quality of the data and procedures for analysis. The OSMB 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 of the NIDDK and the Study Group regarding interpretation and implications of the results.
4. Review of all proposed major modifications to the Protocol or Manual of Operations 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. Prepare 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.

### 7.2.4 Executive Committee

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 / Co-Chairs of the Study Group, the Principal Investigator and Director of the Data Coordinating Center, Principal Investigator of the Clinical Coordinating Center, the Program Officer from the NIDDK Diabetes Clinical Studies Program Office, and the Vice Chair who also is the chair of the Publications and Presentations Committee. The chairs of the Adherence Monitoring Committee and the Data Quality Committee were added to the Executive Committee in 2010. 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. Voting by the Study Group will occur in-person at a Study Group meeting or

remotely via electronic communication if a decision is needed in the interim between Study Group meetings.

### 7.2.5 Working Committees

The Working Committees that support the Study Group were revised and renamed in fall, 2010 and are comprised of: Adherence Monitoring Committee, Data Quality Assurance Committee, Publications and Presentations Committee, the Study Coordinators Group, and Research Review Committee. These committees are appointed by the Executive Committee from among the professional personnel from each of the clinical centers, the Data and Clinical Coordinating Centers staff, the NIDDK staff, and necessary consultants. The members of the Executive Committee are *ex-officio* members of each of the working committees.

## 7.3 Study Operations

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

### 7.3.1 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 and Coordinator will work with the Data and Clinical Coordinating Centers, 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. See Table 7.1 for a list of the 27 clinical centers.

The clinical centers are expected to perform the following functions:

a) Obtain informed consent from all participants
b) Maintain contact with all participants
c) Schedule, perform and arrange for performance of all study-related procedures within specified times
d) Collect and properly ship all specimens
e) Receive results from central labs and reading units and transmit them promptly to participants and their physicians (with permission from the participants)
f) Maintain files of results for response to interval requests for information
g) Obtain validating information on all participants-reported outcome events as specified in the Manual of Operations
h) Keep participants current on pertinent advances in diabetes research and diabetes care
j) Prepare yearly budgets
k) Maintain current approvals by local human subjects review committees and other regulatory committees as required for study implementation

### 7.3.2 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).

#### 7.3.2.1 Adherence Monitoring Committee (AMC)

The Adherence Monitoring Committee will assist the Data Coordinating Center in monitoring the completeness of the data being collected and adherence to the study protocol and will develop strategies intended to optimize patient adherence. Specifically, this committee will:

i. Monitor adherence of volunteers,
ii. Monitor completeness and promptness of data collection,
iii. Develop strategies to maintain adherence, and
iv. Recommend methods for remediation of problems.

#### 7.3.2.2 Data Quality Assurance (DQA)

The Data Quality Assurance Committee will assist the Data Coordinating Center in monitoring the performance of the central units (Central Biochemistry Laboratory, Central Ophthalmic Reading Unit, and Central ECG Reading Unit) and will consider any proposals for changes in procedures as specified in the Protocol and the Manual of Operations. Specifically, this committee will:

i. Monitor quality of data collection,
ii. Monitor performance of central units, and
iii. Review and recommend proposals for addition or change of procedures.

#### 7.3.2.3 Publication and Presentations Committee (P&P)

The Publications and Presentations Committee will coordinate, monitor, review and assume responsibility for arranging the preparation of all press releases, interviews, presentations and publications relating to the study. Specifically, this committee will:

i. Recommend policy and procedures for review and approval of all communications,
ii. Propose policy guidelines for authorship,
iii. Help establish writing groups,
iv. Oversee the activities of the manuscript writing groups
v. Monitor manuscript development and publication process, and
vi. Review and approve all abstracts and manuscripts prior to submission

#### 7.3.2.4 Research Review Committee (RRC)

The Research Review Committee will review all research requests for use of study participants, study specimens or accumulating study data. Specifically, this committee will:

i. Review requests for ancillary studies (studies not included in the EDIC Core Protocol),
ii. Review requests for use of study specimens, and

iii. Assist NIDDK in reviewing requests for use of stored DCCT specimens as requested.

