SEARCH for Diabetes in Youth

Protocol - Version 5

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SEARCH For Diabetes in Youth
Executive Summary

Background

Diabetes mellitus, a leading cause of nephropathy, retinopathy, neuropathy, and coronary and peripheral vascular disease, is the third most prevalent severe chronic disease of childhood in the United States. People with diabetes diagnosed before age 20 have a life expectancy that is 15-27 years shorter than non-diabetic people.

Until recently, diabetes diagnosed in children and adolescents was almost entirely considered to be type 1, which is usually due to the destruction of the beta cells of the pancreas leading to an absolute deficiency of insulin. Diabetes in children and adolescents is now acknowledged to be a complex disorder with heterogeneity in its pathogenesis, clinical presentation, and clinical outcome. However, because recognition of the broader spectrum of diabetes in children and adolescents is recent, there are no gold standard definitions for differentiating the types of diabetes in this age group.

Also recent are reports of children who present with diabetes that has the clinical characteristics of type 2 diabetes, which was heretofore considered a disease of adults. The incidence of type 2 diabetes in adolescents, especially minority adolescents, appears to be increasing at alarming rates, but the magnitude of this increase is not known.

Finally, information about the clinical course and evolution of diabetes in children and youth, particularly type 2 diabetes, is limited.

Objectives

The study "SEARCH for Diabetes in Youth" will identify prevalent and incident cases of diabetes among individuals under age 20 years in order to:

a) Estimate the population prevalence and incidence of type 1, type 2, and other types (or hybrids) of diabetes rates overall and by age and ethnicity.

b) Develop efficient and practical approaches to classification of diabetes type for prevalent and incident cases.

c) Describe and compare clinical presentation and course of type 1, type 2, and other types (or hybrids) of diabetes.

Secondarily, the study will:

a) Describe the distribution of risk factors for selected micro- and macrovascular disease complications and how they differ by diabetes type separately for prevalent and incidence cases.

b) Describe the distribution of selected acute and chronic complications and how they differ by diabetes types separately for prevalent and incidence cases.

c) Describe the health care utilization, processes of care, and quality of life separately for prevalent and incidence cases.

Finally, SEARCH will develop system(s) to maintain contact with study participants in order to facilitate ancillary studies and long term follow-up, and it will establish a repository for long-term storage of biologic specimens obtained as a part of SEARCH and establish processes for access to these specimens.

Methods

SEARCH involves six centers, located in Cincinnati, Ohio; Colorado; Seattle, Washington; South Carolina; Hawaii; and Southern California, that will identify prevalent and incident cases of diabetes in youth less than 20 years of age in defined populations. Four centers (Cincinnati, Colorado, Seattle, South Carolina) are geographically based—diabetes cases will be identified from a geographically defined population. Two centers (Hawaii and Southern California) are membership-based—diabetes cases will be identified among members of participating health plans.

Diabetes cases that are prevalent in 2001 and cases incident starting January 1, 2002 will be identified. The approach to identification of prevalent cases varies by center as a reflection of availability of an existing diabetes registry or database and access to clinics, physicians, and computer-stored data resources. At all six SEARCH centers, the primary approach to identification of incident cases is a rapid reporting network of clinics and health care providers, including in some instances diabetes educators and school nurses.

It is expected that about 6,350 prevalent cases and 785 incident cases per year will be identified across the six SEARCH centers.

Data collection in SEARCH includes, at baseline, both for prevalent and incident cases, questionnaire surveys and an invitation to an in-person visit. For incident cases and a subset of prevalent cases, data collection includes medical record review. Incident cases will be asked to return annually for an in-person visit.

The baseline surveys will gather information on date and setting of diagnosis; clinical presentation, age and body size at diagnosis; other medical history and use of prescription medications, race/ethnicity and socioeconomic status, family structure, and quality of life. Additional questions about health behaviors (e.g., diet, activity, sleep, and smoking) and depression will be asked of youth over 10 who complete surveys at the time of the baseline in-person visit.

The baseline in-person visit includes a physical examination and the collection of blood to measure diabetes autoantibodies, HbA_{1c} , and fasting C-peptide, glucose, and lipids, and urine to measure albumin and creatinine. Children whose diabetes type cannot be determined based on information gathered at the first baseline visit along with a subset of children 8+ years of age will be asked to undergo a stimulated C-peptide test.

Medical record review will gather information to classify diabetes type.

Annual follow-up visits among incident cases will gather information to define the evolution of diabetes and assess the occurrence of complications.

1. SEARCH Study Objectives

1.1. GOAL

To identify prevalent and incident cases of diabetes among individuals under age 20 to meet the following aims:

1.2. PRIMARY AIMS

a) Estimate the population prevalence and incidence of type 1, type 2, and other types (or hybrids) of diabetes rates overall and by age, gender and ethnicity.

b) Develop efficient and practical approaches to classification of diabetes type for prevalent and incident cases.

c) Describe and compare clinical presentation and course of type 1, type 2, and other types (or hybrids) of diabetes

1.3. SECONDARY AIMS

a) Describe the distribution of risk factors for selected micro- and macrovascular disease complications and how they differ by diabetes type separately for prevalent and incidence cases.

b) Describe the distribution of selected acute and chronic complications and how they differ by diabetes types separately for prevalent and incidence cases.

c) Describe the health care utilization, processes of care, and quality of life separately for prevalent and incidence cases.

1.4. SUPPORTING ACTIVITIES

In support of the Primary and Secondary Aims, the study will:

a) Develop system(s) to maintain contact with study participants in order to facilitate ancillary studies and long term follow-up.

b) Establish a repository for long-term storage of biologic specimens obtained as a part of SEARCH protocol, and establish processes for access to these specimens.

SEARCH Protocol Section 2
Background and Rationale
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2. Background and Rationale

Diabetes mellitus is the third most prevalent severe chronic disease of childhood. In 1990, the estimated U.S. prevalence of diabetes in individuals under 20 years of age was 1.7/1,000[1]. Until recently, diabetes diagnosed in children and adolescents was almost entirely considered to be type 1 (insulin dependent), formerly known as "juvenile diabetes." However, childhood diabetes, as adult diabetes, is now acknowledged to be a complex and heterogeneous disorder.

2.1. CLASSIFICATION OF PEDIATRIC (< 20 YEARS) DIABETES

The American Diabetes Association (ADA) and the World Health Organization (WHO) revised the classification of diabetes mellitus[2,3]. The new classification of diabetes is now based on pathogenesis rather than the requirement for insulin therapy.

The most common form of childhood diabetes is type 1A diabetes, caused by the autoimmune destruction of the beta cells of the pancreas leading to an absolute deficiency of insulin.

Recently, reports of children with diabetes presenting with clinical characteristics of type 2 diabetes (typically considered a disease of adults) are appearing[4,5]. The incidence of type 2 diabetes in the pediatric population is increasing at alarming rates, especially in adolescents and minority populations.

Other categories of specific disorders, (onset usually during childhood) include mitochondrial mutations[6-8] and various forms of Maturity Onset Diabetes of Youth (MODY), characterized by mild to severe insulin deficiency [9]. In addition, a form of diabetes termed "atypical diabetes mellitus in adolescents" is being reported to occur in approximately 10% of African Americans and is associated with episodes of ketoacidosis followed by disease remissions where insulin therapy is not required to prevent ketoacidosis (Winter NEJM 1987). It is, therefore, clear that the spectrum of diabetes in childhood has broadened and is more complex than previously thought.

Since the broader spectrum of diabetes in youth is recent, there are no existing gold standard definitions for differentiating the types of childhood diabetes. Many of the previous methods of classification relied on clinical factors such as age at onset, obesity, family history, acuteness of onset, and insulin therapy to differentiate the types of diabetes.[10,11]. These factors do not, however, reliably differentiate the types. For example, adolescents with type 2 diabetes can present with diabetic ketoacidosis (DKA). Conversely, patients with type 1 diabetes may be obese and may not have DKA episodes. Thus, misclassification of types can occur with existing systems of classification, and this may result in improper disease management. There is a need to develop reliable and valid classifications of diabetes that

will: 1) differentiate the types of diabetes in children; 2) be suitable for estimating the frequency of the types of diabetes in various populations; and 3) provide effective classification(s) for clinical diagnosis, research studies, and population surveillance. When possible, classification methods must utilize simple low-cost tests in order to allow application in all economic settings. Whether these goals can be met with a simple set of measurement tools is one of the important research questions for the SEARCH study to answer.

2.2. EPIDEMIOLOGY OF CHILDHOOD DIABETES

Type 1 and type 2 diabetes are the major forms of diabetes in youth. Other types of diabetes, such as maturity-onset-diabetes-of youth (MODY), account for only a small numbers of cases. Thus, this review of known epidemiology is restricted to the two main types of diabetes.

2.2.1. Type 1.

The prevalence and incidence of type 1diabetes vary by geographic location, ethnicity, age, gender, and time period. One of the most striking characteristics of type 1 diabetes is the large geographic variability in the incidence [12]. In most European and North American populations, the prevalence of type 1 diabetes in the age group 0-19 years ranges from 0.05% to 0.3% [13]. The incidence varies from 0.1/100,000 per year in China and Venezuela to 36.8/100,000 per year in Sardinia, Italy and 36.5/100,000 per year in Finland. In the U.S., the incidence of type 1 diabetes in 10-14 year old children ranges from 19.8 in Chicago Illinois to 25.3/100,000 per year in Allegheny County, Pennsylvania [12]. The Diabetes Epidemiology Research International Group (DERI), an international effort to study the incidence of type 1 diabetes in persons under age 15, found racial differences in the incidence of type 1diabetes also exist. For example, American non-Hispanic whites are about one and a half times as likely to develop type 1 diabetes as African American or Hispanics [14]. In Allegheny County registry, the incidence of type 1 diabetes among African Americans aged 15-19 years was almost 3 times higher than among whites (30.4 vs. 11.2/100,000 per year) [15]. Moreover, the incidence of diabetes among African American children during 1990-1994 was more than 3 times higher than the 1980-84 incidence. This difference may be due to misclassification of some children with type 2 diabetes as having type 1 diabetes. There is evidence that the incidence of type 1 diabetes is increasing worldwide both in low and high incidence populations [16]. A study conducted in Europe estimated that over a 6-year period the average annual rate of increase in the incidence of type 1 diabetes was 3.4%; it was higher for children aged 0 to 4 years (6.3%) [17]. In the U. S., data on temporal trends in type 1 diabetes incidence are controversial. The incidence of type 1 diabetes appears to be stable in Colorado, Hawaii and Chicago, Illinois, but has been reported to be

increasing in Allegheny County [16,18]. Some of the inconsistencies may be attributed to insufficient observation time, small numbers of cases, or to the lack of standardized definitions for both type 1 and type 2 diabetes during childhood. To assess temporal changes in diabetes incidence, it is imperative to establish population-based registries that utilize standard criteria for classifying diabetes.

2.2.2. Type 2.

The first cases of type 2 diabetes among adolescents were reported among the Pima Indians [19]. The residents of the Gila River Indian Community in Central Arizona (most of whom are Pima Indians) participated in a longitudinal epidemiological study of diabetes since 1965 [20]. Diabetes is highly prevalent in the Pima Indians [21] and is virtually always type 2 - even when occurring at a young age [22,23]. A recent analysis that included data collected on 5,274 Pima Indian children less than 20 years of age, described a strong increase in the prevalence of type 2 diabetes from 1967 through 1996 [23]. Over this 30-year period, the prevalence of diabetes increased in boys aged 15-19 from 2.4% in the 1967-1976 to 3.8% in 1987-1996; in girls aged 15-19 the prevalence increased from 2.73% in 1967-1976 to 5.3% in 1987-1996. Since 1981, the Indian Health Service (IHS) has collected data on reported diabetes (type 1 and 2) from outpatient clinics serving American Indian populations. This data provided an estimate of the prevalence of diabetes among those aged 15 to 19 years of 2.9 per 1,000 in 1988 and 4.5 per 1,000 in 1996 [24]. The magnitude of the problem in other major ethnic groups is not as clear. In case reports limited to the 1990s, type 2 accounted for 8%-45% of all new pediatric cases of diabetes (types 1 and 2) [25]. Generally, before the mid-1990s, type 2 diabetes accounted for less than 5% of new pediatric cases of diabetes. Other data on type 2 diabetes in North American children and adolescents are summarized in Table 1.

Characteristics of 578 youth diagnosed with type 2 diabetes (Table 2) were available from 6 U.S. case series for whites, African Americans and Hispanics, from one registry of type 1 diabetes, and from 3 reports for American Indians and First Nation People. About 94% of the children and adolescents belonged to minority communities. Mean age at diagnosis was close to the age of puberty (approximately 12 to 14 years), except among the Pima Indians, where it was 16 years of age. Only a few cases occurred in children who were younger than 10 years old at diagnosis, and the youngest was a 4-year-old Pima Indian child. The disease is seen more frequently in females than males. Obesity, a family history of diabetes, and acanthosis nigricans were common among cases. Most of the cases were identified because of the presence of glycosuria during urine testing for school, sport, or employment medical examinations. Vaginal moniliasis was a chief complaint in one study and was reported in 24% of girls; weight loss and ketosis were common, and ketoacidosis was also reported. Among Pima Indian youth, both low and high birthweight, maternal diabetes during pregnancy (either gestational or

type 2 diabetes), and bottle-feeding from birth were associated with type 2 diabetes. At diagnosis, insulin and C-peptide concentrations may be elevated, normal or low. Islet cell antibody titers are negative.

2.3. BURDEN OF COMPLICATIONS AND LEVEL OF CARE

Diabetes mellitus is a major cause of morbidity, mortality, and compromised quality of life [26]. Diabetes is a leading cause of nephropathy, retinopathy, neuropathy, and coronary and peripheral vascular disease. People with diabetes diagnosed before age 20 have a life expectancy, which is 15-27 years shorter than non-diabetic people in the United States [26]. Among those with onset of diabetes <30 years, 44% of deaths are from diabetes-related causes and 30% of deaths are from heart disease. Children under 15 years of age with diabetes account for 5.4% of all hospital admissions, which is disproportionately higher than the prevalence of diabetes in this age group. Among individuals younger than 17 years of age, acute metabolic complications of diabetes account for approximately 20 out of 1,000 hospital discharges and nearly half of all diabetes-related hospital discharges [26]. In 1991 in the U. S., there were 4,113 end-stage renal disease cases - 1,629 on dialysis and 2,544 post transplantation - among all persons with diabetes younger than 20 years of age[26].

There are several epidemiological studies of diabetes complications among people with type 1 diabetes, but published data for patients <20 years (other than acute complications, hospital discharges, and end stage renal disease) are scarce. Data is available for young adults. In the Epidemiology of Diabetes Interventions (EDIC) Study of type 1 diabetes (mean age 33 years), at 4 years of follow up (the DCCT control group) the median glycosylated hemoglobin was 8.2%. Seventy-five percent of participants were on multiple daily injections or on an insulin pump - less than half were performing self-monitoring of blood glucose four times or more per day. Thirteen percent had albumin excretion >28 μg/min, 18% had proliferative or severe nonproliferative retinopathy, 14% had macular edema, and 13% had received photocoagulation therapy. At entry, data of the EDIC cohort indicated that: 13-18% had hypertension, the mean LDL-C was 115 mg/dl, and 18% were smokers. Among participants aged 15-29 years of age in the Epidemiology of Diabetes Complications (EDC) study (1986-88) in the U. S. and the EURODIAB (1988-90) study in Europe, 21-26% had microalbuminuria, and 10-18% had macroalbuminuria. In these two studies, participants >15 years of age only 1-15% had glycosylated hemoglobin within the normal range, 14-25% had hypertension, and 37-49% were smokers.

In patients with type 2 diabetes who are less than 20 year old, data are even scarcer. In general, glucose control appears to be poor with mean glycosylated hemoglobin at diagnosis of between 10% and 13% [5]. Among Pima Indians with a median age of 26

years and diabetes duration of 10 years, micro-albuminuria (albumin: creatinine ratio ≥ 30 and <300 mg/g) and macro-albuminuria (albumin: creatinine ratio ≥ 300 mg/g) were present in 58% and 16% of the cases, respectively. Hypertension was present in 14%, hypercholesterolemia (>200 mg/dl) in 30%, and hypertriglyceridemia (>200 mg/dl) was seen in 55% of cases.

There are several efficacious treatments for preventing diabetes complications but the implementation of these treatments in adults in often sub-optimal. The magnitude of complications and the processes of care and use of available treatments in the pediatric age group (<20 years) are not clearly documented. The major complications of diabetes require many years to develop. Therefore, the occurrence of overt chronic complications under 20 years of age may be uncommon, but the antecedents (e.g., microalbuminuria, raised blood pressure, lipid abnormalities, early retinal changes) may be prevalent even in childhood diabetes. Early onset of diabetes may thus mean a greater lifetime burden of morbidity and loss of quality of life. In addition whether risk factors for diabetes complications (microvascular and macrovascular) differ by diabetes type or by ethnicity is not clear. The pediatric age group offers an ideal setting to explore these questions.

2.3.1. Limitations

The SEARCH assesses the prevalence and incidence of childhood diabetes in a multi-ethnic population of children *diagnosed* with diabetes. This study will not be able to assess the relative proportion of children with undiagnosed diabetes and whether that proportion varies by age or ethnic group. The undiagnosed population is primarily an issue for children with type 2 diabetes because, unlike type 1 diabetes, type 2 diabetes may have a long latency period before symptoms are recognized [27]. Consequently, our estimates may preferentially underestimate the prevalence and incidence of type 2 diabetes in children because of not assessing undiagnosed diabetes.

With increasing public awareness of the epidemic of type 2 in children (2, 3) as well as recent guidelines to screen high-risk children for type 2 diabetes (1), the diagnosed rate of type 2 diabetes may also increase because of secular trends in screening without a true increase in incidence. To address this potential bias, SEARCH will assess how the initial diagnosis of diabetes was made and determine if the proportion of children asymptomatic at diagnosis is changing.

2.3.2. Conclusion

The magnitude of diabetes in youth in the U. S. is not known and precise estimates in many ethnic groups are not available. Furthermore, the magnitude of diabetes by type is also not clear except in a few selected groups. A major challenge is to develop better methods of classifying types of diabetes. In addition, the burden of disease and the

frequency and impact of microvascular complications, cardiovascular risk factors, and macrovascular complications in pediatric diabetes are not known. Similarly, the extent of implementation of the processes of care and available treatments is unclear.

To address these issues, SEARCH, a multi-center collaborative 5-year study of diabetes in youth aged <20 years in the United States was established. SEARCH will recruit approximately 6,000 prevalent cases across these sites and establish a registry system to identify an estimated 800 incident cases per year. The study will use a uniform population-based approach using a common protocol developed by study investigator consensus.

Table 2 -1. Selected current estimates of the magnitude of type 2 diabetes in North American children and adolescents, in population- and clinic-based studies and case series[5].