#### 7.3.2.5 Mortality and Morbidity Review Committee (MMRC)

The Mortality and Morbidity Review Committee will review pertinent materials documenting all identified deaths and reported non-fatal cardiovascular outcome events (see Chapter 3) in the EDIC cohort. Specifically, this committee will:

i. myocardial infarction (as a result of a procedure or not),
ii. coronary artery disease (as defined by documented atherosclerotic disease resulting in the need for or actual coronary artery bypass or angioplasty),
iii. angina resulting in hospitalization (confirmed by angiography and/or ischemic changes on testing, or unconfirmed)
iv. peripheral artery bypass or revascularization,
v. amputations,
vi. strokes, and
vii. transient ischemic attacks.

The participant materials will be forwarded by the clinical centers to the Data Coordinating Center where they are masked to the participants' identity, clinic center, and randomization group before being sent to the MMRC. The MMRC, which consists of individuals with appropriate clinical, and epidemiological 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.

#### 7.3.2.6 Study Coordinators Committee

The Study Coordinators Committee is comprised of the Study coordinator at each of the clinical sites. This Committee meets to share best practices, review, develop and train in new study methods, and in general to provide support for protocol implementation.

### 7.3.3 Coordinating Centers

#### 7.3.3.1 Clinical Coordinating Center

The Clinical Coordinating Center (CCC) will provide overall coordination of all fiscal aspects of the study. The CCC will manage protocol implementation and oversee all aspects of the 27 clinical centers' performance. The CCC will prepare the annual report and budget request. The Director of the Clinical Coordinating Center will serve on the EDIC Executive Committee. She / he will interact with the Director of the Data Coordinating Center on a regular basis 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.

#### 7.3.3.2 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 Data Coordinating Center are members of the Study Group 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 OSMB, and to the NIDDK Director. They are responsible for all aspects of intra-study communication and will work with the Publications and Presentations 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 central units are the responsibility of the Data Coordinating Center. In general, these units provide study data and analysis of participant evaluations, scientific and technical guidance to the Study Group, specific working committees, and the Data Coordinating Center.

### 7.3.4 Central Units

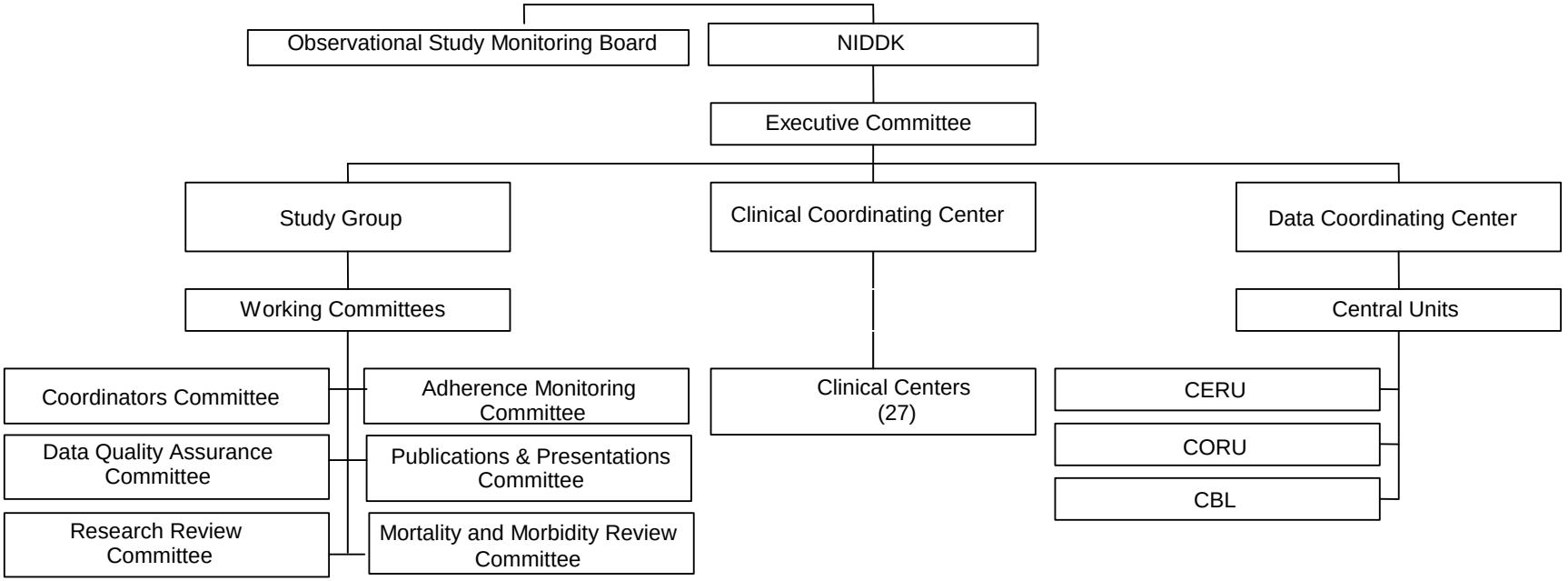
There are three (3) Central Units involved in the Core EDIC Protocol. These include the:

i. **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.

ii. **Central Biochemistry Laboratory**: The laboratory will provide baseline and repeated measurements of HbA1c, lipids, and serum and urine constituents.

iii. **Central ECG Reading Unit**: The Central ECG Reading Unit will provide baseline and follow-up coding of all ECG tracings from study participants.

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




** Central Units

*CBL* *Central Biochemistry Laboratory*
*CERU* *Central ECG Reading Unit*
*CORU* *Central Ophthalmologic Reading Unit*

**Table 7.1**
**List of Clinical Centers (Clinic Number)**

Case Western Reserve University (01)
Cleveland, OH

University of Pennsylvania (02)
Philadelphia, PA

Cornell University Medical College (03)
New York, NY

Henry Ford Medical Center-New Center One (04)
Detroit, MI

Joslin Diabetes Center, Inc. (05)
Boston, MA

Massachusetts General Hospital (06)
Boston, MA

Mayo Foundation (07)
Rochester, MN

Medical University of South Carolina (08)
Charleston, SC

International Diabetes Center (09)
Minneapolis, MN

University of Iowa (10)
Iowa City, IA

University of Minnesota (11)
Minneapolis, MN

University of Missouri (12)
Columbia, MO

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

University of Washington (17)
Seattle, WA

University of Western Ontario (18)
London, Ontario, Canada

Vanderbilt University (19)
Nashville, TN

Washington University at St. Louis (20)
St. Louis, MO

Yale University School of Medicine (21)
New Haven, CT

Northwestern University (23)
Chicago, IL

University of California - San Diego (24)
La Jolla, CA

University of Maryland (25)
Baltimore, MD

University of New Mexico School of Medicine (26)
Albuquerque, NM

University of South Florida College of Medicine (27)
Tampa, FL

University of Michigan (41)
Ann Arbor, MI

Effective September 1, 2012, Albert Einstein College of Medicine (22) was closed and participants were given the option to transfer to another conveniently located clinical center.

# 8. POLICY MATTERS

This section of the protocol includes the policies and procedures specific to publications and presentation, authorship, ancillary studies and external collaborations involving the DCCT/EDIC study, protocol changes and transfer of DCCT/EDIC biosamples and data to the NIDDK repositories.

## 8.1 Editorial Policy

The "DCCT/EDIC Research Group" is used when referring to or citing the DCT/EDIC Study Group in publications and presentations of the DCCT/EDIC study.

The Publications and Presentations 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 Publications and Presentations Committee

Specifically, the Committee shall:

1. Recommend policy and procedures for review and approval of all communications (written and spoken) regarding the study 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 or individuals whenever appropriate. The review will be conducted pursuant to the following editorial policy guidelines:

    a) Ensure that all publications preserve the scientific integrity of the study
    b) Maintain the highest standards in the preparation of presentations and publications
    c) Correct factual and conceptual inaccuracies if necessary
    d) Safeguard the rights of volunteer participants
    e) Prepare comments to assist collaborating scientists in publishing papers of the highest quality and clarity

f) Inform the Executive Committee, Study Group, NIDDK, and advisory groups of all public dissemination of information about the study and coordinate press releases with the NIDDK

g) Avoid conflict with and/or duplication of other publications

h) Coordinate releases of major 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 conflict with the policies or 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 the Executive Committee.

## 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 Publications and Presentations and Executive Committees 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 locally need not have received prior approval from the Publications and Presentations Committee. If a center is solicited for a press release or interview, then such may be given without prior review and approval by the Publications and Presentations 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 Chair of the Publications and Presentations 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 Publications and Presentations Committee provided that the content is limited to substantive information available in 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 Publications and Presentations Committee as described below:

1. Forum Identification: The Publications and Presentations 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 Publications and Presentations Committee itself and individual investigators and brought to the Study Group for approval. The Publications and Presentations 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 DCCT/EDIC Study Group are personally invited to present EDIC data or represent the EDIC Study Group, the invitation must be forwarded to the Publications and Presentations Committee as soon as possible. The Publications and Presentations Committee reserves the right to accept or not accept the invitation and/or suggest a presenter other than the EDIC Study Group member who received the original invitation. The Publications and Presentations Committee recommendation(s) will be reviewed by the Executive Committee.
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 Publications and Presentations Committee Chair at least 14 days prior to the scientific society's deadline for receipt of abstract to provide time for review, possible revision, and rewrite.