STUDY AND REFERENCE*	YEARS	RACE/ETHNICITY	AGE (YEARS)	SAMPLE SIZE	NUMBER OF CASES	ESTIMATES
						Prevalence per 1,000 and
• Population-based studies						95 % confidence interval
- New Mexico	1991-1992	Navajo Indians	12-19	142	2†	14.1 *[0 –33.5]* †
- Arizona	1992-1996	Pima Indians	10-14	672	15	22.3 *[11.1–33.5]*
			15-19	530	27	50.9 *[32.2-69.6]*
- Manitoba	1996-1997	Cree and Ojibway Indians	4-19	717	8	11.1 *[3.4-18.8]*
			10-19	-	7	0 for boys and 36.0 for girls
- NHANES III	1988-1994	Whites, and African and Mexican Americans, all U.S.	12-19	2,867	13†	4.1 [0-8.6] †
• Clinic-based studies						
- Indian Health Services	1996	American Indians, all U.S.	0-14	402,580	518†	1.3†
			15-19	111,239	498†	4.5†
- Manitoba	1998	Cree and Ojibway Indians	5-14	20,900	20	1.0
			15-19	8,400	19	2.3
• Clinic-based study						Incidence per 100,000/year
- Cincinnati, OH	1994	Whites and African Americans	0-19	-	-	3.5
			10-19	-	-	7.2

STUDY AND REFERENCE*	YEARS	RACE/ETHNICITY	AGE (YEARS)	SAMPLE SIZE	NUMBER OF CASES	ESTIMATES
• Case series				‡		% of type 2 diabetes among new cases of diabetes
- Cincinnati, OH	1982-1994	Whites and African Americans	0-19	1,027§	54§	16§ (in 1994)
			10-19	-	-	33§ (in 1994)
- Charleston, SC	1997	African Americans	10-19	97	45	46
- Little Rock, AK	1988-1995	Whites, Hispanics, and African Americans	0-19	-	50	-
- San Diego, CA	1993-1994	Whites, Hispanics, and African and Asian Americans	0-16	160§	13§	8§
- San Antonio, TX	1990-1997	Whites, Hispanics	-	560§	101§	18§
- Ventura, CA	1990-1994	Hispanics	0-17	31§	14§	45§

† Estimates include cases of type 1 diabetes.

‡ In case series, the sample size refers to the total number of cases of diabetes (type 1 and 2).

§ Incident cases.

Note: numbers in italics are estimates. – corresponds to unknown data.

Table 2 - 2. Characteristics of 578 North American children and adolescents at diagnosis of type 2 diabetes[5]

CHARACTERISTICS		STUDY REFERENCE* AND SAMPLE SIZE									
		Cincinnati OH (ref 14) n=54	Charleston NC (ref 15) n=39	Little Rock AK (ref 17) n=50	San Diego CA (ref 19) n=18	San Antonio TX (ref 20) n=101	Ventura CA (ref 21) n=21	Chicago IL (ref 28) n=160	Sioux Lookout Zone Ontario (ref 9) n=15	Manitoba (ref 5) n=20	Gila River AZ† (ref 12) n=100
Ethnicity (%)	African American	69	100	74	11	-		75			
	Hispanic			2	67	83	100	25			
	White	31		24	17	-					
	American Indian				‡				100	100	100
Female:male ratio		1.7	1.3	1.6	2.0	*3.0*	0.8	1.7	1.4	4.0	1.7
Family history (%)1st or 2nd degree		85	*95*	-	*87*	*74*	*100*	-	*93*	*100*	-
	1st degree relative	65	72	-	*80*	*45*	*>60*	50	*69*	*100*	-
Mean age (years)		14	13	14	13	*13*	14	14	12	12	16
Youngest age (years)		*8*	*7*	8	5	*6*	10	-	7	7	4
Mean BMI (kg/m^2)		38	30	35	27	-	33	33	*29*	*26*	35
Acanthosis nigricans (%)		60	56	86	67	92	-	-	-	-	-
Presence of weight loss (%)		*19-100*	*31*§	40	-	*50*	-	*62*	*30*	0	-
Mean HbA1C (%)		-	12	11	-	-	10	-	*13*	13	6
Ketosis (%)		-	79§	16-18	*33*	-	33	-	*50*	25	-

CHARACTERISTICS	STUDY REFERENCE* AND SAMPLE SIZE									
Ketoacidosis (%)	-	46§	>25	*14*	-	5	52	-	-	-
Diagnosis due to (%) Symptoms	*66*	-	-	-	-	86	-	100	25	-
Screening	*2***	-	-	-	-	14**	-	0	-	100
Urinalysis	*32*	-	-	-	-		-	0	75	-

* Numbered references may be found in reference list. Numbers of cases may differ from those reported in table 1 due to missing data for some cases or inclusion of additional cases from satellite-clinics.

† This case series included youth diagnosed by systematic screening between 1965 and 1998.

‡ One Cambodian case.

§ History of weight loss, ketosis or keto-acidosis.

** Evaluation for obesity or strong family history of diabetes.

Note: numbers in italics were either inferred from the original publication, estimated from a smaller total number of cases due to missing information, or obtained from personal communication. – corresponds to unknown data.

SEARCH Protocol – Section 3
Study Centers and Population
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3. Description of Study Centers and Populations

SEARCH has six centers, located in Cincinnati, Ohio; Colorado; Seattle, Washington, South Carolina; Hawaii; and Southern California.

Four SEARCH centers (Cincinnati, Colorado, Seattle, South Carolina) are geographically based—that is, diabetes cases will be identified from a geographically defined population of children. Two SEARCH centers (Hawaii and Southern California) are membership-based—that is, diabetes cases will be identified among members of participating health plans.

Tables 3-1 and 3-2 describe the base population and the diabetes case finding approaches for the prevalence and incidence components of the study for each SEARCH center. The following is a narrative description of the each study center, its case finding approaches, approach to denominator estimation, and the characteristics of the population. Further detail on denominator estimation and case finding approaches appears in Section 4.

3.1. CINCINNATI-CINCINNATI CHILDREN'S HOSPITAL MEDICAL CENTER

This Cincinnati center is located in Cincinnati, OH at Children Hospital Medical Center. For both the prevalence and incidence components of the study prevalent and incident cases, children with diabetes who reside in Cincinnati and the eight counties that surround Cincinnati will be identified and invited to participate.

Children's Hospital, established in 1883, is the only pediatric facility serving southwest Ohio, northern Kentucky, and southwest Indiana. As a result children and youth with complex medical problems are referred to Children's Hospital. The diabetes team, established in 1978, has provided care and education for pediatric diabetes patients in the greater Cincinnati area. In 1988, a computer database containing demographic and other data on all patients diagnosed with diabetes since 1978 was established. For SEARCH, the Cincinnati center will use the information in this existing computer database supplemented by prospectively collected data over a four-year period from newly diagnosed patients with childhood diabetes.

Although a majority of the care and management of childhood diabetes is provided at Children's Hospital, in order to insure complete ascertainment the investigators have established a network that identifies, contacts and collects data from the small number of patients with childhood diabetes who are not diagnosed at Children's Hospital.

The Cincinnati center will use the U.S. census as the source of denominator estimates.

In 2000, approximately 550,000 children and youth less than 20 years of age resided in the eight counties surrounding Cincinnati, including about 15% of non-white racial/ethnic background.

3.2. COLORADO-WESTERN REGISTRY OF DIABETES IN YOUTH

The Colorado center is located in Denver at the University of Colorado Health Sciences Center. For the prevalence component of the study, children with diabetes who reside in the urban-suburban counties surrounding Denver (Denver, Adams, Douglas, Jefferson, Boulder), six rural counties in south-central Colorado (Conejos, Costilla, Alamosa, Sauguache, Mineral, Rio Grande), Mesa county in western Colorado, and the Navajo Nation Native American reservation in Arizona/New Mexico, the Gila River Pima Indian Reservation in Arizona, and the Apache Indian Reservations White Mountain and San Carlos in Arizona will be asked to participate. For the incidence component of the study, case ascertainment will be expanded to all 63 counties in Colorado, and several additional Native American reservation populations will be approached to participate.

For the prevalence component of SEARCH, the Colorado center will use multiple sources, which are site and area dependent. The types of data sources include: pediatric endocrinologist computerized databases, HMO computerized diabetes registries, diabetes registries based on the Diabetes Electronic Management System (DEMS), school based health clinic charts, primary care practices, computer-stored hospital discharge records, diabetes educators' case records, Indian Health Service computer-stored hospital and ambulatory databases, NIH/NIDDK research databases, and death certificates. For the incidence component of SEARCH, Colorado center will expand its case identification to all of Colorado cases. Cases will be identified using a network of reporting clinics, physicians, and diabetes educators supplemented with information from hospital discharge records and computer-stored data sources.

The Colorado center will use the U.S. census as the source of denominator estimates.

In 2000, approximately 1,400,000 children and youth less than 20 years of age resided in Colorado and the Native American reservations included in the study. About 35% of the children/youth encompassed by the Colorado Center are of non-white racial/ethnic background.

3.3. HAWAII—PACIFIC HEALTH RESEARCH INSTITUTE

The Hawaii center is located in Honolulu, Hawaii at the Pacific Health Research Institute. Partners in this project with the Pacific Health Research Institute (PHRI) at the Hawaii Center will include Kaiser Permanente-Hawaii, the Hawaii Medical Service Association (HMSA), and the State of Hawaii Department of Human Services, Med-QUEST Division. For the prevalence component of the study, children with diabetes who are members the major health plans in Hawaii (the Hawaii Medical Service Association (HMSA), Kaiser Permanente-Hawaii and the State of Hawaii, and Department of Human Services Med-QUEST) in 2001 and reside on Oahu will be asked to participate. For the

incidence component of the study, case ascertainment will be expanded to include members of these three health plans on all the six major islands of Hawaii (Oahu, Hawaii, Maui, Kauai, Molokai and Lanai). The combined membership of these three plans includes over 90% of the state's non-military residential population under age 20 as determined by the US Census.

The Pacific Health Research Institute (PHRI) is a non-profit research institute created in 1960. Since 1996, HMSA and Kaiser Permanente-Hawaii have been contributing data to the Hawaii Diabetes Data Network (HDDN). For the prevalence component of SEARCH, the Hawaii center will use the information in the existing computer database. For the incidence component of SEARCH, cases will be identified using a rapid reporting system of clinics and physicians.

The Hawaii center will use administrative membership databases from the participating health systems as the source of denominator information. Estimates of the number of children in each ethnic group will be made based on the U.S. census with the assumption that the membership of the health plans is representative of the geographic base from which cases are drawn.

In 2000, approximately 300,000 children and adolescents less than 20 years of age resided on the six Hawaiian islands, including approximately 70% Asian and Pacific Islanders. All patients in the state's Medicaid program. (Med-QUEST) will be included.

3.4. SEATTLE/PUGET SOUND—CHILDREN'S HOSPITAL & REGIONAL MEDICAL CENTER

The Seattle center is located in Seattle at the Children's Hospital & Regional Medical Center (CHRMC). For both the prevalence and incidence components of the study children with diabetes who reside in the five counties that comprise the Puget Sound Region of Washington (King, Kitsap, Pierce, Snohomish, Thurston) will be asked to participate.

Prevalent cases will be identified using a combination of clinical and non-clinical and administrative data sources including the following: pediatric and adult endocrinology practices in the Puget Sound region, the two major pediatric hospitals serving Puget Sound region, other hospitals with a history of admitting youth with diabetes, primary care clinics, data from the Community Diabetes Initiative (CDI) diabetes registry, the Group Health diabetes registry, the Washington State Comprehensive Hospital Abstract Reporting System (CHARS), and administrative data from four health plans (Medicaid, Group Health, and the two largest private insurers). For the incidence component of SEARCH, the Washington center will apply the same case identification strategies to identification of incident cases.

The Seattle center will use the U.S. census as the source of denominator estimates.

In 2000, approximately 1 million children and youth less than 20 years of age resided in the five counties of Puget Sound. This is the most populous and ethnically diverse region in the state, with approximately 6% African Americans, 5% Hispanics, 9% Asians/Pacific Islanders, and 1% Native Americans.

3.5. SOUTH CAROLINA

The South Carolina center is located in Columbia, South Carolina at the University of South Carolina (USC). For the prevalence component of the study, children with diabetes who reside in a four-county area (Richland, Lexington, Orangeburg and Calhoun) will be asked to participate. The majority of these cases were included in the Richland/Lexington County Child and Adolescent Diabetes Registry (RLDR). For the incidence component of the study, case ascertainment will be expanded to all 46 counties in South Carolina.

In 1999, the Richland/Lexington County Child and Adolescent Diabetes Registry (RLDR) was started by Dr. Beth Mayer-Davis, a SEARCH PI, and colleagues to document the population prevalence of physician-diagnosed diabetes among individuals aged 0-18 years in a two-county region of South Carolina. Information for the registry comes from the following: the four hospitals in Richland and Lexington counties, the single pediatric endocrinologist serving the two counties, the two adult endocrinology practices, the USC pediatric outpatient clinic and family medicine clinics, the five largest private pediatric clinics, the three largest Family Medicine practices and camp lists provided by Camp Adam Fisher for children with diabetes. For the prevalence component of SEARCH, the South Carolina center will apply the same case identification methods used in the previous two-county registry. For the incidence component of SEARCH, the South Carolina will expand its case identification to all of South Carolina applying the same case identification strategies but with reliance on rapid case reporting by pediatric endocrinologists.

The South Carolina center will use the U.S. census as the source of denominator estimates.

In 2000, approximately 1.1 million children and youth less than 20 years of age resided in South Carolina, including about 39% of non-white racial/ethnic background. South Carolina ranks 14th nationwide on the poverty scale and 23% of children under age 19 live in poverty. 19.9% of the non-white, and 13.9 % of the white population are uninsured. 32% of South Carolina children do not graduate from high school. Over 30.5% of South Carolina children live in rural counties and 75% of the state's 46 counties are designated by the US Public Health Service as "medically under-served".

3.6. SOUTHERN CALIFORNIA KAISER PERMANENTE

This Kaiser Permanente Southern California (KPSC) center is located in Pasadena, California at the Department of Research and Evaluation. For both the prevalence and incidence components of the study, children with diabetes who are members of KPSC other than members in San Diego (SD) will be identified and invited to participate.

Kaiser Permanente is a group model HMO that delivers comprehensive medical care on a prepaid basis to 3 million resident of southern California. The Department of Research and Evaluation is the internal research arm of KPSC that is committed to the conduct of research in the public domain. Starting in 1995, Dr. Diana Petitti, a SEARCH PI, initiated the KPSC diabetes case identification database as a resource for research and quality assessment and improvement. The database builds on work done in other Kaiser Permanente regions, using computer record linkage to identify possible cases of diabetes. For the prevalence component of SEARCH, the KPSC center will use the information in the existing computer database. For the incidence component of SEARCH, cases will be identified using a rapid reporting system of clinics and physicians supplemented with computer-stored data on prescriptions and laboratory testing.

The Kaiser Permanente Southern California center will use its administrative membership database as the source of denominator information. Estimates of the number of children in each ethnic group will be made based on block-level geocoding of address information to the 2000 U.S. census.

In 2000, approximately 700,000 children and youth less than 20 years of age were members of the Kaiser Permanente Southern California other than in San Diego, including about 29% of Hispanic, 10% African American, and 11% of Asian/Pacific Islander ethnic/racial origin. The KPSC membership less than 20 years of age includes about 45,000 children who are members of the Health Plan via Medicaid or other programs designed to provide low-income families with access to insurance.

Table 3 - 1: Description of Base Population and Summary of Source of Estimates Cases for Prevalence Component

	Base Population	Source of Cases	2001 Estimated, Denominator / Cases
Cincinnati (Children's Hospital)	Cincinnati and 8 surrounding urban counties (Hamilton, Butler, Warren, Clermont OH; Boone, Kenton, Campbell KY; Dearborn IN).	Existing pediatric diabetes database based on clinical visits to Children's Hospital	550,430 / 1,036
Colorado (University of Colorado Health Sciences Center)	Thirteen counties in Colorado; All interested Native American reservations in Arizona and New Mexico	Diabetes registry to be established	808,503 / 1,430
Hawaii (Pacific Health Research Institute)	Members of the Hawaii Medical Service Association, Kaiser Foundation Health Plan - Hawaii, and the Hawaii State Department of Human Services, Med-QUEST Division, in Oahu county.	Existing diabetes database based on record linkage	240,260 / 535
Seattle (Children's Hospital)	King, Pierce, Snohomish, Kitsap, Thurston counties	Diabetes registry to be established	982,920 / 1,735
South Carolina (University of South Carolina)	Richard, Lexington, Orangeburg, Calhoun counties	Existing network of sources including pediatric and adult endocrinologists, hospitals incl. Outpatient clinics, federally funded primary health care clinic	179,238 / 361
Southern California (Kaiser Permanente Southern California)	Members of the Kaiser Permanente Medical Care Program in Southern California except San Diego	Existing pediatric diabetes case identification database based on record linkage	700,450/ 1,281
All Sites			3,461,801 / 6,378

Table 3 - 2: Description of Base Population and Summary of Source of Estimated Cases for Incidence Component

	Base Population	Source of Cases	2001 Estimated, Denominator / Annual Cases
Cincinnati (Children's Hospital)	Cincinnati and 8 surrounding urban counties (Hamilton, Butler, Warren, Clermont OH; Boone, Kenton, Campbell KY; Dearborn IN).	New cases seen at Children's; referral to study by reporting network of pediatric endocrinologists	550,430 / 89
Colorado (University of Colorado Health Sciences Center)	All counties in Colorado; All interested Native American reservations in Arizona and New Mexico	Referral to study by reporting network of clinics, pediatric endocrinologists, and diabetes educators; updated diabetes registry to be established	1,420,839 / 217
Hawaii (Pacific Health Research Institute)	Members of the Hawaii Medical Service Association, Kaiser Foundation Health Plan - Hawaii, and the Hawaii State Department of Human Services, Med-QUEST Division, in all counties in Hawaii.	Referral to study by reporting network of clinics and pediatric endocrinologists; updated record linkage database	300,327 / 42
Seattle (Children's Hospital)	King, Pierce, Snohomish, Kitsap, Thurston counties	Referral to study by reporting network of clinics, pediatric and adult endocrinologists, hospitals supplemented with record linkage	982,920 / 151
South Carolina (University of South Carolina)	All counties in South Carolina	Referral to study by reporting network of clinics, pediatric and adult endocrinologists, hospitals supplemented with record linkage	1,118,022 / 183
Southern California (Kaiser Permanente Southern California)	Members of the Kaiser Permanente Medical Care Program Health Plan in Southern California except San Diego	Referral to study by KPSC reporting network of pediatric endocrinologists; quarterly updated record linkage database	700,450 / 103
All Sites			5,072,988 / 785

SEARCH Protocol – Section 4
Case Ascertainment
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4. Methods: General Overview

4.1. GOAL

The goal of case ascertainment is to identify and validate all unique, eligible cases of diabetes in youth less than 20 years residing in the SEARCH prevalence area in 2001 and all unique, eligible, newly diagnosed cases of diabetes in youth less than 20 years residing in the SEARCH incidence area in 2002-2004. This will allow SEARCH to estimate the population prevalence and incidence of childhood type 1, type 2, and other types (or hybrids) of diabetes.

This section provides a general overview of the methods that will be used to accomplish the goal (Methods: General Overview), as well as more detailed site-specific information (Methods: Site-Specific Case Ascertainment Methods)

To identify cases for SEARCH it is necessary to review protected health information. Access to such information is subject to federal regulation, state laws and institutional policies. SEARCH is aware of these regulations and addresses them in Section 11.

4.2. DENOMINATOR ESTIMATION

Overview

To estimate incidence and prevalence accurately, it is necessary to align the numerator and the denominator. That is, the cases of diabetes that are counted in the numerator for prevalence and incidence must derive from the same population that is defined as the denominator. To estimate incidence and prevalence accurately, it is also necessary to have accurate information on the denominator of children 0-19 years of age in which diabetes cases exist (for prevalence) or occur (for incidence). Every effort will be made in SEARCH to assure that numerator and denominator are aligned by applying the same criteria for inclusion in the denominator to eligibility for the study and to include case-finding data sources that would identify cases that would arise from the denominator.