### 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 Publications and Presentations Committee. Publication of results of ancillary studies by individual investigators will be allowed with approval by the Publications and Presentations Committee. Approval of publications or presentation of ancillary studies that may jeopardize the conduct of EDIC may be withheld until such time as is deemed appropriate by the Publications and Presentations Committee.

1. Journal Identification: The Publications and Presentations 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 directed towards its known leadership.
2. Preparation and Review Schedule: The Publications and Presentation and Executive Committees will select a writing group of three to seven individuals for each proposed manuscript. One individual will be designated as chair and will be responsible for preparing the first draft of the publication. The first draft should be produced

within 6 months following approval by the Executive Committee.

3. Prioritization: The Executive Committee will assign each approved paper a priority based on the anticipated requirements of a particular proposal, and the availability of Data Coordinating Center staff to address the data requirements, to help effectively manage the workload and production of manuscripts.

### 8.3.4 Manuscript Proposals

Proposals for manuscript development can be generated by the P&P Committee, or submitted by a member of the DCCT/EDIC Study Group, a collaborating partner or by the Executive Committee.

A. **Member of the DCCT/EDIC Study Group:** Any member of the DCCT/EDIC Study Group can submit a proposal for a new manuscript topic to the Publications and Presentations Committee. Proposals should be submitted to the Data Coordinating Center who will then coordinate review with Publications and Presentations Committee Chair. The proposal should explicitly describe the background of the proposal and its justification, the objectives to be addressed, and the data to be used as the basis for the analyses. The Publications and Presentations Committee will provide a review of the proposal on the basis of scientific merit. The proposal and the review, whether favorable or not, will then be submitted to the Executive Committee for review. If approved by the Executive Committee, a writing committee and committee chair will then be appointed by the Executive Committee, with due regard for fairness in distributing authorship opportunities. Subsequently, the manuscript will be entered into the work queue at the Data Coordinating Center.

B. **Collaborators:** Investigators with whom we are collaborating may also propose a manuscript requiring analyses of DCCT/EDIC data stored at the Data Coordinating Center. Such proposals should follow the process outlined above. The collaborating investigator may recommend other individuals outside the DCCT/EDIC Study Group as writing group members. The writing group for such a paper will be appointed by the Publications and Presentations Committee and it should include a current DCCT/EDIC Principal Investigator who will be the liaison to the DCCT/EDIC Study Group, as well as appropriate members of the Data Coordinating Center. The constituents of the writing group will be reviewed by the Executive Committee.

C. **Executive Committee:** The Executive Committee may also recommend new manuscripts, and the Publications and Presentations Committee may generate proposals for manuscripts for review by the Executive Committee at any time.

### 8.3.5 Management of Manuscript Development

A. The Data Coordinating Center will maintain a ledger of all approved manuscript proposals that identifies the writing group chair, the date approved by the Executive Committee, the Data Coordinating Center statistician assigned to support the manuscript, the projected completion date, the target journal and whether (and when) a presentation is planned.

B. As new manuscripts are approved or others completed, the ledger will be updated and shared with the Publications and Presentations Committee Chair. Periodically, at least every 3 months, or when new proposals are approved, the Executive Committee will review all approved proposals and re-adjust priorities as appropriate.

C. The Data Coordinating Center will work jointly with the writing group to develop a detailed analysis plan for each manuscript. The analysis plan will state each specific hypothesis, objective or question to be addressed and the specific analyses to be conducted. Analyses will commence after this plan has been completed and approved by the Director of the Data Coordinating Center.

D. The writing group chair may request that the DCCT/EDIC data be shared with the investigator's local statistician who would perform the analyses specified in the analysis plan. Such a request must also be approved by the Publications and Presentations and the Executive Committees.

E. The assigned statistician will work with the writing group to generate a draft of the manuscript. The manuscript will then be distributed to the Publications and Presentations and Executive Committees for joint review. The Chair of the Publications and Presentations Committee will receive the individual reviews and provide final instructions on revision of the manuscript through the Data Coordinating Center.

F. After appropriate revisions and approval from the Chair of the Publications and Presentations Committee, the manuscript will be distributed to the Study Group for review and approval for submission to the designated journal.

G. Fourteen days after distribution to the EDIC centers, a manuscript approved by the Study Group may be submitted for publication. Any member of the EDIC Study Group wishing to comment on the manuscript must communicate his/her comments within the 14 days to the Data Coordinating Center. Once received, the comments will be forwarded to the Chair of Publications and Presentations Committee who will be responsible for corresponding with the writing group. The Publications and Presentations Committee Chair or the Executive Committee may delay the submission until resolution is reached.

### 8.3.6 Standards of Excellence

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

If, in the opinion of the members of the Publications and Presentations Committee, there is no member of the EDIC Study Group who has sufficient scientific background to review the pertinent material, then outside expert consultants will be selected by the Publications and Presentations Committee and asked to critique the material. However, it is expected that sufficient expertise will be available from the members of the Study Group to provide a review of most 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 participants during the study including reasons for loss to follow-up. Data should be presented to demonstrate comparability of the subjects who participated and who exited from each treatment group throughout the follow-up.

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.

## 8.4 Publication and Authorship Policies

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 Study 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. The DCCT/EDIC publication and authorship policies have evolved similarly, producing a greater number of manuscripts with named authors and the DCCT/EDIC Research Group. The categories of papers are classified as follows:

A. **Primary Outcome Manuscripts**: These manuscripts address the major primary outcomes of the DCCT/EDIC study, e.g. effects of the DCCT randomly assigned interventions and/or glycemia and related mechanisms on microvascular and cardiovascular disease and mortality.

B. **Other Outcomes Manuscripts**: These manuscripts report various analyses of complication outcomes, metabolic intermediates and biomarkers, or natural history of type 1 diabetes that utilize the database from the entire cohort. This will represent the majority of the manuscripts. These manuscripts would also include sub-studies and ancillary studies conducted as additional initiatives beyond the initial DCCT/EDIC protocol.

C. **Miscellaneous Manuscripts:** These manuscripts generally focus on methodological issues and may include results of subgroup analyses that do not include data from the entire DCCT/EDIC cohort.

Responsibility for the category assignment for all manuscripts will rest with the Publications and Presentations Committee, in consultation with the Executive Committee.

The following authorship principles will apply.

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

II. **Category 2 (Outcomes) Manuscripts:** The authorship will be the writing group: A Smith (Chairperson), A, B, C, etc. and the DCCT/EDIC Research Group.

III. **Category 3 (Miscellaneous) Manuscripts:** Authors A, B, C, etc.; the DCCT/EDIC Research Group is acknowledged** in the manuscript but not included as a named author.

** Acknowledgement of the DCCT/EDIC Research Group will cite the most recently published official DCCT/EDIC manuscript where the complete DCCT/EDIC Research Group has been listed.

## 8.5 Ancillary Studies

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 participants and investigators. To protect the integrity of the EDIC 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 EDIC study as a whole.

### 8.5.1 Definition of an Ancillary Study

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

### 8.5.2 Requirement of Approval

All ancillary studies must be reviewed and approved prior to implementation. DCCT/EDIC investigators and participants 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 EDIC 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 at the Data 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

### 8.5.3 Review of Proposals for Ancillary Studies

Proposals for ancillary study are submitted to the Research Review Committee for review. Questions and recommended revisions identified during this review are returned to the ancillary study investigator to be addressed. The investigator's response and revised proposal are returned to the Research Review Committee for review and approval. Once the proposal has been reviewed and approved by the Research Review and Executive Committees and the Study Group, final approval is contingent on the Research Review Committee receiving a letter signed by the principal and all collaborating investigators in which they agree to abide by the EDIC policies for ancillary studies herein described including those regarding publication or presentation of results.

### 8.5.4 Funding of Ancillary Studies

The EDIC study will not provide funds for ancillary studies. In particular, no funds are provided for Central Biochemistry Laboratory or other central 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, pharmaceutical company, etc.) The anticipated source of funds must always be identified.

### 8.5.5 Publication of Ancillary Study Results

All manuscripts based on ancillary EDIC study data must be reviewed and approved by the Publications and Presentations Committee, the Executive Committees and the Study Group before publication.