The four geographically based SEARCH centers (Cincinnati, Colorado, Seattle, South Carolina) will use the US Census non-institutionalized non-military resident population in the area from which cases are drawn as the total denominator for estimation of prevalence and incidence. For the prevalence component of the study, 2000 US Census data will be used. For the incidence component of SEARCH, the geographically based centers will use projections of population changes based on the 2000 Census. A resident is defined by the Census as a person with a permanent address within the defined

geographic area at any time in the index year, who is not noted to be living elsewhere or only temporarily residing at the eligible address.

The membership-based centers (Hawaii and Southern California) will use administrative data on membership 0-19 years in the participating health plans as the total denominator for estimation of both incidence and prevalence. For both the prevalence and incidence components of the study, the number of health plan members on July 1 in the given year will be used.

Special populations

College students are counted in the Census in their residence location as of April 1. This will usually be the college/town where they attend school. An attempt will be made to identify diabetes cases in age-eligible college students resident in geographic areas of SEARCH case ascertainment so that numerator and denominator will be aligned. Youth who are attending college while still members of the participating health plans cannot be identified as attending college using administrative data. Thus, they will be included in the denominator for the member-based centers. Prevalent cases in college students are likely to be known to SEARCH and incident cases can be identified through member databases. Thus, numerator and denominator remain aligned. The handling of college students is also consistent between the geographically based and membership-based sites by including these youth in both the numerator and denominator.

Military personnel are counted in the Census at the base/community where they are assigned. Initial total population estimates include these persons. However, as the Census results are further refined, the military personnel are identified separately. No attempt will be made to identify diabetes cases in active-duty military personnel. Thus, final numerator and denominator estimates will exclude active-duty military service members.

Military dependents are counted in the Census at their usual residence, whether on or off base. Thus, they will be counted in the non-military denominator. Medical care for dependents will differ between base locations and access to care systems (military or civilian) will determine the ability to identify cases. Every attempt will be made to identify such cases in a consistent way across centers to align numerator and denominator similarly across sites. Center specific documents define how each center will identify cases in the military dependent population.

Institutionalized persons living in prisons, chronic care hospitals, and other institutions are removed from the counts of the civilian, non-institutionalized denominator, and will not be eligible as cases to align numerator and denominator.

Age, Gender, and Race/Ethnicity: Prevalence

For the geographically based centers (Cincinnati, Colorado, Seattle, South Carolina), Census data by age, gender and race/ethnicity will be used to estimate the number of persons in the denominator by age, gender and race/ethnicity. Year 2000 Census data will be used to calculate age, gender, and race/ethnicity specific denominators.

For the membership-based Hawaii center, it will be assumed that membership in the participating health plans is representative of the population of Hawaii with regard to race/ethnicity. The Census proportions of the Hawaii population aged 0-19 years by race/ethnicity will be applied to the age and sex-specific membership denominators.

For the membership-based Southern California center, direct counts of members 0-19 years by age and gender will be obtained from membership records. Data on race/ethnicity will be obtained by linking address information to block-level data from the Census using a process called geocoding.

For all centers, race/ethnicity data will be collapsed into groups (Non-Hispanic white, Hispanic American, African American, Asian, Pacific Islander, Native American, Other and Unknown) using rules and conventions developed by the Census.

Age, Gender, and Race/Ethnicity: Incidence

For years 2002 and beyond of the incidence study, the geographically-based sites (Cincinnati, Colorado, Seattle, South Carolina) will use projections of population changes that are based on the 2000 Census. The methods for making these projections will vary by location, but will be standardized as much as possible across sites using demographically acceptable methods. Population projections may not be available by age, gender, and race/ethnicity at the level of detail needed. Projected denominators, therefore, will be estimated using 2000 Census proportions by gender and race/ethnicity within age-specific groups, at least through 2005.

For the membership-based centers (Hawaii and Southern California), membership counts by age and gender will be updated annually. For each of these sites, Census projections of race/ethnicity will be applied to the updated member-based denominators.

4.2.1. **Prevalence Component**

4.2.1.1. **Eligibility Criteria**

The eligibility criteria for prevalent cases of diabetes are as follows:

a. Prevalent in 2001,

b. Age less than 20 years on December 31, 2001; this corresponds to a birth year: 1/1/82 – 12/31/2001 for the prevalence year of 2001. Subjects reaching age 20 in the prevalence year are not eligible,

c. Resident of the population defined for prevalent cases at any time in the prevalence year (for geographically-based centers) or member of the participating health plan in the prevalence year,

d. Not active-duty military,

e. Not living in an institution (defined as such by the Census),

f. Not gestational diabetes.

For geographically-based centers, resident is defined to align numerator and denominator and includes anyone documented to have resided in that center's geographical area at any time during the prevalence year.

Prevalent cases of diabetes in active duty military personnel are ineligible because it is anticipated that access to military medical records will be difficult. It is unlikely that the prevalent diabetes cases will be present among active duty military because diabetes precludes active duty military service.

Prevalent cases of diabetes in dependents of military personnel having access to civilian medical facilities will be eligible, recognizing that prevalent diabetes cases receiving care only at military facilities can be ascertained only if access to military records is obtained.

Prevalent cases of diabetes in college students are eligible for SEARCH as these youth are counted in the Census as resident at their college address. Additionally, college students identified as cases by membership-based centers cannot be removed from the membership-based administrative records that are the source of denominator data for these centers.

4.2.1.2. **Case Finding Approaches**

The approach to case-finding for prevalent cases varies by center as a reflection of availability of an existing diabetes registry or database and access to clinics, physicians, and computer-stored data resources. The data sources that will be used to ascertain cases include: hospital administrative data, hospital discharge records, laboratory records, prescription records, ambulatory administrative records, ambulatory clinical records (including: pediatric and adult endocrine practices, and primary care practices); diabetes registries; state insurance plans; and vital records.

For geographically based centers, database searches for potential cases may be retrospective to January 1, 1998, if data are available. Case searches in databases prior to this date were shown to be less effective (unpublished data, Colorado and South Carolina) in terms of locating eligible cases. The center-specific protocols for case ascertainment provide detail on the case finding approaches for each SEARCH center.

Table 4-1 summarizes the data sources that will be used at each center to identify prevalent cases.

Table 4-1. Data Sources Used to Identify Prevalent Cases by Center

Center	Hospital Discharge	Laboratory	Prescription	Ambulatory Billing	Pediatric Endocrinology Case List	Other
Cincinnati	x			x	x	x
Colorado	x			x	x	x
Hawaii	x	x	x	x	x	x
Seattle	x			x	x	x
S. Carolina	x			x	x	x
S. California		x	x			

4.2.1.3. **Case Validation**

It is important that cases of diabetes be true cases of diabetes. For prevalent cases, the information that is necessary to establish that the case meets the ADA criteria for diabetes will not be accessible, due to lack of chart review.

Prevalent cases of diabetes are validated if the case has either:

a. a physician diagnosis of diabetes; or

b. parent or youth self-reports a physician diagnosis of diabetes at the time of an interview or survey.

A “physician diagnosis” of diabetes is made if any of the following conditions are met:

a. review of any medical record reveals a physician diagnosis of diabetes;

b. the diagnosis of diabetes is directly verified, or the diabetes case is “referred” to the study, by a clinician;

c. diabetes is listed as the underlying or contributing cause of death on a death certificate;

d. the case is included in a clinical database that has a requirement for verification of diagnosis by a clinician.

4.2.1.4. **Estimated Number of Prevalent Cases**

The estimated number of prevalent cases that will be identified by center, age, race/ethnicity and type is shown in Table 4-2. These estimates were based on prevalence of type 1 and type 2 diabetes derived from the literature and unpublished data available to SEARCH investigators (see Table 4-2), which were applied to the center-specific denominator estimates by age group and race/ethnicity.

Table 4-2. Estimated Number of Prevalent Cases by Center, Age Group, and Race/Ethnicity.

Age	NHW	AA	Hispanic	Asian	PI	N.Am	Total
0 thru 9							
California	178	33	63	4	7	0	285
Colorado	317	23	35	0	1	25	401
Hawaii	27	3	7	25	45	0	107
Ohio	246	32	0	0	0	0	278
Seattle	402	33	16	6	8	3	468
S Carolina	46	38	1	0	0	0	85
10 thru 19							
California	463	115	342	47	27	2	996
Colorado	677	64	159	10	5	114	1,029
Hawaii	73	11	47	185	112	0	428
Ohio	646	112	0	0	0	0	758
Seattle	985	98	79	59	33	13	1,267
S Carolina	127	142	7	0	0	0	276
Total	**4,187**	**704**	**756**	**336**	**238**	**157**	**6,378**

4.2.2. **Incidence Component of SEARCH**

4.2.2.1. **Eligibility Criteria**

The beginning year for identification of incident cases is 2002. Identification of incident cases will continue for the duration of the study.

The eligibility criteria for incident cases of diabetes are as follows:

Onset of diabetes (January 1 through December 31) in the incidence year; “onset of diabetes” is the date of first clinical diagnosis of diabetes in a non-pregnant state

a. Age less than 20 years on December 31 of the onset year. Participants who turn 20 in the onset year are not eligible.

b. Resident of population defined for incident cases in the onset year (for geographically-based centers) or member of the participating health plan in the onset year.

c. Not active duty military.

d. Not living in an institution (defined as such by the Census).

e. Not gestational diabetes.

For geographically-based centers, resident is defined to align numerator and denominator and includes anyone documented to have resided in the geographic area for that center at any time during the onset year.

4.2.2.2. **Case Finding Approaches**

At all six SEARCH centers, the primary approach to case-finding for incident cases of diabetes will be rapid reporting networks of clinics and health care providers, including in some instances diabetes educators and school nurses. This approach is viable because a relatively small number of referral practices care for a high proportion of potentially eligible youth with new-onset diabetes (e.g. pediatric endocrinologists, adult endocrinologists, adolescent medicine specialists). Each center will develop a network of cooperative providers and other practice locations willing to participate in SEARCH.

Details of the recruitment of physicians and children/parents to the study are provided in Section 6 of the protocol.

In addition to identification of incident cases based on active reporting with involvement of the treating physicians, updates of databases using record linkage will be used to identify incident cases. Thus, on a regular basis, the data sources used to identify cases in the prevalence study will be queried and matched with cases reported to SEARCH by the rapid reporting network to identify cases that might have been missed through active surveillance.

4.2.2.3. **Case Validation**

The criteria used to validate incident cases are the same as those used to validate prevalent cases. Thus, incident cases of diabetes will be validated if the case has either: 1) a physician diagnosis of diabetes; or 2) the parent or the youth self-reports a physician diagnosis of diabetes at the time of an interview or survey.

The criteria for considering that there is a "physician diagnosis" of diabetes are the same for incident cases as for prevalent cases. Thus, a physician diagnosis is made if any of the following conditions are met:

a. review of the medical records reveals a physician diagnosis of diabetes,

b. the diagnosis of diabetes is directly verified, or the diabetes case is "referred" to the study, by a clinician,

c. diabetes is listed as the underlying or contributing cause of death on a death certificate,

d. the case is included in a clinical database that has a requirement for verification of diagnosis by a clinician.

4.2.2.4. **Estimated Number of Incident Cases**

In order to assess the statistical power of the study and to plan the amount of resources needed for the study, the number of incident cases that would be identified in SEARCH by center, age, and race/ethnicity and type was estimated (Table 4-3). These estimates were based on incidence rates of type 1 and type 2 diabetes derived from the literature and unpublished data available to SEARCH investigators (see Appendix V), which were applied to the center-specific denominator estimates by age, gender and race/ethnicity.

Table 4-3. Estimated Number of Incident Cases per year by Center, Age Group, and Race/Ethnicity

Age	NHW	AA	Hispanic	Asian	PI	NA	Total
0 thru 9							
California	24	4	8	0	0	0	36
Colorado	71	4	10	0	0	3	88
Hawaii	4	0	1	3	4	0	12
Ohio	32	3	0	0	0	0	35
Seattle	53	4	1	0	1	0	59
S Carolina	45	27	1	0	0	0	73
10 thru 19							
California	34	6	22	4	1	0	67
Colorado	88	4	20	1	0	16	129
Hawaii	6	0	3	11	10	0	30
Ohio	48	6	0	0	0	0	54
Seattle	74	5	4	6	2	1	92
S Carolina	65	43	2	0	0	0	110
Total	**544**	**106**	**72**	**25**	**18**	**20**	**785**

4.2.3. **Identification and Elimination of Possible Duplicate Cases**

At all centers, cases will be identified based on various record sources. In addition, incident case reports must be compared to prevalent reports to determine whether the case is actually an incident case, or a missed prevalent case. Thus, it

is necessary to identify and eliminate possible duplicate cases. This involves establishing a method to match records at each center.

The membership-based centers will be able to use unique identifying information on membership number, name, and date of birth to identify duplicates and to match records in order to remove duplicates. The Cincinnati center has a registration system for cases that will permit duplicates to be identified as they are entered into the diabetes database based on name, date of birth, and other identifying information about the child and parents.

The other three geographically-based centers (Colorado, Seattle, South Carolina) will employ record-linkage methods that make use of partial identifying information. For these centers, the following items may serve as possible matching variables to use in record matching to identify duplicate cases. Duplicate cases will be removed when identified.

Potential Variables for Matching to Eliminate Duplicates

a. Name

b. Gender

c. Date of Birth

d. Race/Ethnicity

e. Medical Record Number

f. Parent's last name

g. Mother's maiden name

h. Admission date of hospitalization(s)

i. Address, zip code

j. Telephone number

k. Social Security Number (as determined by local site)

The specific approaches to duplicate removal are described in the center-specific protocols.

Personal identifiers are required to remove duplicates. This information will not be sent to the Coordinating Center.

4.2.4. **Gestational Diabetes**

The study will not attempt to ascertain gestational diabetes, defined as diabetes mellitus with onset or first recognition during pregnancy. When case finding approaches identify gestational diabetes, these will be excluded. However, in some situation, women with gestational diabetes may wrongly be assigned diagnostic codes for diabetes. During the validation process (chart review and/or survey), these cases will be identified and then excluded from SEARCH.

If a woman's diabetes is first recognized during pregnancy and persists after the pregnancy ends, the case will be registered. The onset date will be defined as the date of first clinical diagnosis of diabetes in the non-pregnant state (usually at the first post-partum visit).

4.3. ASSESSMENT OF THE COMPLETENESS OF CASE ASCERTAINMENT

Overview

The validity of incidence and prevalence estimates from SEARCH is critically dependent on complete ascertainment of cases through the case-finding approaches described above. An attempt to assess the completeness of case-ascertainment is thus crucial to the SEARCH objectives. The theoretically ideal way to determine the completeness of case ascertainment would be 100% review of every medical record in a geographic area to determine if a valid case exists. This requires resources beyond those available for SEARCH.

4.3.1. **Capture-Recapture**

Capture-recapture [28-31]is a statistical approach that attempts to estimate the completeness from incomplete samples. This method requires a minimum of two data sources in which a case can be identified. The data elements that are required to derive estimates of the completeness of case ascertainment using capture-recapture methods are 1) the source(s) of the case record for each unique case identified and 2) the date of inclusion in the data source. Records must be non-duplicates. These data elements will be collected in SEARCH from unduplicated records. The best statistical methods will be used, incorporating multiple ascertainment sources, with adjustment for non-independence of data sources. Capture-recapture methods will be used in the geographically-based SEARCH centers with multiple sources of cases (Cincinnati, Colorado, Seattle, South Carolina).

4.3.2. **Intensive Case-Finding**

Another way to estimate the completeness of case ascertainment is to conduct extended, intensive case-finding of all available potential sources of cases, or to identify multiple independent computerized databases. While possible, limited resources preclude complete review of all records in defined geographic areas with multiple providers that do not share common information systems.

At the Seattle, South Carolina, and Colorado centers, intensive case-finding will be done based on a mailed survey to a defined sample of providers in specialties likely to see youth with diabetes who are not included in primary case ascertainment. Such specialties include: pediatrics, family medicine, general internal medicine, adolescent medicine, and adult endocrinology. Other specialties such as OB/GYN, school–based clinics, emergency medicine, alternative providers, and PAs or NPs who work with providers previously listed will be considered for survey to establish practice and referral patterns for youth with diabetes in these geographic areas.

A random sample of providers who indicate that they care for children with diabetes will be asked to review their clinical and billing databases and/or chart review to find cases of diabetes in children. These cases will be compared with cases that have already been identified by SEARCH as permitted by local IRBs.

This survey will also inform incident case identification. Those providers that care for eligible youth with diabetes and do not routinely refer them to members of the rapid reporting network will be contacted on a regular basis depending on the number of children they see per year. Low volume practices will be contacted yearly. Higher volume practices will be asked to join the rapid reporting network. If they are found not to report cases, they will be called regularly and asked if cases exist that could be registered.

4.3.3. **Use of Death Certificates**

Identification of deaths for persons listed with diabetes with birth years and geographic residence that would make them eligible for SEARCH has three purposes: 1) case ascertainment; 2) completeness; and 3) mortality among validated cases. Death certificate searches will be conducted every 2 years in all sites. Deaths with any cause of death listed of diabetes (ICD-9-Code 250.x, ICD-10 codes E10.x-E14.9) in persons will be identified. Information from the death certificates of these individuals will be requested from state and local Departments of Vital Statistics. This information will be matched against the local SEARCH database to identify potential missed cases, or to identify known cases that have died. Any cases identified using only death certificates will be classified as death certificate-only cases. However, given the specificity of death

certificate diagnoses, such cases will be considered validated cases. Attempts to collect information on these cases will be done on a center-specific basis.

4.4. ASSESSMENT OF POSSIBLE BIAS DUE TO INCOMPLETE/MISSING INFORMATION ON VALIDATED CASES

Eligible and validated cases will be registered. For geographically based centers, given the approaches to case finding that will be used, in some validated cases one or more eligibility criteria, such as residence, will not be documented. Limiting registration of validated cases for which residence in the geographic population of SEARCH can be confirmed may selectively bias towards underestimating prevalence and/or incidence in groups where migration is more likely (e.g. college age youth). To estimate this possible bias, potentially eligible, validated cases, such as cases whose residence in the prevalence or onset year cannot be confirmed, will be registered separately.

SEARCH Protocol – Section 5
Data Collection
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5. Data Collection

5.1. GOALS

The SEARCH data collection strategy strives to maximize the response rate and completeness of information collection, protect confidentiality and minimize respondent burden. The data collection methods will be standardized across all sites so study data can be pooled.