### 8.5.6 Submission and Review Process

A request to conduct an ancillary study in the DCCT/EDIC Study or using previously collected data from the DCCT/EDIC cohort is submitted to the Data Coordinating Center. The request will be reviewed by the Executive Committee to ensure that the aforementioned criteria (Section 8.5.2) are met and if appropriate, will be sent to the Research Review Committee for detailed review.

The request for approval of an ancillary study (proposal) 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; the proposal may be used as the basis for the request. Full details should be given concerning any procedures or tests to be carried out on DCCT/EDIC participants including: any ophthalmologic, renal, cardiovascular, neurologic, psychological, or other evaluation to be performed, as well as tests on biological samples; any substances to be injected or otherwise administered to the participants; any observations to be made or procedures to be conducted on participants outside of the clinic; any extra clinic visits required of the participant or any prolongation of the participant'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 participant 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 investigator should send his/her ancillary study proposal to the Data Coordinating Center. After discussion with the Executive Committee, the Data Coordinating Center will distribute the proposal 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 study. 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 Chair of the Research Review Committee will summarize the questions and objections (if any) identified 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.

The approval statement and recommendation of the Research Review Committee will be forwarded to Study Group by the Data Coordinating Center with a request for review and approval after approval of the Executive Committee. Study Group members should respond to Data Coordinating Center within the designated review period. The results of voting will be forwarded to the Chairs of the Research Review Committee and the Executive Committee. No response will be considered as approval.

## 8.6 EDIC Protocol Changes

The objectives of the EDIC study 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 that improve or enhance achievement of the core protocol.

### 8.6.1 Study Group Policy

Major changes in the Protocol will be recommended by the Study Group only if they are required to ensure subject safety, will significantly enhance the scientific validity of the study or in response to fiscal constraints assuming validated scientific data can justifiably support the change. To recommend a major Protocol change, three-fourths of the Study Group must approve the change. The voting body for the EDIC study includes all clinical center principal investigators and coordinators, and one vote from the Data Coordinating Center, the Clinical Coordinating Center and the NIDDK scientific project officer for the EDIC study. The EDIC Study Chair/Co-Chairs will have the tie-breaking vote(s), if needed.

Ideally, matters requiring Study Group vote will occur at the in-person Study Group meetings. However, when issues arise between the meetings that require more immediate input and a vote from the Study Group, the Data Coordinating Center will prepare the necessary materials to provide Study Group members with adequate background information to make an informed decision. These materials will be sent via surface or electronic communication to each voting member of the Study Group with a request for review and vote. Study Group members will be asked to reply within a specified period of time. No response will be interpreted as acceptance. Concerns or questions regarding the proposed protocol change will be sent to the Data Coordinating Center who will be responsible for conveying these concerns to the Executive Committee for further action.

### 8.6.2 Procedures

The Executive Committee will consider proposals for Protocol changes that may originate from the NIDDK, the OSMB, 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 Executive Committee 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.

## 8.7 Collaborations

The DCCT/EDIC Study Group welcomes scientific collaboration with investigators in the field of diabetic complications. The Study 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 following sections outline the policies to be implemented in any collaborative agreement between an external group and the DCCT/EDIC Study Group.

### 8.7.1 Use of DCCT/EDIC Samples

A Data or Materials Use Agreement (Use Agreement) will be developed for all approved collaborations with the EDIC study. All specific measurements that will be made on DCCT/EDIC samples must be agreed on in advance and designated in the Use Agreement. The Use Agreement will be generated by the legal department for the Data Coordinating Center and will specify: 1) the biosamples and/or data requested, 2) use and disposition of residual samples, and 3) adherence to the EDIC publication and collaboration policies. 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 Study Group. Access to DCCT/EDIC biosamples and/or data is contingent upon review and approval of the Use Agreement by the collaborator. Only then can the Use Agreement be executed.

The reasons for this policy are 3 fold:

1. The DCCT/EDIC Study Group wishes to be an active intellectual partner in any collaboration, rather than simply a passive useful source of biosamples and phenotypic data.

2. Sample volumes that remain after completing the original planned analyses should be returned to the DCCT/EDIC repository and stored for other potential future use.

3. Situations in which more than one laboratory, unbeknownst to EDIC, are measuring the same analyte on identical specimens must be avoided. This avoids 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 EDIC study and its directions.

## 8.7.2 Publications Resulting from Collaborations with External Partners

### 8.7.2.1 General Considerations

Three classes of manuscripts have been defined according to the origin of hypotheses and actual writing of the manuscript. Most manuscripts will have a number of individual authors (from the collaborating group and/or the DCCT/EDIC Study Group), followed by the one or other group (the DCCT/EDIC Research Group or external collaborating group). In these papers, a group, if present, will always appear as the 'final author'. The collaborating investigator initiating the study and primarily responsible for it or his delegate will ordinarily be the first author. The senior author will be the last named author, and his/her name will be followed by a group name (the DCCT/EDIC Research Group or external collaborating group), if present, which may be placed at any place in the authorship list (not just at the end).

### 8.7.2.2 Author Responsibilities

#### A. First Author

1. Take responsibility for integrating all aspects of the manuscript, maintaining the latest working draft

2. Develop a one page summary outline of the proposed manuscript, including title, proposed authors, and a general plan of content (Figures,

Tables, main conclusions); circulate this to proposed co-authors; ensure nobody is left out; discuss and get general agreement to proceed

3. Draft manuscript in a timely fashion. When a draft containing the essential information is ready, circulate again for input. For example, once the essentials of the paper are ready (Methods and Results sections, Figures and Tables, and drafts of Introduction, Discussion), it can be circulated while Discussion and Reference sections are still being prepared
4. Incorporate feedback and prepare final draft; circulate again

**B. Other Named Authors**

1. Contribute an identifiable individual effort to the manuscript
2. Respond promptly to first author requests for analysis, information, feedback on drafts, etc.

### 8.7.2.3 Manuscript Classification

A. **Class 1:** Manuscripts in this category will describe studies where hypotheses and/or molecular risk factor data have originated from the collaborating investigator/group, but which use DCCT/EDIC complications outcomes and clinical characterizations as critical elements. The first and senior authors will be collaborating investigators. EDIC investigators may be included as individual authors at the discretion of the ancillary study principal investigator to recognize individual contributions to the ancillary study. The DCCT/EDIC Research Group will be included in the “last author” position. Inclusion as an individual author implies a meaningful individual role in data analyses, data presentation, and/or manuscript preparation.

B. **Class 2:** Manuscripts in this category will describe studies whose hypotheses and/or the bulk of the primary data to address the hypotheses originated in DCCT/EDIC, but which contain some data from the collaborating investigator/group. These studies will be initiated by members of the DCCT/EDIC Study Group and will have the DCCT/EDIC Research Group or an individual EDIC investigator as first author. The individual collaborating investigator(s) or the collaborating group may be included, at the discretion of the collaborating investigator/group (as for EDIC investigators in Class 1). In these studies, data from the collaborating investigator/group will comprise a significant, but not predominant, element of the DCCT/EDIC study.

C. **Class 3:** Manuscripts in this category will describe studies using biosamples obtained by the collaborating investigator/group from DCCT/EDIC, but in which DCCT/EDIC complications outcomes and clinical characterizations are not featured or are not central elements. Examples might include studies comparing two or more parameters measured by the collaborating investigator/group, or for new methods development or assay validation. Such data may be generated in the course of the collaboration, and relationships studied may be largely independent of participant characteristics, and would be publishable without any knowledge of individual participant characteristics. Alternatively, these manuscripts will utilize simple

descriptive information about participants (e.g., age, gender, BMI) but will not include complication outcomes. These manuscripts will have the collaborating investigator and or collaborating group as authors, and the DCCT/EDIC Research Group will be given authorship credit.

The DCCT/EDIC Study Group will be given the opportunity to review and discuss prepared manuscripts before submission.

## 8.8 EDIC Participants and Other Research Studies

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 Executive Committee.

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 DCCT/EDIC investigators or not.

If an external study is being conducted by a DCCT/EDIC investigator, the 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 DCCT/EDIC study, the Executive Committee 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.

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

## 8.9 NIDDK Central Repositories

Specimens and data transferred to the NIDDK Central Repositories will be de-identified (i.e., individual data will be stripped of all personally identifiable information according to accepted standards). The Repositories will take measures to protect participants' privacy, although no guarantee of confidentiality can be absolute.

Should a participant decline continued sharing of his/her saved samples with the NIDDK Central Repositories, the Principal Investigator/Study Coordinator will communicate this information to the Data Coordinating Center which will be responsible for implementing this request. Previously submitted samples are not able to be withdrawn from the NIDDK Repositories.

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