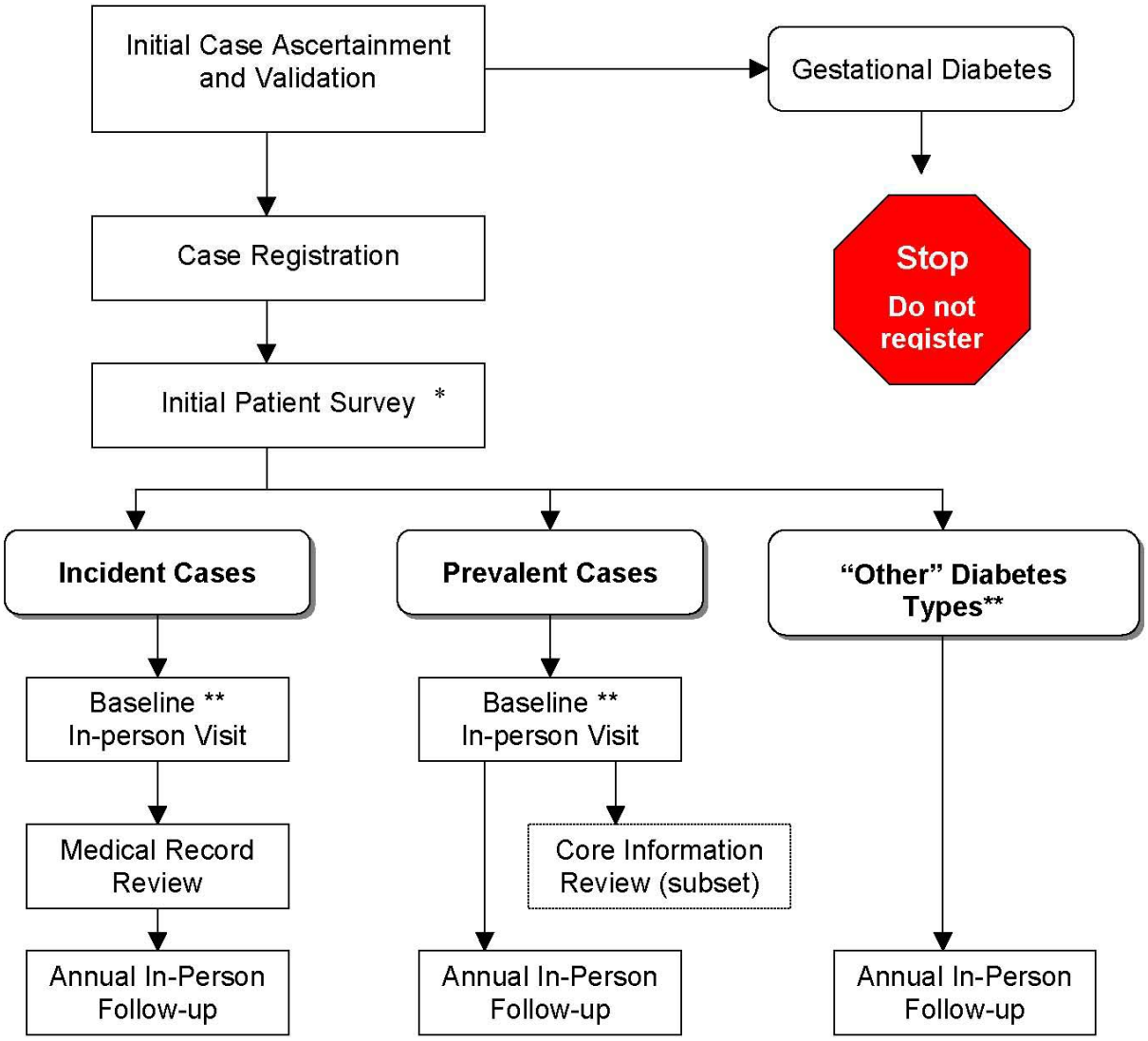
Prevalent cases (index year, 2001): Data collection will begin in April 2002.

Incident cases (index year beginning 2002): Data will begin April 2002 and continue until the end of study funding in 2005.

5.2. SUMMARY OF APPROACH

Data collection is organized in "modules." Modules are designed to maximize local clinic operational efficiency while maintaining a high level of standardization. Figure 5-1 shows the flow of data collection; Table 5-1 provides summary information about each of the data collection modules.

Figure 5-1 Overall Data Collection



* Initial patient survey may be needed to complete validation sufficient for case registration.
**"Other" diabetes types with prior knowledge of genetic deficit in beta cell function (i.e., MODY) will be asked to participate in the Baseline In-Person Visit.

Solid lines indicate the path of choice and should be attempted first. Dashed lines indicate a secondary path and should be attempted if the initial path is unsuccessful.

Table 5-1. Summary of Data Collection Modules

Module	Case Type	Components	Source*	Form (Est. Patient time)	Content
Case Registration	All	Limited to medical record and/or provider-based information	2	Data downloaded from local tracking database	▪ ID ▪ Age ▪ DOB ▪ Gender ▪ Race/ethnicity ▪ County of residence ▪ Zip Code ▪ Diabetes validated (yes) ▪ Method of validation (Medical record review/Direct verification by a physician/Clinically verified database/Death certificate/Self-report) ▪ Diabetes Status (Prevalent/Incident) ▪ Date of Diagnosis ▪ Secondary Diabetes [diabetes caused by another source e.g., illness or medication] (Yes/No) ▪ Residence Eligibility (Eligible/Pending/Not Applicable) ▪ Health Plan Eligibility (Eligible/Pending/Not Applicable) ▪ Military Eligibility (Eligible, Unknown) ▪ Institutional Eligibility (Eligible, Unknown) ▪ Date registered

Module	Case Type	Components	Source*	Form (Est. Patient time)	Content
Initial Patient Survey Module	All	Introductory Letter		N/A	▪ General overview of the study ▪ Description of Initial Patient Survey ▪ Provision allowing Patient to fill out and return the Initial Patient Survey by mail, complete via telephone interview, or complete at an in-person visit. ▪ Contact information for SEARCH staff member to answer questions and/or to complete the survey by phone (for local use only) ▪ Notification that either the local provider or a SEARCH staff member will be contacting the Patient to discuss the study.
		Initial Patient Survey	1	Initial Patient Survey (10 min)	▪ Date of birth and gender ▪ Date of diagnosis, age at diagnosis, setting of diagnosis, approximate body size at diagnosis, ▪ Past history concerning DKA and/or vomiting and insulin use ▪ Prescription medications and other medical history ▪ Status as active or dependant military or a college student ▪ Race/race/ethnicity of Patient using Census 2000 categories ▪ Confirmation of residence during index year ▪ (For local use only) Name and contact information

Module	Case Type	Components	Source*	Form (Est. Patient time)	Content
In-Person Visit Module (Estimated time for completion of the module is 2 to 5.5 hours based on age and diabetes typology)	Incident Prevalent	Physical Examination	1	Physical Exam Form (20 min)	▪ Anthropometric Measures: height, weight, waist circumference ▪ Blood pressure ▪ Acanthosis Nigricans (examination of neck)
		Laboratory Specimen	1	Specimen Collection Form (20 min for all) (additional 1 hr for C-peptide) Stimulated C-peptide Form (≥ 8 years of age)	▪ Diabetes autoantibodies ▪ Fasting C-peptide and glucose ▪ HgbA1c ▪ Lipid profile (fasting): total cholesterol, HDL, LDL, and triglycerides ▪ Urine albumin & creatinine ▪ Diabetes medications ▪ Stimulated C-peptide (possible second visit)
		Questionnaires	1	Health Questionnaire (50-60 min)	▪ Co-morbidities ▪ Clinical presentation and diagnosis ▪ Medication inventory (for age < 10 yrs) ▪ Processes of care ▪ Socioeconomic status ▪ Family history ▪ Current family structure ▪ General and diabetes specific quality of life (age-specific)
			1 1 1	Supplemental Health Questionnaire (age 10 and over) (50-60 min) CES-D Peds QL™ FFQ Tanner staging	▪ Health behaviors (e.g., diet, activity, sleep, smoking) ▪ Medication inventory ▪ Pubertal development

Module	Case Type	Components	Source*	Form (Est. Patient time)	Content
Medical Record Module	Incident	Medical Record Abstraction **	2	Medical Record Abstraction Form	▪ Diabetes autoantibodies, C-peptide ▪ Clinical presentation ▪ Selected acute and chronic diabetes complications ▪ Selected co-morbidities ▪ Medications, including insulin use ▪ Processes of care ▪ Diabetes-related genetic testing ▪ Pubertal development (subset)

	Prevalent (subset)	Diabetes Typology Medical Record Abstraction**	2	Core Form	▪ Patient gender
					▪ Race/ethnicity
					▪ Information for typology
					  ▪ Diagnosis
					  ▪ Diagnostician
					  ▪ Laboratory values
					  ▪ Insulin use
					▪ Height and weight

Annual Follow-Up Visit Module	Incident	▪ In-person Module (all components)	1	(See In-Person Visit Module above)	(See In-Person Visit Module above. All elements subject to change over time will be repeated)
Annual Follow-Up Mail Module	Prevalent	▪ 12-month mailed survey	1	Mailed Survey Form (10 min)	▪ Health utilization ▪ Contact information (local use only)
	Other Diabetes Types	▪ 12-month mailed survey	1	Mailed Survey Form (10 min)	▪ Health utilization ▪ Contact information (local use only)
	All	▪ Vital status	2	N/A	▪ Death certificate if applicable
		Medical Record Module	2	Medical Record Abstraction Form (incident cases) Limited Typology Abstraction Form (prevalent cases)	▪ Same content as for Medical Record Module – see above

* 1 -primary data source including Patient and/or parent or legal guardian; 2 -secondary data source including medical record review, provider information

5.3. LANGUAGE

English and Spanish forms will be provided by the study. Some sites (e.g., Southern California and Colorado) will require personnel that are bilingual in English and Spanish.

Some potential Patients will speak languages other than English and Spanish. Local sites will make arrangements to accommodate languages other than English or Spanish using a local translator or using other resources such as the ATT translation line.

Patients will not be excluded based on language.

5.4. CASE REGISTRATION MODULE (INCIDENT AND PREVALENT CASES)

Eligible Patients: Incident and Prevalent Cases

Case Registration closes the gap between case ascertainment, which is a local effort and data collection, which is a national effort. Case Registration occurs when a unique (unduplicated) case is validated and age and residence eligibility are established. The process of case registration initiates all other data collection. Information gathered at the time of case registration is minimal. Depending on the local case ascertainment approach, some data elements requested for case registration may be missing at the time of registration and will be completed or verified within a later data collection module (e.g., Initial Patient Survey). At some centers, Case Registration will occur based on anonymous case reports collected by the local center. For all centers, when identifying information becomes available, it will remain at the local center and will not be forwarded to the Coordinating Center.

5.5. INITIAL PATIENT SURVEY MODULE

Eligible Patients: Incident and Prevalent Cases

This module will be initiated once a case is registered. The Initial Patient Survey Module includes two components: the Introductory Letter and the Initial Patient Survey. The Survey will facilitate confirmation of case validation, residence and age eligibility, status as an incident or prevalent case, and uniqueness of the case. In addition, critical demographic and typology- related data would be collected. Contact information will be updated for local use only.

If a case is identified as having Gestational Diabetes because of information provided at the time of the initial survey, no further data will be collected and the case will be removed from case registration.

If a case is identified as "Other Specific Type" (except beta cell defect), only the Initial Patient Survey Module will be conducted at baseline. Contact information will be updated annually

Definitions of "Other" Specific Types of diabetes appear in Appendix VI.

5.5.1. Introductory Letter

The Introductory Letter describes the purpose of the study to potential Patients and/or their parents. Common information about the study will be provided across all sites but each site will customize the letter according to their local operation, including IRB requirements. Letters to Patients 18 years of age and older will be addressed to the Patient. Letters to those under the age of 18 will be addressed to their parent or guardian.

5.5.2. Initial Patient Survey

Estimated Patient time for completion: 10 min

The Initial Patient Survey may be completed either as a self-administered form, a telephone interview, or in-person interview. Three options maximize the likelihood of completing this module and assure a minimal amount of data is available on the maximum number of Patients. The data collection form is identical regardless of the mode of administration.

5.6. IN-PERSON VISIT MODULE

Eligible Patients: Incident and Prevalent Cases

Estimated time of completion: 2 to 3 hours, depending on age and measurements to be collected (See Table 5-1 for details)

The In-Person Visit Module consists of three components: the physical examination, the collection of blood and urine specimens, and the interview/questionnaires. It is expected that all components of the In–Person Visit Module will be completed within a one-month window, although exceptions may occur (e.g., recurrent episodes of DKA). Alert values will be established for this module to ensure timely referrals as needed, with appropriate informed consent by Patients for release of information to the appropriate health care professionals.

For most Patients, the three in-person components will be completed at the same time, although it is acceptable to conduct the physical exam, laboratory, and in-person interviews at separate times, in any order. Local sites will make the final determination

as to the logistics that will result in the most efficient operation with the highest possible data completion rate for any given Patient.

The In-Person Visit Module is designed to be resource efficient (time and cost) while meeting study goals, including maximizing response rate through avoidance of unpleasant or invasive testing and provision for flexibility within local study logistical constraints.

5.6.1. Physical Examination

Physical examinations will be performed on study patients over three years old. Elements of the physical examination can be found in Table 5-1.

5.6.1.1. Laboratory: Collection of Blood and Urine Specimens

Biochemical measures to be obtained are listed in Table 5-1.

Laboratory specimens must be obtained under conditions of metabolic stability, defined as no DKA during the previous month, except for diabetes autoantibodies that can be collected at any time after initial diagnosis

Stimulated C-peptide (mixed meal challenge): Selected Patients 8 years of age or older at the time of their baseline In-Person Visit will be invited to have a stimulated C-peptide test. A fasting C-peptide and HbA_{1c} will be obtained. Following a mixed meal (Boost) challenge, C-peptide samples will be drawn at designated intervals consistent with current science. The stimulated C-peptide test will be used as follows:

a. To establish criterion measures for insulin production among Patients with biochemically defined diabetes. This age cut-point was selected because of potentially increased difficulty to clinically diagnose type 1 versus type 2 (or hybrid) diabetes in youth at or beyond the early pubertal stage. Furthermore, based on prior work, it is expected that almost all type 2 patients will be at least 8 years of age. Detail on the use of this information is provided in Section 7 – Typology.

b. To observe the natural history of insulin production among type 2 diabetes cases.

c. To observe insulin production among Patients whose diabetes type is unknown according to baseline SEARCH data collection efforts. Criterion measures will be applied to these Patients (see Section - Typology).

d. To observe the natural history of insulin production among all incident cases and prevalent cases with hybrid diabetes.

e. To assess insulin production in both incident and prevalent cases with previously known genetic beta cell defects.

Sample storage (repository). With the appropriate process of obtaining informed consent in accordance with local IRB requirements, biologic samples will be stored for future analyses, pending acquisition of the necessary funding. See Section 11 - Human Subjects - for further description of the sample repository.

5.6.2. Health Questionnaires

Eligible Patients: Incident and Prevalent Cases

The questionnaires will be administered in site-determined venues (e.g., a research clinic, van, and home). A supplemental questionnaire will be administered to those Patients that are age 10 years and older. Some of the questionnaire components are designed to be self-administered (e.g., quality of life). If necessary, some components of the questionnaires can be conducted over the telephone. The mode of administration (e.g., interview v self-administered; in-person v phone) and the respondent (e.g., Patient, parent) will be documented. See Table 5-1 for a summary of the content of the questionnaires.

5.6.2.1. Health Questionnaires - All Patients

The primary respondent for young children will be a parent or legal guardian. For older children, the child typically will be the respondent.

5.6.2.2. Supplemental Health Questionnaires - Age 10 and Older

The premise for this additional set of adolescent questions is that:

a) Some interviews have not been validated in younger children and/or are not appropriate

b) In this age group, it is expected to see Type 2 diabetes and the potential occurrence of cardiovascular disease risk factors (e.g. dyslipidemia) that may be related to health behaviors

Parents will be asked to waive their right to review answers to be provided by their children, with the assurance that appropriate referrals for care will be made according to established alert values.

5.6.2.3. Assessment of Tanner Stage - Age 8 and Older (Adopted by Steering Committee 4/29/04)

This assessment is answered more accurately by the child. Tanner stage self-assessment questionnaires will be provided for children ages 8 and older.

Girls who have reached menarche will be assigned Tanner stage 5.

Boys will continue to complete self-assessment forms until they reach Tanner stage 5.

Patients will receive this questionnaire annually until they reach Tanner stage 5.

5.7. MEDICAL RECORD MODULE

Eligible Patients: Incident Cases and a Subset of Prevalent Cases

5.7.1. Medical Record Review, Incident Cases

For incident cases, standardized medical record reviews will describe 1) characteristics related to typology, 2) clinical presentation, 3) presence of selected complications, co-morbidities, and medications, 4) processes of care including health care utilization and diabetes education, and 5) Tanner staging.

Data will be collected from all provider visits (in-patient and out-patient) occurring during the window of 2 months preceding and 6 months following initial diabetes diagnosis.

Information regarding insulin use and occurrences of DKA (up to 6 months after diagnosis) may be required to establish typology (see Section 7) for a small number of incident cases.

5.7.2. Typology Medical Record Review, Subset of Prevalent Cases

For prevalent cases participating in the Laboratory component of the In-Person Visit Module and who are diabetes auto-antibodies (DAA) negative, the data abstraction for prior DAA and C-peptide results and limited clinical presentation information will be conducted if data are readily available. All available data will be documented on the Core Form for each prevalent case that is eligible for typology abstraction.

5.8. FOLLOW-UP VISITS

Eligible Patients: All Incident Cases and Prevalent Hybrid Cases

All incident cases who had an initial examination will be invited to an annual follow-up, in-person examination. Table 5.2 shows the data elements and laboratory visits that will be conducted on the first follow-up visit.

5.9. TWELVE-MONTH MAILED SURVEY

Eligible Patients: Prevalent cases and All Cases (Incident and Prevalent) with "Other Specific Diabetes Type"

For all prevalent cases responding to the Initial Patient Survey, a survey designed to update health care utilization and contact information will be mailed annually after initial data collection. For cases with "Other Specific Diabetes Type", contact information will be updated (for local use only).

5.10. CORE INFORMATION

Eligible Patients: Incident and Prevalent Cases

In order to meet a main goal of the SEARCH study, estimation of incidence and prevalence of diabetes by diabetes type, age, sex, and race/ethnicity, it is critical to have core information related to Patient's diabetes type and demographic information. Efforts will be made to obtain participation and complete information from all identified eligible patients. The goal for these core items is to have information that will permit the percentage of registered cases that have the four core items as "known" as high as possible.

For all prevalent cases, the SEARCH study will attempt to obtain information regarding the type of diabetes diagnosis made by the Patient's Physician or recorded in the Patient's medical record.

Information will also be sought to assist typology. Typology information includes height, weight, insulin use, C-peptide levels, diabetic ketoacidosis and diabetes autoantibodies (DAA). Resources available do not allow for completion of information for all SEARCH prevalent cases.

5.11. VITAL STATUS

Eligible Patients: All cases.

Vital status will be documented throughout the SEARCH study based on vital status at the time of each data collection module. If death occurs, cause of death will be documented and, if possible, a death certificate obtained.

5.12. SPECIAL CONDITIONS

5.12.1. Gestational diabetes

Defined as glucose intolerance first recognized during pregnancy. Only women with diabetes (not gestational diabetes) verified by a physician post-partum are eligible for SEARCH. Persons who are pregnant will have their In-Person Visit deferred and be encouraged to return once the pregnancy is completed. Only women with a diagnosis of diabetes validated in the non-pregnant state will be eligible for participation.

5.12.2. Other Specific Diabetes Types:

Individuals for whom there is definite, prior knowledge of a genetic defect associated with beta cell dysfunction will be invited to participate in all modules. Individuals with any Other Specific Type of diabetes will be asked to participate in the Initial Patient Survey and will be contacted annually for contact information updates.

5.13. SUMMARY OF MEASURES

Table 5-2 summarizes the measures to be taken over time for the SEARCH cohort. Note, the type of case generally will not be known until the baseline data are collected.

Table 5-2. Summary of Data Collection Measure Time Points

		Year of Data Collection	
Case Type	**Data Element**	**Baseline**	**FU Year 1**
INCIDENT			
(Except known beta cell and other diabetes types of diabetes – see below)	Initial Patient Survey	X	
	In-Person, Physical Exam	X	X
	In-Person, Questionnaires	X	X
	In-Person Lab		
	DAA	X	X
	Glucose, HbA1c, lipids	X	X
	Urine albumin & creatinine	X	X
	Storage	X	X

		Year of Data Collection	
Case Type	**Data Element**	**Baseline**	**FU Year 1**
	Fasting C-peptide (< 8 years old at baseline)	X	X
	Stimulated C-peptide (≥ 8 years old)	X	X
	Medical Record Review/ Clinical Presentation & Utilization	X	
PREVALENT **(Except known beta cell and other diabetes types of diabetes – see below)**	Initial Patient Survey	X	
	In-Person, Physical Exam	X	
	In-Person, Questionnaires	X	
	In-Person, Lab		
	DAA	X	
	Glucose, HbA1c, lipids	X	
	Urine alb. & creatinine	X	
	Storage	X	
	Fasting C-peptide	X	
	Follow-up Mailed Questionnaire		X
KNOWN GENETIC B-CELL DEFECT (Incident or Prevalent)	Initial Patient Survey	X	
	In-Person, Physical Exam	X	
	In-Person, Questionnaires	X	X
	In-Person Lab		
	DAA	X	X
	Glucose, HbA1c, lipids	X	
	Urine albumin & creatinine	X	
	Storage	X	X
	Fasting C-peptide (< 8 years old at baseline)	X	X
	Stimulated C-peptide (≥ 8 years old at baseline)	X	X
	Medical Record/Core Review*	X	
OTHER DIABETES TYPES	Initial Patient Survey	X	
	Follow-up Mailed Questionnaire		X

* This medical record review will be done for incident cases only.

Hybrid diabetes is diabetes with biochemical features of both type 1 and type 2 diabetes.

Other diabetes types refer to diabetes with a known cause such as steroid-induced diabetes – See Appendix VI for greater detail.

5.13.1. Follow-up of Stimulated C-peptide Tests in Prevalent Cases

A subset of prevalent patients, 8 years of age or older at the time of their baseline In-Person Visit, will be invited to undergo stimulated C-peptide test(s) as follows:

Table 5-3. Follow-up Fasting Stimulated C-peptide Tests in Prevalent Cases

Prevalent
▪ Untypeable*
▪ Hybrid
▪ Genetic B-cell function defect

** Positive OR Negative DAA and C-peptide ≥ 0.8 ng/ml and < 3.7 ng/ml. (-See Section 7)
Hybrid diabetes is diabetes with biochemical features of both type 1 and type 2 diabetes

SEARCH Protocol – Section 6
Recruitment and Retention
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6. Recruitment and Retention

6.1. GOAL

The goal of this section is to provide an explanation of strategies the may be used to recruit and retain as many children and youth with diabetes to the study as possible, while assuring that participation is informed and voluntary.

6.2. RECRUITMENT

6.2.1. Recruitment Strategies

Recruitment strategies that have worked in other epidemiologic studies will be used. These include:

6.2.1.1. Education

Education of health care professionals about SEARCH including a "Dear Colleague" letter, a study brochure, one-on-one meetings with physicians and other potential collaborators; presentations and Grand Rounds to physicians, school nurses, and other healthcare professionals,

6.2.1.2. Brochures

Making study brochures available in physicians' offices.

6.2.1.3. Information Dissemination

- Introduction of the study to potential participants in a letter signed by the patients physician as well as by study investigators,
- Dissemination of information about SEARCH to the community in articles describing SEARCH in participating health plan and hospital newsletters, local medical and nursing newsletters; and local chapters of diabetes associations communications (e.g., the Juvenile Diabetes Foundation for Research), and in press releases in local newspapers,

6.2.1.4. Incentives

Provision of patient/family financial incentives commensurate with the level of involvement and effort,

6.2.1.5. Patient Assistance

- Making participation convenient and easy through flexibility in clinic visit times and locations and provision of examination information including maps and information about parking,
- Provision of reminders of appointment times by mail and phone.

6.3. RETENTION

6.3.1. Retention Methods

The methods that will be used to foster retention in SEARCH are:

- A yearly newsletter which will provide information about diabetes and about the study
- Provision of periodic information about the results of SEARCH either as part of the newsletter or as a separate communication
- Provision of clinical feedback about SEARCH test results to participants and their physicians (when consent has been given)

6.3.2. Maintaining Contact

To maintain contact with participants, information on address and phone number of the youth and his/her parents will be collected at baseline. In addition, the study will gather information about addresses and phone numbers of several family members and friends outside the household who could be contacted if SEARCH is unable to reach the participants at the most recent address and phone number. Information in the tracking systems that would identify individuals will be maintained at each local site and will not be made available except for the conduct of approved research studies in accordance with local IRB regulations.

SEARCH Protocol – Section 7
Typology
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7. Typology

7.1. GOALS

- To develop efficient and practical approaches to classification of diabetes type for prevalent and incident cases.
- To describe and compare clinical presentation and course of type 1, type 2, and other types (or hybrids) of diabetes.

7.2. METHOD OF TYPOLOGY

Background

The report of the American Diabetes Association (ADA) Expert Committee on the Diagnosis and Classification of Diabetes Mellitus published in *Diabetes Care* [32] serves as the basis of definitions of the types of diabetes used in this study. The fundamental principle of the classification scheme is that definitions of diabetes types reflect pathogenesis. As a result, diabetes autoantibodies (DAA) and C-peptide information will be collected on incident and prevalent cases as the primary method of classification in this study. However, due to gaps in knowledge of diabetes pathophysiology, heterogeneity of diabetes, and that assignment of type depends on the circumstances at diagnosis, many patients are not easily categorized or typeable. To combat these limitations, the following two approaches will be used.

a. Participants, who, at initial evaluation, cannot be classified by pathogenic criteria, will be followed longitudinally to explore the evolution of diabetes and classification will be reassigned if etiology and pathogenesis becomes clear.

b. At study completion, clinical characteristics identified in those participants classified based on pathophysiological characteristics of diabetes type will be used to "redefine" clinical definitions of diabetes type. These "redefined" clinical definitions will be used to re-type patients who have only clinical data available.

7.3. DEFINITIONS OF TERMS USED FOR TYPOLOGY

7.3.1. **Type 1 diabetes**

The progressive destruction of the beta cells leading to an absolute deficiency of insulin (see insulinopenia below) that results in diabetes.

Type 1 diabetes will be established if all diabetes autoantibodies (DAA – see autoimmunity below) are negative and any of the following are present:

a. Fasting C-peptide < 0.8 ng/ml;

Or

b. Diagnosis of diabetes was made when the subject was < 10 years of age with a weight < the 25th percentile for chronological age or BMI < 50th percentile for chronological age;

Or

c. Duration of diabetes > 1 year and if daily administration of insulin is stopped it results in DKA.

7.3.2. **Type 1A diabetes (general)**

The autoimmune destruction of the beta cells leading to an absolute deficiency of insulin resulting in diabetes.

7.3.3. **Type 1A diabetes (biochemical)**

The presence, in plasma, of any specific diabetes autoantibody and a fasting C-peptide < 3.7 ng/ml. These markers include antibodies to glutamic acid decarboxylase (GAD), IA-2, and insulin autoantibodies (IAA) measured by radioassay and cytoplasmic islet cell antibodies measured by immunofluorescence (ICA). The frequency of the presence of immune markers decreases with increased duration of disease with only 65% of Type 1A patients having one or more positive immune markers with duration of disease of 10 years[33,34].

7.3.4. **Type 2 diabetes (general)**

The presence of insulin resistance (see insulin resistance) and beta cell dysfunction resulting in diabetes. Type 2 diabetes will be established if one of the following exists:

a. Duration of diabetes > 1 year and no insulin therapy for > 1 month without an episode of diabetic ketoacidosis

Or

b. Duration of diabetes > 6 months and never treated with insulin.

7.3.5. **Type 2 diabetes (biochemical)**

The presence of diabetes and insulin resistance (C-peptide ≥ 3.7 ng/ml) and the absence of autoimmune markers (see autoimmunity) for type 1A diabetes.

7.3.6. **Other specific types of diabetes**

The presence of a disease or the administration of a drug that results in beta cell destruction or dysfunction or inhibits the action of insulin resulting in diabetes (see Appendix VI). Autoimmune destruction of the beta cells is excluded from this category.

7.3.7. **Hybrid diabetes**

Biochemical evidence of more than one type of diabetes.

7.3.8. **Gestational diabetes**

Glucose intolerance first recognized during pregnancy. Only women with diabetes (not gestational diabetes) verified by a physician post-partum are eligible for SEARCH.

7.3.9. **Autoimmunity**

The presence of diabetes autoantibodies (DAA) to a) glutamic acid decarboxylase (GAD), b) IA-2, c) insulin autoantibody titer (IAA) if never treated with insulin, or d) islet cell antibody by immunoflorescence. The date of determination of antibody titer will be compared to the date of diagnosis. Previously collected results of Islet cell antibody (performed by immunofluorescence) will only be used when an in-person visit with direct measurement of GAD, IA-2, and IAA is not possible.

7.3.10. **Insulinopenia**

A fasting plasma C-peptide < 0.8 ng/ml obtained when a patient is metabolically stable (no episodes of DKA for one month prior to obtaining any laboratory tests). This concentration of C-peptide was chosen based on the following

information: a) patients with type 1 diabetes in the Diabetes Complications and Control Trial had fasting C-peptides less than 0.6 ng/ml; b) the 5th percentile for fasting plasma C-peptide in non-diabetic, healthy adolescents in the Bogalusa Heart Study was 0.8 ng/ml; and c) in non-diabetic, healthy, Swedish individuals (age range 6-22 years), the lowest value for fasting c-peptide was 0.7 ng/ml. Early in the course of type 1 diabetes, participants may have fasting C-peptide levels in the normal range [35,36].

- **Insulin resistance**: a fasting plasma C-peptide concentration $\geq$ 3.7 ng/ml based on findings in the Bogalusa Heart Study that fasting plasma C-peptide of 3.7 ng/ml exceeded the 95th percentile in non-diabetic, healthy adolescents.

7.4. ALGORITHMS

7.4.1. **General description**

The prevalent and incident algorithms employ DAA, plasma C-peptide tests, and clinical presentation to assign a specific classification of a type of diabetes. The algorithms are presented to indicate how to evaluate laboratory results and clinical findings as collected in Table 5-2.

SEARCH investigators recognize that a number of participants will not be able to be classified using the initial information collected. For initially untypeable cases, information from stimulated C-peptide tests (SCP) will be used for classification. Where SCP data from the initially untypeable participants are comparable to the SCP data from type 1A and type 2 incident participants, the initially untypeable group will be classified as type 1 or type 2. In participants who cannot be classified by this method, clinical definitions of diabetes will be used to classify the participants.

Participants identified as having Other Specific Types of Diabetes (see Appendix VI) will have the specific type of diabetes recorded. SCP and DAA testing will be followed in SEARCH patients having a genetic defect in beta cell function.

SEARCH investigators recognize that new information will become available during the data collection phase of this protocol concerning the biochemical, genetic, and clinical classifications of the types of diabetes. Examples of new information that may become available include: 1) previously unrecognized DAA to identify autoimmune diabetes; 2) plasma or other markers that identify types of beta cell destruction that are presently classified as idiopathic; and 3) genes that identify specific types of diabetes (e.g., new types of MODY, type 1A, type 2). As this new information becomes available, appropriate testing may be performed

and the typology algorithm may be modified to reflect the most accurate and current methods of classifying the types of diabetes.

7.4.2. **Incident algorithms**

The incident algorithm will be used to establish type of diabetes for incident cases. This algorithm displays use of data collected from the In-Person Visit Module. For incident cases for whom the In-Person Visit is not available, typology will proceed using data collected from the Medical Record Module or the Core Form. (See Data Collection, Section 5, for descriptions)

Algorithm - Incident cases– Information Available from In-Person Visit

a. Type 1A diabetes will be established if any of the three DAA (GAD, IAA, and IA-2) is positive and the fasting C-peptide is < 3.7 ng/ml.

b. Type 2 diabetes will be established if the DAA titers are all negative and the fasting C-peptide is ≥ 3.7 ng/ml.

c. Hybrid diabetes is established if any DAA are positive and fasting C-peptide is ≥ 3.7 ng/ml.

d. DAA negative participants ≥ 8 years of age at their baseline examination who have a fasting C-peptide concentration < 3.7 ng/ml will undergo additional DAA and SCP testing as described in Section 5 – Data Collection. These data will be used to classify participants in the following manner.

   i. If any subsequent DAA become positive, a classification of 'type 1A diabetes' will be made.

   ii. If all subsequent DAA remain negative and one or more fasting C-peptide concentrations < 3.7 ng/ml, classification will be made in the following manner. Clinical characteristics and SCP data collected over time will be compared to the same data generated in the sub-group of the incident cases classified as type 1A or all incident cases classified as type 2 diabetes. Where the data matches these groups, a classification of type 1 or type 2 will be made.

   iii. In remaining participants who cannot be classified by the method described in 'ii' (above), clinical definitions of the types of diabetes found in appendix VI will be used to classify participants as type 1 and type 2 diabetes.

iv. The remaining participants who cannot be classified by the method described in 'iii' (above) will be classified as untypeable.

Algorithm - Incident cases – Information from In-Person Visit Not Available

Among incident cases for which the In-person Module is not available, information may be available from the Core Form and/or Medical Record review. The following information will be obtained: 1) DAA and plasma C-peptide tests and the laboratory at which these tests were performed, and 2) limited clinical data.

7.4.3. **Prevalent algorithms**

The prevalent algorithm is used to establish the type of diabetes for prevalent cases. This algorithm displays use of data collected from the In-Person Visit Module. For prevalent cases for whom the In-Person Visit is not available, typology will proceed using data collected from the Core Form. (See Data Collection, Section 5, for descriptions)

Algorithm - Prevalent Cases – Information Available from In-Person Visit

a. Type 1A diabetes will be established if any of the three DAA (GAD, IAA, and IA-2) are positive and a fasting C-peptide < 0.8 ng/ml (see appendix VII).

b. Type 1 diabetes will be established if all DAA are negative and a fasting C-peptide < 0.8 ng/ml;

c. Type 2 diabetes will be established if *all* DAA titers are negative and a fasting C-peptide is $\geq$ 3.7 ng/ml.

d. Hybrid diabetes is established if any DAA is positive and fasting C-peptide $\geq$ 3.7 ng/ml.

e. DAA positive patients $\geq$ 8 years of age at their baseline examination who have a fasting C-peptide $\geq$ 0.8 ng/ml and < 3.7 ng/ml will undergo a single SCP test. These data will be used to type the participants in the following manner:

i. The clinical and SCP data will be compared to the same data generated in the sub-groups of the incident cases classified as type 1A, hybrid diabetes and type 2.

ii. The clinical and SCP data will be compared to the same data generated in the prevalent cases classified as hybrid diabetes and prevalent cases that are untypeable.

f. DAA negative patients ≥8 years of age at their baseline examination who have a fasting C-peptide ≥ 0.8 ng/ml and < 3.7 ng/ml will undergo a single SCP test. These data will be used to type the participants in the following manner:

i. The SCP data will be compared to the same data generated in the sub-groups of the incident cases classified as type 1A diabetes and type 2 diabetes. When the data is comparable to the sub-groups, a classification of type 1 or type 2 will be made.

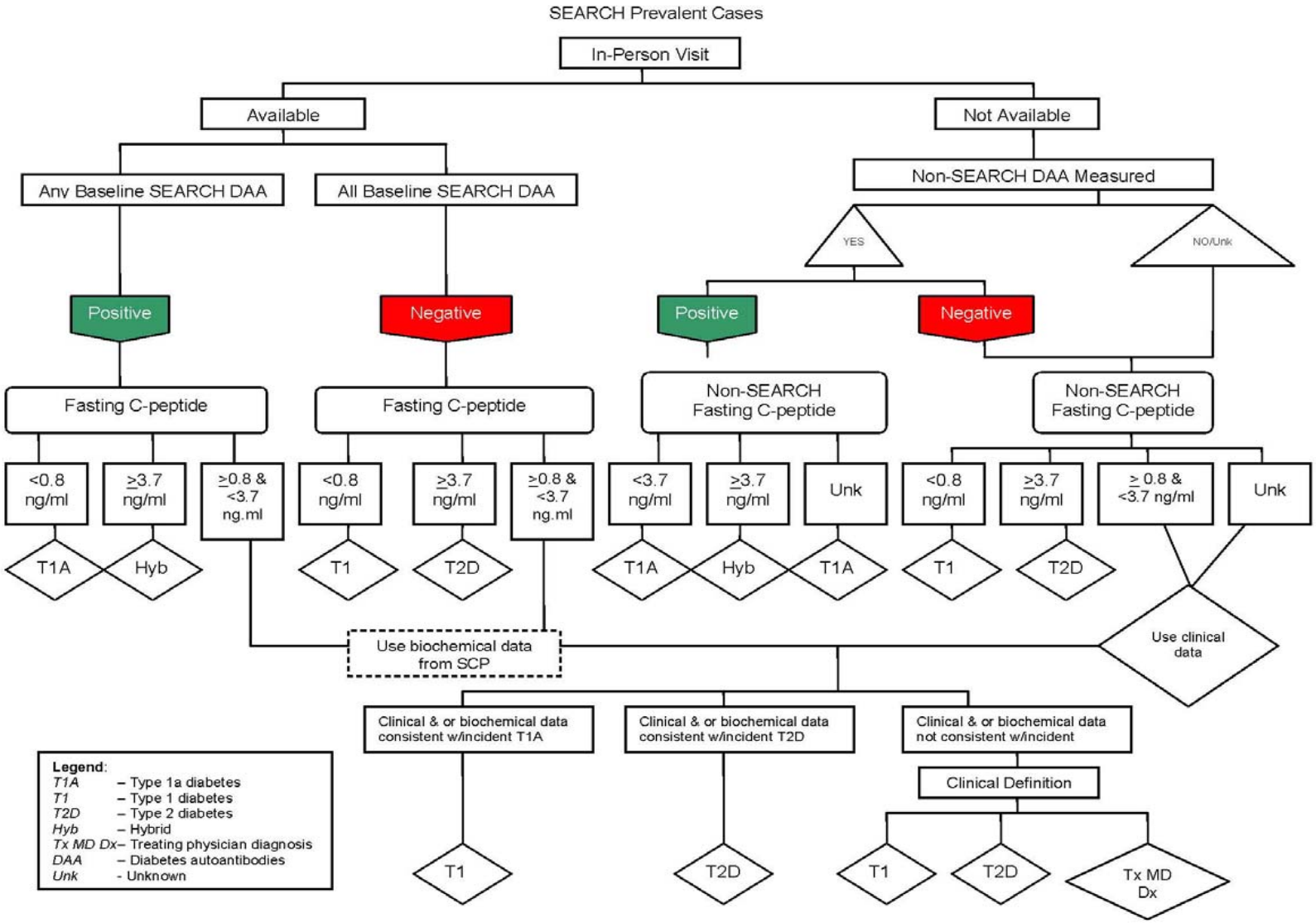
ii. In the remaining participants who cannot be classified by the method described in 'i' (above), the clinical definitions of the types of diabetes found in appendix VI will be used to classify participants as type 1 and type 2 diabetes.

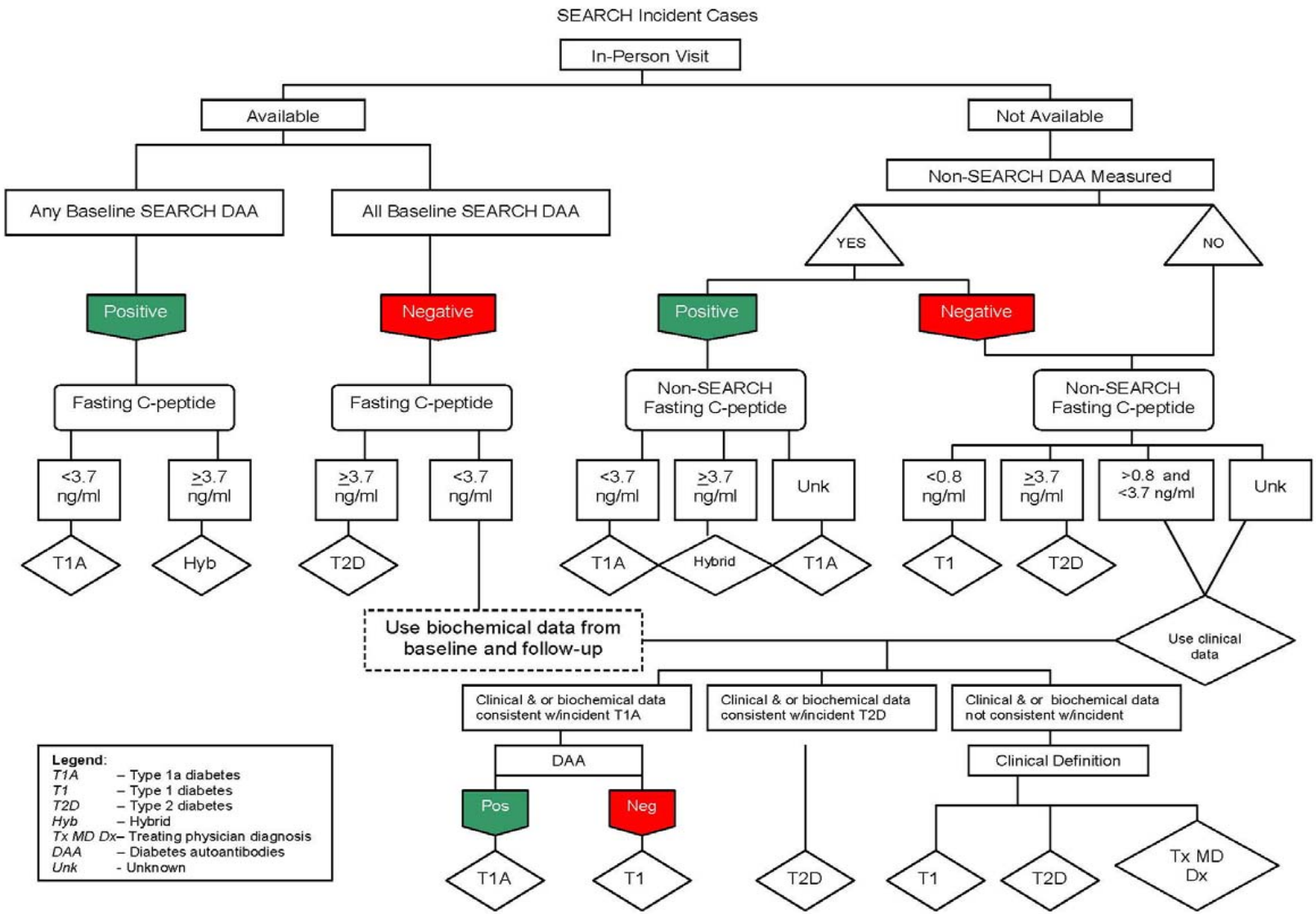
iii. The remaining participants who cannot be classified by the method described in 'ii' (above) will be classified as untypeable.

Algorithm- Prevalent cases – Information Available from In-Person Visit Not Available

Prevalent cases for which the In-person Module is not available, information may be available from the Core Form (including the limited medical record review for typology, for prevalent cases; see Section 5 - Data Collection). The following information will be obtained: 1) DAA and plasma C-peptide tests and the laboratory at which these tests were performed, and 2) limited clinical data.

7.4.4. **SEARCH Algorithms**


SEARCH Prevalent Cases
In-Person Visit
Available
Not Available
Any Baseline SEARCH DAA
All Baseline SEARCH DAA
Non-SEARCH DAA Measured
YES
NO/Unk
Positive
Negative
Positive
Negative
Fasting C-peptide
Fasting C-peptide
Non-SEARCH Fasting C-peptide
Non-SEARCH Fasting C-peptide
<0.8 ng/ml
≥3.7 ng/ml
≥0.8 & <3.7 ng.ml
<0.8 ng/ml
≥3.7 ng/ml
≥0.8 & <3.7 ng.ml
<3.7 ng/ml
≥3.7 ng/ml
Unk
<0.8 ng/ml
≥3.7 ng/ml
≥ 0.8 & <3.7 ng/ml
Unk
T1A
Hyb
T1
T2D
T1A
Hyb
T1A
T1
T2D
Use biochemical data from SCP
Use clinical data
Clinical & or biochemical data consistent w/incident T1A
Clinical & or biochemical data consistent w/incident T2D
Clinical & or biochemical data not consistent w/incident
Clinical Definition
T1
T2D
T1
T2D
Tx MD Dx
Legend:
T1A – Type 1a diabetes
T1 – Type 1 diabetes
T2D – Type 2 diabetes
Hyb – Hybrid
Tx MD Dx – Treating physician diagnosis
DAA – Diabetes autoantibodies
Unk - Unknown


SEARCH Incident Cases
In-Person Visit
Available
Not Available
Any Baseline SEARCH DAA
All Baseline SEARCH DAA
Non-SEARCH DAA Measured
YES
NO
Positive
Negative
Positive
Negative
Fasting C-peptide
Fasting C-peptide
Non-SEARCH Fasting C-peptide
Non-SEARCH Fasting C-peptide
<3.7 ng/ml
≥3.7 ng/ml
≥3.7 ng/ml
<3.7 ng/ml
<3.7 ng/ml
≥3.7 ng/ml
Unk
<0.8 ng/ml
≥3.7 ng/ml
>0.8 and <3.7 ng/ml
Unk
T1A
Hyb
T2D
T1A
Hybrid
T1A
T1
T2D
Use biochemical data from baseline and follow-up
Use clinical data
Clinical & or biochemical data consistent w/incident T1A
Clinical & or biochemical data consistent w/incident T2D
Clinical & or biochemical data not consistent w/incident
DAA
Clinical Definition
Pos
Neg
T1A
T1
T2D
T1
T2D
Tx MD Dx
Legend:
T1A – Type 1a diabetes
T1 – Type 1 diabetes
T2D – Type 2 diabetes
Hyb – Hybrid
Tx MD Dx – Treating physician diagnosis
DAA – Diabetes autoantibodies
Unk - Unknown

SEARCH Protocol – Section 8
Statistical Considerations
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8. Statistical Considerations

8.1 STATISTICAL ANALYSES

8.1.1 **Estimation of prevalence and incidence**

The methods for determining the numerator and denominators for estimates of prevalence and incidence are described in section 4.1. These data allow estimates of prevalence and incidence for each of the six clinical sites. In addition, these estimates will be calculated by Type (1, 2, hybrids), race/ethnicity categories (NHW, AA, Hispanic, Asian, PI, NA), gender, and age groups (10 year, 5 year, and single year). National estimates of prevalence and incidence will be achieved by using age, sex, and race/ethnicity adjusted estimates, adjusted to the distribution of age, sex, and race/ethnicity for the 2000 US national population. Completeness of ascertainment will be assessed by examining the rates of concordant and discordant detection among ascertainment modes. When more than two modes are used, log-linear models will be fitted to assess the dependency between complementary modes of ascertainment[28].

8.1.2 **Comparison of methods for classification of diabetes type**

The accuracy of evaluating different approaches to the classification of diabetes type for prevalent and incident cases will be based on misclassification ratios. The number of misclassifications will be used to estimate the proportion of false positives, false negatives, sensitivity and specificity. In evaluation of potential measures that are continuous or ordinal, receiver operator curves (ROC) will be used to evaluate and test the usefulness of the diagnostic measure.

8.1.3 **Comparison of type 1 and type 2 and other types of diabetes**

Patient characteristics and clinical presentation will be compared between types of diabetes. These factors include measures of clinical presentation, risk factors for micro- and macrovascular disease complications, health care utilization, and quality of life. Comparisons between the disease types will be made by Chi-square tests for categorical measures, Wilcoxon rank-sum tests for ordinal measures, and analysis of variance for continuous measures. Analyses will be performed separately for prevalent and incident cases. Analysis of covariance procedures will be used to compare risk factors between types of diabetes adjusting for possible confounders (e.g. age, sex, and race/ethnicity).

8.1.4 **Estimation of the clinical course**

The clinical course of incident subjects will be estimated from longitudinal data collected once per year. The natural history and comparison between disease types will be estimated and tested using repeated measures analysis of covariance and mixed models[37]. Maximum likelihood will be used to fit these models. This allows increased precision and minimizes bias associated with varying lengths of follow-up among participants.

8.2 SAMPLE SIZE AND POWER ANALYSES

The projected study sample sizes of prevalent and incident cases are 6,378 and 785 per year, respectively. The bases for these estimates are discussed in Section 4.1. This sample size will allow very good precision in estimating the overall prevalence (per 1000 subjects) with a 95% confidence interval (CI) that is + or – 2.5% of the estimate. It will also provide age, gender, and race/ethnicity specific estimates that have CIs of + or – 10% of the estimate for most race/ethnicities.

Table 6-1. Precision of Confidence Interval (CI) Estimates for Prevalence

		Estimated # of Cases	Denominator	Prevalence	Standard Error	95% CI as % estimate
Overall		6378	3,518,342	1.81	0.023	2.5%
Age	0-9	1624	1,758692	0.92	0.023	4.9%
	10-19	4754	1,759,650	2.70	0.039	2.8%
Gender	Male	3219	1,709,171	1.83	0.116	22.1%
	Female	3218	1,709,171	1.83	0.116	22.1%
Race/ethnicity	NHW	4187	2,312,452	1.81	0.028	3.0%
	Black	704	322,968	2.18	0.082	7.4%
	Hispanic	756	395,230	1.91	0.070	7.1%
	Asian	336	254,480	1.32	0.072	10.7%
	PI	238	80,309	2.96	0.192	12.7%
	Native Am	157	152,903	1.03	0.082	15.6%

This sample size will allow the estimation of total and age, gender, or race/ethnicity specific incidence (per 10,000 subjects) for a given year with the following precision:

Table 6-2. Precision of Confidence Interval (CI) Estimates for Incidence

		Estimated # of Cases	Denominator	Incidence	Standard Error	95% CI as % estimate
Overall		785	5,072,988	1.55	0.057	7.0%
Age	0-9	303	2,533,318	1.20	0.069	11.2%
	10-19	482	2,539,670	1.90	0.086	8.9%
Gender	Male	412	2,536,494	1.64	0.081	9.9%
	Female	411	2,536,494	1.64	0.081	9.9%
Race/ethnicity	NHW	544	3,284,466	1.66	0.071	8.4%
	Black	106	672,587	1.58	0.153	19.0%
	Hispanic	72	549,501	1.31	0.154	23.1%
	Asian	25	301,875	0.83	0.166	39.2%
	PI	18	89,162	2.02	0.476	46.2%
	Native Am	20	175,397	1.14	0.255	43.8%

Distributions of continuous measures (e.g., measures of vascular disease, complications, and health care utilization) will be compared between type 1 and non-type 1 cases. Assuming that 75% of identified subjects will participate in the study; the study will be able to detect differences in terms of the standard deviation (SD) of the characteristic being considered between type 1s and non-type 1s in the overall and age, gender, or race/ethnicity specific prevalent populations:

Table 6-3. Standardized difference that can be detected between type 1s and non-type 1s

		# Type 1	# Type 2	Difference that can be detected (SD) 80% Power	90% Power
Overall		3736	1048	0.10	0.11
Age	0-9	1119	99	0.29	0.34
	10-19	2617	949	0.11	0.12
Gender	Male	1868	524	0.14	0.16
	Female	1868	524	0.14	0.16
Race/ethnicity	NHW	2764	376	0.15	0.18
	Black	383	145	0.27	0.32
	Hispanic	337	230	0.24	0.28
	Asian	124	128	0.35	0.41
	PI	128	51	0.46	0.54
	Native Am	0	118	-	-

SEARCH Protocol – Section 9
Data Management
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9. Data Management

The Coordinating Center will develop and maintain the computerized data management system for SEARCH data. Use of the SEARCH data management system will be restricted to only those persons having access authority. In addition to data entry, SEARCH site-specific reports, e.g. recruitment goals, follow-up rates, will be available via the study's web site.

9.1. DATA ENTRY CERTIFICATION

Prior to entering data, each data entry person will be required to complete the SEARCH certification module. This requires that each individual enter a standardized data set into the certification system. Once these data are entered, an overall quality score will be given. A perfect score must be obtained prior to entering SEARCH study data. Once the acceptable score is attained, the individual will be provided access to the "live" SEARCH site to enter data. An annual re-certification will be required for all data entry personnel. If an acceptable score is not achieved on the certification exam, retraining will be required before the individual may re-attempt certification.

9.2. DATA ENTRY

Clinical Sites will use the World Wide Web (WWW) to enter the SEARCH data collected on paper forms from each participant. The Coordinating Center will develop electronic versions of forms mimicking the paper form as closely as possible. Once forms are completed and reviewed for inconsistencies, they are manually entered at the site using a computerized data management system.

9.3. LOCAL TRACKING APPLICATION

Each site will be provided a local tracking application, written in MS Access, to be used to track study participants. The local application will allow the SEARCH personnel to input demographic, contact, ancillary study, and other data about individual participants. Access to the local application will be restricted by use of individual username and passwords and will not be available to the National Coordinating Center. A backup utility will be included in the application allowing each center the ability to make routine data backups.

9.4. EDIT CHECKS

Computerized data validation routines will be used to enhance data quality, including,: a) initial screening of data, using logic and range checks built into data entry screens; b) cross-form functional and consistency checks; and c) edits assessing the serial integrity of data, particularly in longitudinal studies.

9.5. PASSWORDS

Access to the SEARCH web site will be controlled by user authentication. Each user will be given a username and password. Passwords limit access to specific areas of the web site. A user must not share their login information with others, which result in a breach of security; if this occurs, the user account will be disabled. Each site will

have a password-protected area within the SEARCH web site through which data will be entered.

9.6. SECURITY

The web-based data entry system will protect confidentiality and data security by utilizing 128-bit encryption and Secure Socket Layer (SSL). Once a user logs on the web site, all communication between the user and the server will be encrypted. Standard protections will be implemented against computer malicious or unauthorized access.

The Coordinating Center will ensure that routine data backups will occur and available if, for any reason, there is a need to restore data. Backup tapes will be kept in a locked, fire- and waterproof storage cabinet separate from the central computer room. Additional back-up tapes will be stored at a separate location within the Wake Forest University School of Medicine campus.

Recovery from natural disasters (e.g., water, fire, or electrical) is possible through the ability to reconstruct both the database management system and the data through the use of nightly backups.

SEARCH Protocol – Section 10
Study Organization
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10.Study Organization

10.1. PARTICIPANT ORGANIZATION

10.1.1. **Clinical Centers**

Each clinical center consists of an interdisciplinary team of investigators who provide the areas of expertise necessary for the successful completion of the SEARCH protocol. Clinical center responsibilities include:

a) Collaborating in design and monitoring of the study, including regular attendance at Steering Committee meetings

b) Identifying children and youth eligible for the study

c) Recruiting and retaining study participants,

d) Collecting high quality data in a systematic and standardized fashion consistent with the study protocol,

e) Collaborating in the analysis and dissemination of study results.

10.1.2. **Coordinating Center**

The coordinating center has primary responsibility for monitoring quality and analyzing data generated in the study. Additional responsibilities of the Coordinating Center include:

a) Preparing the protocol, forms, manuals, and educational and recruitment materials with the guidance and assistance of study investigators, CDC, and NIH personnel;

b) Collaborating on development of the statistical design;

c) Working with the investigators in developing and pre-testing of forms and procedures, and assuming responsibility for the reproduction and distribution of forms, hardware, and software associated with data entry;

d) Training data coordinators and other clinical center personnel;

e) Assuring data quality, study performance, and laboratory procedures;

f) Summarizing clinical center performance at regular intervals for the Steering Committee;

g) Providing detailed reports regarding eligible subjects, participant recruitment and data collection;

h) Preparing, in collaboration with the clinical investigators, various manuscripts of study results.

10.1.3. **Federal Sponsors**

SEARCH is sponsored by the Centers for Disease Control and Prevention (CDC) and supported by the NIDDK. The CDC Project Office is responsible for the funding, cooperative agreement administration, monitoring, and overall scientific integrity of the study. Other Federal sponsors of SEARCH include the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH). While the Principal Investigators will lead the scientific aspects of the study, representatives of the Federal agencies (CDC/NIDDK) will participate in all phases of planning, scientific design, implementation, evaluation and communication relating to SEARCH.

The CDC reserves the right to terminate or curtail the study (or an individual award) in the event of human subject ethical issues that may dictate a premature termination.

10.1.4. **Data Ownership**

The data collected as part of SEARCH will belong to the ownership of the respective clinical centers, and not the government or the Coordinating Center. The Principal Investigator of each site will be the responsible custodian of the data. All personally identifiable data will reside at the respective clinical sites in the safe custody of the Principal Investigator. As part of the SEARCH cooperative agreement and collaboration, each clinical center will share non- personally identifiable data with the coordinating center to create aggregate data sets, perform analysis, and prepare scientific presentations and communications.

10.2. COMMITTEE STRUCTURE

The following administrative committees are established for SEARCH:

10.2.1. **Coordination and Planning Committee**

A Coordination and Planning Committee, consisting of the study chair and vice chair, the CDC Project Officer, and the CoC PI. The committee will meet via conference call to set the agendas for the calls and meetings, set priorities for use of call and meeting time, and to troubleshoot minor administrative problems.

10.2.2. **Governance Committee**

A Governance Committee, consisting of the PI and one other member from each site, two members from the CDC, one member from the NIH, two members from the CoC, and one person from the Central Lab. The Governance Committee would meet via conference call and as needed during face-to-face meetings.

Clinical sites and the CoC will designate specific individuals as members of the Governance Committee. Only these individuals will participate in calls. Alternates can attend Governance Committee meetings at face-to-face meetings when it is impossible for the designated members of this committee to attend.

All members of the Governance Committee are full participants in discussions and work of this committee. In matters that require a vote, each clinical site, the CoC, the CDC, the NIH, and the Central Laboratory have one vote.

The Governance Committee makes final decisions on protocol changes, gives final approval to manuscripts, and directs the work of Standing Committees and Task Groups.

10.2.3. **Steering Committee**

A Steering Committee, consisting of everyone actively participating in the SEARCH study. The Steering Committee will accomplish the scientific work of SEARCH. Members of the SC who are not on the Governance Committee will participate in SEARCH through membership in standing committees, task groups, and writing groups and attendance at meetings when requested.

The Steering Committee will meet by conference call. These calls will serve primarily to convey information study status and as informational sessions. Members of the SC who are not members of the Governance Committee will attend in-person meetings as needed to conduct the work of SEARCH.

10.2.4. **Face-to-Face Meetings**

Face-to-face meetings of the Governance Committee will be held on a regular basis. The priorities for these meetings are determined by the Governance Committee. All members of the Governance Committee are invited to these meetings.

Members of the Steering Committee who are not members of the Governance Committee are invited to the face-to-face meetings as needed to accomplish the work of SEARCH.

Other face-to-face meetings of writing groups, task groups or standing committees are held on an as-needed basis when approved by the Governance Committee.

10.2.5. **Task Groups**

Task groups appointed by the Steering Committee are comprised of investigators and staff from the clinical centers and coordinating center. These task groups are involved in design of the protocol and manual of operations and develop specific recommendations about other scientific, technical, and policy documents as needed during the course of the study. The Task Groups report to the Steering Committee. Membership on task groups will be according to expertise.

Task groups may seek the input of consultants and include representatives of central resources. In addition, representatives from sponsoring organizations may be invited to attend task group meetings. Not every clinical center is necessarily represented on each task group although each center has an option to participate.

10.2.6. **Standing Committees**

The SEARCH Governance Committee will constitute standing committees of investigators and staff throughout the study for ongoing functions of the study (e.g. review of ancillary studies and preparation of publications). Standing committee membership will be predicated on nomination from principal investigators and approval from the Governance Committee. Standing Committees report to the Governance Committee.

Central Resources

The SEARCH study group will develop central laboratories, and repositories and other central resources as needed for conduct of the study. Investigators and staff from these centers may participate in training and quality control activities, but will not participate in policy issues or study governance. Thus, while these individuals may be invited to attend committee meetings, they will hold no rights to voting. Individuals from central resource centers may be invited to participate in the publication of SEARCH data under the publication policy for the study.

10.3. STUDY TIMELINE

SEARCH will be conducted over a five-year period from October 1, 2000 to December 30, 2005. The operation phases for this study are:

Study Activities	Due Date
Protocol Development and Review	March 2002
Central Staff Training	March 2002
Recruitment Material	March 2002
MOP Finalization	March 2002
Final data entry screens	March 2002
Prevalence case ascertainment	December 2001
Incident case ascertainment	January 2002 through August 2005
Case finding – incident	
Case reporting	Site dependent
Data collection	April 2002 – end of project period
Final report and summary of study	End of last year of funding

10.4. SEARCH COLLABORATORS

10.4.1. **Clinical Sites**

SEARCH has six centers, located in Cincinnati, Ohio; Colorado; Seattle, Washington, South Carolina; Hawaii; and Southern California**.**

Four SEARCH centers (Cincinnati, Colorado, Seattle, South Carolina) are geographically based — that is, diabetes cases will be identified from a geographically defined population of children. Two SEARCH centers (Hawaii and Southern California) are membership-based — that is, diabetes cases will be identified among members of participating health plans.

Location	***Site***	***Principal Investigator***
Colorado	University of Colorado Health Sciences Center Denver, CO	Dana Dabelea, MD, PhD
Hawaii	Pacific Health Research Institute Honolulu, HI	Beatriz L. Rodriguez, MD, PhD
Ohio	Children's Hospital Medical Center Cincinnati, OH	Lawrence Dolan, MD
Seattle/Puget Sound	Children's Hospital and Medical Center Seattle, WA	Catherine Pihoker, MD
South Carolina	University of South Carolina Columbia, SC	Elizabeth J. Mayer-Davis, PhD
Southern California	Kaiser Permanente Southern California Pasadena, CA	Diana B. Petitti, MD, MPH

10.4.2. **Coordinating Center**

Wake Forest University School of Medicine
Winston-Salem, North Carolina

10.4.3. **Federal Sponsors**

Centers for Disease Control and Prevention
National Institute of Diabetes and Digestive and Kidney Diseases

10.4.4. **Central Resource Centers**

Northwest Lipid Laboratory
University of Washington
Seattle, Washington

SEARCH Protocol – Section 11
Human Subjects
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11. Human Subjects

11.1. GOALS

The goals of this section are as follows:

a. to obtain the highest level of informed, voluntary participation from eligible patients;
b. to follow all local and national human subjects regulations;
c. to respects the wishes of the patient and family, regarding participation, continuation in study, and receipt of results;
d. to protect patient confidentiality;
e. to ensure safety of patients relative to study participation; and
f. to ensure fair and equal treatment of all patients.

11.2. OVERVIEW: BACKGROUND INFORMATION

The SEARCH project is a six center study involving people ages less than 20 years of age diagnosed with diabetes. All people in this age group, except for those with gestational diabetes or most types of secondary diabetes will be invited to participate. Prevalent and incident cases will be studied, for a total estimated 6350 prevalent cases and 785 incident cases per year. The study protocol will be standardized across sites. Information will be obtained from multiple sources: patient surveys, in-person visits (including physical exam, questionnaires, laboratory studies of blood and urine, and medical records). Forms used for data collection will be distributed by the Coordinating Center. Data will be transmitted electronically to the Coordinating Center for data analysis. To maintain confidentiality, materials will be sent to the central location with a study number, and no identifiers. Subject identifiers will be maintained in a separate file, which is maintained and protected locally.

Methods of recruitment will vary among sites (see Recruitment section). Similarly, methods of data collection may vary between sites. Sites will obtain local IRB approval, and follow local IRB regulations.

Model consent, assent forms and subject recruitment material will be prepared by the human SEARCH committees, customized by sites and submitted for approval by the local IRB committees.

A certificate of confidentiality 301(d) for all sites is being sought by the CDC, adding another level of protection for the data collected in this study.

11.3. SITE-SPECIFIC GUIDELINES

Each of the six sites in SEARCH will be working with one or more local IRBs, and it is expected that each IRB will have separate requirements. Content of the materials will be

standardized, while also abiding by local IRB regulations. For example, inclusion of a patient's bill of rights is required by some states. This will be added in accord with local regulations. When necessary, all study materials will be provided in English and Spanish. Materials will be provided in additional languages as determined by the local study population demographics. No potentially eligible subject will be excluded based on language.

11.4. RECRUITMENT AND METHODS TO ENTER STUDY

The goals of recruitment are to maximize patient enrollment while respecting the voluntary nature of clinical research. Recruitment will take place at a number of levels: patient/family, community (e.g., diabetes support groups, school nurses, and television/newspaper) and health care practitioner. Methods of recruitment will vary by site. All recruitment materials will be developed in collaboration with the Coordinating Center and may be customized by local sites. Recruitment materials will require local IRB approval. Also, sites may be advertised on web sites, such as the American Diabetes Association or Juvenile Diabetes Research Foundation. Again, such advertisements will be posted or aired in adherence with local IRB guidelines.

Local health care providers will be informed of the study objectives, eligibility criteria, and contact information. They will be assured that the SEARCH study will not interfere with their relationship to their patients. Each site will have a provider network that will be specific to that site. Sites will use or design local databases to provide an efficient, timely surveillance system. Identifiers will be maintained by the local SEARCH personnel and not submitted outside the local site.

11.5. HIPAA PRIVACY ACT

The Office of Civil Rights has established a Privacy Rule for research, OCR Health Insurance Portability and Accountability Act (HIPAA) Privacy TA.5121.001. The Privacy Rules establishes conditions under which protected health information may be used or disclosed for research purposes. The Privacy Rule protects individual's identifiable health information while allowing for the conduct of vital research, with researchers accessing necessary medical information. The means of informing individuals of use or disclosure of medical information are also defined in the Privacy Rule. SEARCH centers will follow HIPAA guidelines as needed by each institution.

11.6. LEVELS OF INVOLVEMENT

Patients may agree to participate in the study at a number of levels. Patients will be encouraged to participate in all aspects of the study for which they are eligible, but it will be clear to participants and their parents or guardians, that all such participation is voluntary.

The following are the levels of involvement, for prevalent and incident cases unless otherwise indicated:

a. Case Registration

b. In-Person Visit Module

- Introductory letter
- Initial Patient Survey
- Physical exam
- Laboratory studies – blood and urine samples
- Questionnaires

c. Medical Record Module – abstraction and typing

d. Annual Follow-up Visit Module – mail or visit

e. Stimulated C-peptide

A separate consent and assent will be given for the mixed meal test (stimulated C-peptide). Risks and benefits specifically of the mixed meal test will be detailed in the consent and assent forms. Procedures for the mixed meal test, including instructions for medications pre- and post-testing, will be outlined in the manual of operations. Laboratory studies will be performed in a standardized fashion, with adjustments of blood volume made as needed based on patient weight and age. The maximum blood volumes for pediatric patients for research purposes, both as a single blood draw and within a 30-day period, will not be exceeded. The manual of procedures will contain tables for age and size-adjusted volumes, along with a table for maximum blood volumes.

11.7. CONSENT FORMS

The Human Subjects Task Group has developed model consent and assent forms. These can be adapted to meet local IRB guidelines and criteria. Consent of at least one parent or legal guardian will be required of all participants under the age of 18 years. Patients 18 and 19 years of age will sign as the subject and will not require additional signature of parent or legal guardian or when an emancipated minors.

Consent forms will contain the following information:

a) Introductory information, explaining the objectives of the study.

b) Procedures

c) Risks, Discomforts, Precautions

d) Incentives/compensation

e) Benefits

f) Alternatives of Care

g) Confidentiality of records

h) Optional receipt of results by patient and/or provider(s)

i) Availability of information

j) Right to withdraw

k) Additional elements of consent

l) Witnessing and signatures

11.8. ASSENT

The age of assent and the method of obtaining assent will be defined according to the guidelines of the local IRB.

11.9. PATIENT INCENTIVES

Patients will receive incentives commensurate with level of involvement and effort. Incentives will be of equal monetary value across sites. However, the specific incentive, e.g., movie gift certificate, sporting good store gift certificate, etc., will vary across sites, and be in accordance with local IRB regulations.

11.10. PATIENT SAFETY

Patient safety will be monitored through site specific protocols or policies. Study-related adverse events will be documented on the Event Reporting Form and submitted to the Coordinating Center. An external review will review all events reported on the Event Reporting Form and report findings to the SEARCH Quality Control Committee.

11.11. RESULTS

Patients will be asked to designate whether or not they wish to receive laboratory results generated by study participation, and/or whether or not they wish their diabetes and/or primary care provider(s) to receive such results. Results of HbA1C, lipid profile, C-peptide, DAA, microalbumin, and glucose laboratory studies will be made available to those who choose this option. Receipt of these results will be viewed as a possible but not definite benefit to the patient, as such information may or may not affect subsequent diabetes (or complication) management. In view of the laboratory measures obtained, it is expected that there will be few if any critical values. If critical laboratory values do occur, the central laboratory will contact

the local PRINCIPLE INVESTIGATOR and/or his/her designee, and the information will be shared with the patient, patient's family and provider if permission from the patient, parent or legal guardian, had been given.

Results of interviews (general interview and 10+ years supplemental interview) will NOT generally be shared with parents or guardians. One exception is the CES-D, a scale for depression, that will remain confidential. Based on scoring cut-off points, site personnel will offer patients assistive referrals if their score is above the cut-off value. Patients ages 10 years and older will be asked to complete a supplemental interview. This interview asks questions related to issues such as eating disorders and depression. Parents will be allowed to review the questionnaires prior to their child's completion of the questionnaire, but will be asked to waive their right to review their child's answers. However, in the event that results alert to critical issues, that material will be shared with patients, parents and their providers if permission had been given.

11.12. REPOSITORY

Testing related to diabetes is limited to basic testing as mentioned in both Section 5 (Data Collection) and Section 7 (Typology). These tests enable medical personnel to evaluate the diabetes status of participants. SEARCH investigators recognize that new information may become available during or following the collection of data that may make it desirable to perform additional biochemical tests on subjects who are no longer available for further data collection.

Since new genetic markers continue to be identified, markers currently available will be enhanced by those developed in the future. These markers will add to the basic knowledge of diabetes. Genetic analyses not currently funded in the SEARCH study, may be more efficiently performed on select, well-characterized group(s) of participants. Thus, genetic material will be available to answer specific questions.

11.12.1. Sample Types

Two types of samples to be collected and stored are:

a) Biochemical: serum, plasma, and/or urine

b) Samples for DNA extraction (buffy coat)

Genetic analyses may be done on the SEARCH population to identify specific markers related to certain types of diabetes. Genetic markers may add to the understanding of diabetes.

11.12.2. **Consent for sample storage**.

The consent process will allow study subjects to consent or refuse to have samples stored in the repository laboratory. Consent will be structured in such a way that subjects can agree to have either serum or DNA or both or neither kept in the repository without affecting their participation in the remainder of the SEARCH protocol.

11.12.3. Sample Maintenance

11.12.3.1. Duration of Storage

Samples will be stored for as long as they last and will be retained in the repository laboratory for the duration of SEARCH funding. The Laboratory Director is responsible for maintaining a current list of all samples to provide to Principle Investigators for matching. In the event that SEARCH funding for repository maintenance is exhausted, the principal investigators will be responsible for determining the disposition of study samples in his or her study center.

11.12.3.2. Sample Destruction

Individual subjects (or their parents if subjects are < 18 years old) may request that their DNA and/or serum samples be destroyed at any time. When this occurs, the principal investigator will notify the laboratory, which will assure destruction of the sample(s).

11.12.4. Use of Repository Samples

Samples will be made available (with Executive Committee approval) only to SEARCH investigators and their collaborators. Samples will be used solely for analyses related to diabetes or its complications or risk factors. All studies using repository samples will be approved additions to the SEARCH protocol or approved ancillary studies. Distribution of samples by the laboratory will be only by direction of the executive committee.

11.13. ANCILLARY STUDIES

It is expected that there will be a number of ancillary studies. Submissions for ancillary studies will be reviewed and approved by the Publication, Presentations and Ancillary Studies Committee and the Executive Committee. Involvement in the ancillary studies will vary by site. Each ancillary study will require separate IRB approval, and a separate source of funding.

11.14. FUTURE STUDIES

SEARCH is designed to provide population-based information about selected aspects of diabetes in youth, with the protocol written by SEARCH investigators to reflect the best design given current knowledge. It is expected that new tests or methods will evolve that would

provide additional information and/or enhance the study. Patients will be asked if they would like to be contacted for future studies. Annual contact will be made with patients, to update information such as address and telephone numbers. Patients who withdraw from the study will be removed from the contact list.

11.15. CERTIFICATE OF CONFIDENTIALITY

Federal law permits researchers to obtain a Certificate of Confidentiality to protect the privacy of individuals who participate in research. Applications to obtain a Certificate of Confidentiality are made to designated federal officials. Researchers who obtain a Certificate of Confidentiality may not be compelled to disclose information about study participants in any federal, state, or local civil, criminal, administrative, legislative or other proceeding although there are certain exceptions (e.g., FDA audit, subject request). A Certificate of Confidentiality was obtained from the CDC for each SEARCH site.

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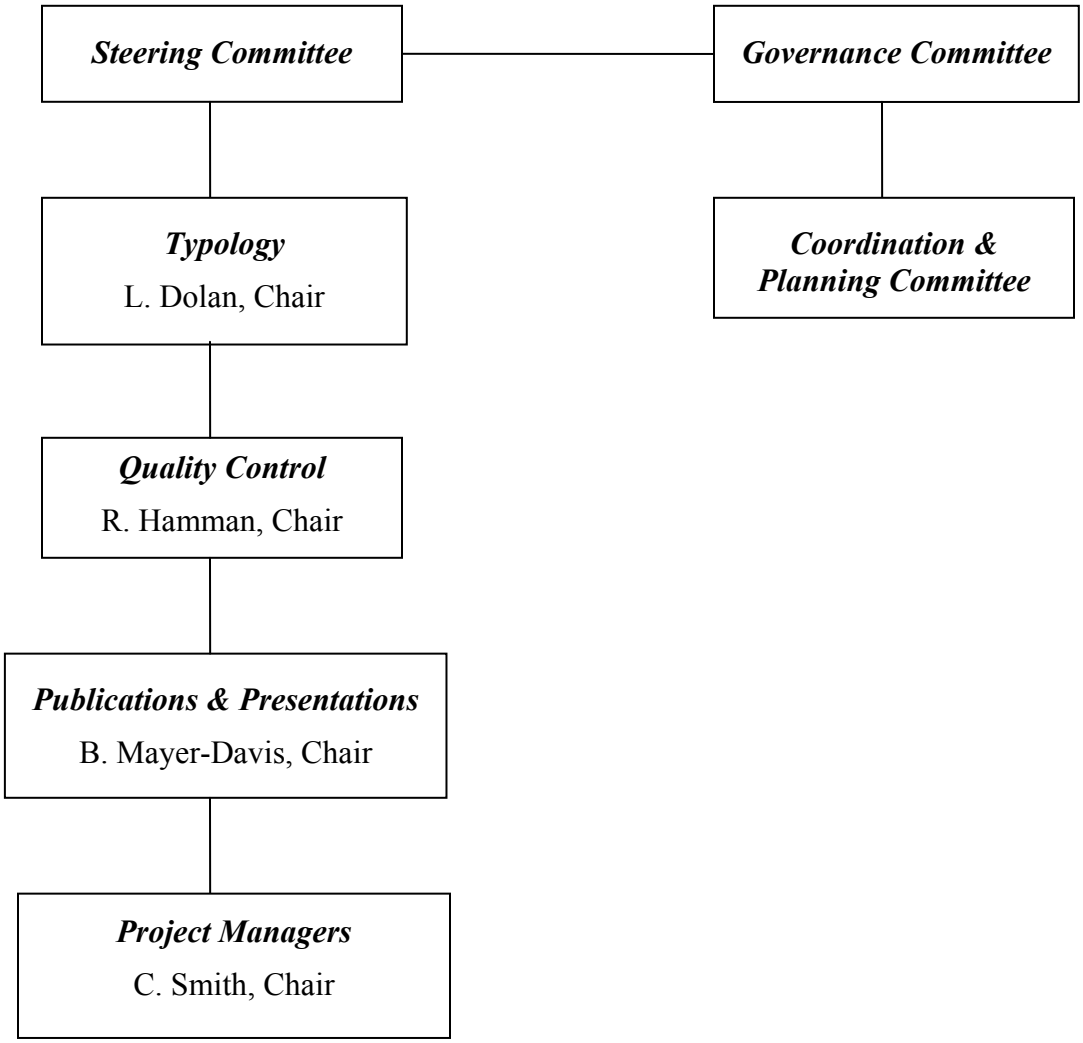
Appendix I

SEARCH Organizational Chart



Appendix II
Ancillary Studies

1. Definition

An ancillary study is an investigation that is not part of the SEARCH Study protocol that uses SEARCH biological samples or other data collected specifically for the SEARCH study. This policy is restricted to data that would not have been collected in the absence of the SEARCH study protocol. In most cases, an ancillary study will involve acquisition of additional data that are not compiled as part of the standard SEARCH data set. Additional studies using the typology data only constitutes an ancillary study if these data are/were not previously being collected by clinicians/researchers at that site as a part of their routine patient care or pre-existing research protocols.

The inclusion of local SEARCH study participants by a SEARCH investigator or another health care provider/agency in other research studies does not constitute an ancillary study.

2. Process for Review of All Proposed Ancillary Studies

To protect the integrity of SEARCH, all ancillary studies must be reviewed and approved before any access to SEARCH data is permitted. The SEARCH Publications and Presentation Committee will review the proposal for scientific merit and project clarification forwarding its recommendations to the Executive Committee. The Executive Committee will have the final decision for approval/disapproval.

2.1. Inclusion of Sites

Each Principal Investigator may determine whether or not their site will participate in a proposed ancillary study. The investigator proposing the ancillary study should consult each PI independently to determine whether they want to participate in the proposed ancillary study prior to submitting the ancillary study proposal. Each PI who wishes to participate in the ancillary study must be given the opportunity to review and critique the proposal before it is submitted to the Executive Committee for their review. Any funding sought for ancillary studies should include a budget appropriate for each of the sites that have agreed to participate in the study. If a site has opted out of a proposed ancillary study, their information and data may not be included in funding proposals.

A SEARCH principal investigator or co-investigator must be included as a co-investigator in every ancillary study proposal in which they participate. In general, if a SEARCH Study center provides their subjects' data for the ancillary study, a member of that center will be included as a co-investigator. In order to avoid misunderstandings, all communication with the SEARCH Data Coordinating Center must take place between the senior SEARCH investigator involved in the ancillary study and the Data Coordinating Center liaison. Following approval of an ancillary study by the Executive Committee, there can be no substantial changes in the type or amount of data requested from the Data Coordinating Center. If major changes are made, the Executive Committee must reconsider both the data request and the priority of the ancillary study.

2.2. Submission of Proposals for Ancillary Studies

In order to expedite review of ancillary studies, the SEARCH study team has developed an information form that provides a synopsis of the proposed study and describes its impact on the participants or resources of SEARCH. In addition, investigators should provide a two to three page synopsis of the proposed study to the review group.

The summary should contain:

2.2.1. Identifiers:

1.1.1.1. Initiating investigators, collaborators, sites involved

1.1.1.2. Planned starting date, conclusion date

1.1.1.3. Estimated cost and plans for funding the ancillary study

2.2.2. Design and Methods:

1.1.1.4. Brief background and rationale

1.1.1.5. Study questions or hypothesis

1.1.1.6. Sample size, justification

1.1.1.7. Methods, data to be collected (additional tests, surveys, etc.)

1.1.1.8. Burden on participants

1.1.1.9. Impact on main SEARCH Study

2.2.3. Data Handling:

1.1.1.10. Data needed from main study for analysis of ancillary study

1.1.1.11. Impact on Data Coordinating Center

2.3. Review Process

All proposed ancillary studies must be submitted to the Executive Committee in time for review and clearance prior to submission to a funding agency. Studies submitted for review less than 60 days prior to a funding application deadline may not receive approval.

Reviewers will use this information to assess the priority of the study in relation to SEARCH objectives, and most importantly, determine its potential impact on the main study (SEARCH). Highest priority will be given to studies that:

2.3.1. Do not interfere with main SEARCH objectives,

2.3.2. Have the highest scientific merit,

2.3.3. Produce the least burden on SEARCH participants,

2.3.4. Have objectives closest to those of SEARCH, and

2.3.5. Require the unique characteristics of the SEARCH cohort.

The Executive Committee will review the proposal primarily to determine that it will not compromise, complicate, or jeopardize the conduct of SEARCH. Review of proposed ancillary studies for scientific merit is not the primary responsibility of this review process, but is a necessary consideration when allocating access to scarce SEARCH resources.

2.4. Monitoring

The Executive Committee will record the progress of approved ancillary studies since the composite impact of the total number of active studies may be unforeseen without central monitoring. Monitoring will include the burden on participants and SEARCH staff, as well as the use of irreplaceable SEARCH resources such as stored blood samples. A database to monitor use of the stored sample repository will be developed by the Data Coordinating Center. Investigators with approved ancillary studies will report to the Executive Committee every six months regarding the status of study funding, initiation and termination dates, success of data collection, and any presentations or publications derived from the ancillary study.

Requests for data analysis for any SEARCH approved ancillary study must be financed in advance by the SEARCH investigator who makes the request. The Data Coordinating Center must be consulted in advance of submission of the proposal for any ancillary study so that the cost of data analysis is included in the budget for the ancillary study.

All requests for data analysis for SEARCH ancillary studies will be met by the staff of the Data Coordinating Center <u>only</u> if such a request does not interfere with the task of data analysis for SEARCH papers listed in the priority listing of SEARCH papers. All SEARCH investigators are expected to be mindful of the priorities imposed upon the Data Coordinating Center for data analysis before making their own personal requests.

Publications resulting from ancillary studies will follow the same policies as described in the Publications and Presentations Policy.

3. Informed Consent

When required by federal regulation, separate informed consent must be obtained from all ancillary study participants for participation in the ancillary study. Any consent documents and associated communication with the participants should clearly identify the ancillary study as one being performed in addition to the main study and inform subjects that their participation in the ancillary study is not necessary for them to continue to be enrolled and involved in the SEARCH Study.

4. Incorporation of Additional Data Collection to SEARCH Study Visit

If investigators wish to collect additional data from the patient at the time of the SEARCH Study visit, they need to consider the impact of the burden of additional tests or survey questions on the patient's participation in the SEARCH Study. Additional data collection at the time of the SEARCH Study visit that has the potential to reduce the participation in the SEARCH Study should be brought to the attention of the Executive Committee.

5. SEARCH Patient Participation in Local Studies

The Executive Committee will need to know when a SEARCH study participant is involved in another study so that accurate assessment of outcome and complications can be determined. This is particularly important if the patient receives an intervention (new treatment protocol, new pharmacological treatment, etc.) as a part of the study. However, the SEARCH Study cannot preclude local (site-specific) investigators from involving SEARCH study participants in other studies of childhood diabetes or other topics.

Appendix III
Publications and Presentation Policy for the SEARCH Study

1. Description of the SEARCH Study Cooperative Agreement

SEARCH for Diabetes in Youth is an observational study funded through a Cooperative Agreement. The goals of the study are to develop case definitions and classification of pediatric diabetes, to assess the magnitude of the problems and trends (prevalence and incidence), to characterize the types of diabetes at diagnosis and over time, and to assess the processes of care for children with diabetes. This study is sponsored by the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIDDK) and aims to identify 6,000 prevalent cases and 800 incident cases per year in children under the age of 20 years with diabetes over a five year period.

The study locations are Kaiser Permanente Southern California, University of Colorado Health Sciences Center, Children's Hospital (Cincinnati) Medical Center, University of South Carolina, Children's Hospital & Regional Medical Center, Seattle, and Pacific Health Research Institute, Honolulu. Wake Forest University is the Coordinating Center and Northwest Lipid Research Laboratories is the Central Laboratory. The project officers are from the CDC and the NIDDK has a liaison.

2. Goals of the Publication, Presentation, and Ancillary Studies (PP&A) Committee

The goals of the PP&A committee are to:

2.1. To stimulate scientific presentations and papers from SEARCH Study investigators.

2.2. To assure that press releases, interviews, abstracts, presentations, and publications of data from the SEARCH Study are accurate and objective, and do not compromise the scientific integrity of this collaborative study.

2.3. To assure that all investigators, particularly those of junior rank, have the opportunity to participate and be recognized in the study-wide publication and presentations of SEARCH study papers. For publications and presentations, it is essential that equal opportunity exist for all investigators from the SEARCH Study to participate. Involvement shall be open equally to investigators of all study sites, the Coordinating Center, and the Centers for Disease Control and Prevention. All of these units shall have equal status with regard to developing protocols, participating in such studies as approved by the PP&A and the Governance Committee, and collaborating in the development and publication of research papers and abstracts based upon the SEARCH Study data.

2.4. To assure and expedite timely presentations of the results of the SEARCH Study to the scientific community.

2.5. Establish procedures for timely review of proposed SEARCH Study publications and presentations.

2.6. To review ancillary studies and make a recommendation to the SEARCH Study Governance Committee regarding the proposals. Refer to Appendix II, Ancillary Study Policies.

2.7. Maintain a complete up-to-date list of SEARCH Study presentations and publications, available to SEARCH Study investigators routinely, via the Study website.

2.8. To approve manuscripts and presentations, to ensure appropriate writing group membership, and to monitor the progress of all proposed manuscripts and presentations to ensure their prompt completion and publication.

3. Committee Membership

Publications, Presentations, and Ancillary Studies (PP&A) Committee will be established with rotating membership to review proposals for papers and presentations, motivate and assure progress on each paper, and to assure quality work before the paper or presentation is submitted. The role of the PP&A related to Ancillary Studies is discussed in Appendix II.

The PP&A, Committee will function as a standing committee. Initial appointments will include a chairperson who will be invited to serve for the five-year term of the study. In addition, one person from each of the six study sites, the Coordinating Center and the CDC will be invited by the Governance committee to join the PP&A Committee. Four persons will be appointed to 2-year terms, and three persons will be appointed to 3-year terms. All members of the Steering Committee (including but not limited to Governance Committee members) are eligible for appointment to the PP&A Committee. The Principal Investigator from each site as well as the Project Officer from the CDC will nominate someone from their site for appointment to the PP&A Committee.

The Chair of PP&A will be appointed by the Governance Committee. The Chair shall be a senior scientist with an extensive record of publications in peer-reviewed journals, and all SEARCH scientists who meet this criterion are eligible. The PP&A Chair is responsible for managing the processes of proposal review and approval, and the monitoring and encouragement of progress of work through to the point of publication of presentation. Process management includes convening and chairing calls and in-person meetings of P&P; assuring equitable access to and use of SEARCH data; overseeing progress on approved manuscripts proposals; and resolution of conflicts. The PP&A Chair will be responsible for

developing and distributing agendas, minutes, and reports, with the support of the SEARCH Coordinating Center. In order to ensure fairness in the management and facilitation activities of the PP&A Chair, the PP&A Chair will not have a vote on the PP&A committee.

There will be a vice-Chair of PP&A, proposed by the PP&A committee and appointed by the Governance Committee. This individual will be selected from among the members of the PP&A Committee. The vice-Chair will facilitate meetings or conference calls and other committee processes when the Chair cannot perform these functions. The vice-Chair will retain his/her voting rights on the PP&A committee.

4. Definitions of Types of Communication

Any communication from the SEARCH Study will be classified as a publication, presentation, press release, or interview.

Publications. A publication is any document (other than an abstract) submitted to a professional journal listed in the Index Medicus or any popular periodical with national circulation.

Presentations. A presentation is the delivery of information to scientific, professional, or public groups. A presentation may include an abstract to be published by the group to which the presentation is made.

Press Releases. A press release is defined as a document given to radio, television, newspapers, popular periodicals, or scientific journals (including publications of pharmaceutical companies or professional organizations) not indexed in Index Medicus.

Interviews. An interview is any discussion with a member of the press, a science writer, or a radio or television commentator, who in turn provides information for public dissemination.

5. Publications

5.1. Categories of Papers

Generally, SEARCH Study papers will be considered in four categories: *group-authored papers*, *major papers, other papers, and ancillary papers*. The PP&A Committee will define as *group-authored* papers those that describe the study methods and the papers that describe the incidence and prevalence of diabetes since a significant number of steering committee members have contributed to the design, methods, analysis plan, and protocol development for this study, all of which are the basis for these papers. *Major papers* are those that report on the remaining main hypotheses and overall results of the study. *Other papers* are papers based on data collected in the SEARCH Study that does not test the main hypotheses and aims of the study. *Ancillary papers* are papers based on ancillary study, which use data from the main study. All papers must be formally

proposed to the PP&A Committee (see below, Section 5.4, Submission of Proposals for Manuscripts).

5.2. Organization of Paper Topics

In order to ensure that the SEARCH group papers, major papers, and other papers appropriately address the scope of science available in SEARCH, general topic areas will be designated that reflect the major aims and hypotheses of the study. Most designated topic areas are expected to yield more than one paper. Specific papers within a topic area may include group author, major, or other papers. The specific topic areas will be approved by the Governance Committee.

For each topic area, a "Topic Area Lead" will be appointed. The role of the Lead is to facilitate development of specific papers to address the topic area, and to coordinate analysis and publications within the topic to avoid inappropriate overlap. The Lead may serve as a writing group chair and lead author for papers in his or her topic area, but is not required to do so. The Chair of a standing committee may be designated as Lead for a given topic area, in order to facilitate efficiency Members of the PP&A committee, including the PP&A Chair, may serve as Lead on a topic area, but are not required to do so. The Lead will be approved by the Governance Committee.

5.3. Eligibility Criteria for Authorship of Publications using SEARCH Study Data

Decisions about authorship for the following categories of papers using collaborative data should use the following guidelines:

5.3.1. For group author papers. The author will be listed as the SEARCH for Diabetes in Youth Steering Committee. The writing group members for each paper will be listed at the end of the paper noting the chair of the writing group first with remaining writing group members listed alphabetically. Following this, all steering committee members will be listed by site. Consistent with the stated goal of providing equal opportunity for investigators to participate in publications and presentations (Section 2.3 above), each of the group author papers will be led by a different SEARCH investigator.

5.3.2. For major papers. Each center will have the opportunity to participate in each a paper. The CDC Co-Project Officer will have authority to nominate a co-author from the CDC for each of these papers paper. One representative from the NIDDK will be invited to participate but it is anticipated that she may not be a named author on every paper since, at this time, there is only one representative from NIDDK.

The chair of the writing group for major papers will be selected by the PP&A and approved by the Governance Committee. The decision about who should chair the writing group for a major paper will be made after consultation with the Lead assigned to the topic area. The decision about who will chair the writing group for major papers will assure equitable distribution of investigators serving as chair of the writing group, consistent with the stated goal of ensuring equal opportunity for SEARCH investigators to participate in publications and presentations from SEARCH (Section 2.3 above). All major papers will include individual authors' names and for the SEARCH for Diabetes in Youth Steering Committee.

5.3.3. Other and Ancillary Study papers, abstracts and invited presentations. The PP&A Committee will review proposals, abstracts, manuscripts and presentations with the same degree of scientific rigor as for the group author and major papers, and will encourage opportunity for investigators across all sites. For the other and ancillary study papers, the PP&A will not have the responsibility or the authority to assign paper topics or designate chairs for the writing groups.

5.3.4. The PP&A Committee will review/approve the ordering of authors as proposed by the writing group chair for all papers, abstracts, and presentations, taking into consideration the level of participation in the analysis and preparation/revisions of the manuscripts. The SEARCH Study Group will be acknowledged as a co-author as permitted by the policies of journals. All members of the writing group who are named as authors, either in the authorship position below the title or in a footnote, will meet the criteria for authorship as specified by the ICBE criteria and any additional requirements imposed by the journal. Writing group members who do not meet these criteria will be listed, with their permission, in the acknowledgments or in an appendix. SEARCH will adhere to the 1997 Uniform requirements for manuscripts submitted to biomedical journals. The following paragraphs are quoted from that document:

Authorship

All persons designated as authors should qualify for authorship. Each author should have participated sufficiently in the work to take public responsibility for the content. Authorship credit should be based only on substantial contributions to 1) conception and design, or analysis and interpretation of data; and to 2) drafting the article or revising it critically for important intellectual content; and on 3) final approval of the version to be published. Conditions 1, 2, and 3 must all be met. Participation solely in the acquisition of funding or the collection of data does not justify authorship. General supervision of the research group is not sufficient for authorship. Any part of an article critical to its main conclusions must be the responsibility of at least one author.

Editors may ask authors to describe what each contributed; this information may be published. Increasingly, multicenter trials are attributed to a corporate author. All members of the group who are named as authors, either in the authorship position below the title or in a footnote, should fully meet the above criteria for authorship. Group members who do not meet these criteria should be listed, with their permission, in the Acknowledgments or in an appendix (see Acknowledgments). The order of authorship should be a joint decision of the coauthors. Because the order is assigned in different ways, its meaning cannot be inferred accurately unless it is stated by the authors. Authors may wish to explain the order of authorship in a footnote. In deciding on the order, authors should be aware that many journals limit the number of authors listed in the table of contents and that the US National Library of Medicine (NLM) lists in MEDLINE only the first 24 plus the last author when there are more than 25 authors.

Acknowledgements At an appropriate place in the article (the title-page footnote or an appendix to the text; see the journal's requirements), one or more statements should specify 1) contributions that need acknowledging but do not justify authorship, such as general support by a departmental chair; 2) acknowledgments of technical help; 3) acknowledgments of financial and material support, which should specify the nature of the support; and 4) relationships that may pose a conflict of interest (see Conflict of Interest). Persons who have contributed intellectually to the paper but whose contributions do not justify authorship may be named and their function or contribution described-for example, "scientific adviser," "critical review of study proposal," "data collection," or "participation in clinical trial." Such persons must have given their permission to be named. Authors are responsible for obtaining written permission from persons acknowledged by name, because readers may infer their endorsement of the data and conclusions.

5.3.5. Technical help should be acknowledged in a paragraph separate from that acknowledging other contributions. For other papers, which may include reports relating to secondary objectives using collaborative data, submission of the proposed analyses to the PP&A Committee is required. Sub analyses involving outcomes related to the primary study questions should be presented after publication of the initial report(s) outlined above. In general, for these analyses the first author will be the individual who took the most responsibility for that specific report, based on genesis of idea, conduct of analysis, and the actual writing of the paper. Final authorship, ordering of authors (and number of authors per site) should be based on development of the study question, enrollment, quality of the data, and participation in analysis and preparation of the manuscript. The PP&A Committee will approve ordering of authors. The SEARCH Steering

Committee will be acknowledged as a co-author as permitted by the policies of journals.

Individuals who made a substantive contribution to the development of the questionnaires, data collection, intervention development, or study design for SEARCH will be given first opportunity to explore secondary hypotheses using collaborative data. Persons who were not involved in study design, data collection, or intervention development (e.g., Epidemic Intelligence Service (EIS) Officers, Fellows) *may* be allowed to conduct analyses and write abstracts/papers using collaborative data if 1) sponsored by a Principal Investigator or Co-principal Investigator, and 2) the proposed project is accepted by all members of the PP&A Committee *and* the Governance Committee prior to analysis (implies that the topic was not planned as an analysis project by other members at that site/CDC/NIDDK).

5.3.6. For reports relating to laboratory studies on secondary hypotheses conducted by laboratory investigators using collaborative data: In most cases, the responsibility and therefore the first authorship credit should belong to the person who designs and directs the analysis and writes the paper. In many cases this will be the respective laboratory group. In terms of authorship, appropriate recognition of study sites and other investigators including laboratory investigators should be given. The nature of recognition will be according to the degree to which the report relates to the study's stated objectives. The SEARCH Steering Committee should be acknowledged as a co-author as permitted by journal policies.

5.4. Analysis and Reporting Results based on Site-Specific Data

The following guidelines apply to analyses using site-specific (single site) data generated as part of the SEARCH study. Individual sites may use site specific data for the purpose of evaluating quality of care within their site and/or for providing feedback of clinical data to clinicians without the permission of either the PP&A or the Governance Committee. They may also use their own data in research proposals without additional permission. The Governance Committee must approve the inclusion of collaborative data in research proposals.

Site-specific analyses are appropriate when an individual study site (or sites) has collected data that are unique to that study site, or are addressing a study question particularly pertinent to that site. Projects using site-specific data require proposal to the PP&A Committee and approval by that committee. In general, the first author should be the individual who took the most responsibility for that specific report based on genesis of idea, conduct of analysis, and the actual writing of the paper. If applicable, other study sites and/or investigators should be recognized as authors. The nature of the

recognition should be based on the degree to which other sites or investigators contributed to the study, and in general, the SEARCH Steering Committee should be acknowledged. All authors should have the opportunity to review any reports on which they are listed prior to their presentation or publication.

Because the SEARCH Study has been designed and conducted as a multi-site collaborative study, no site-specific analyses should be done using primary study hypotheses. Furthermore, reports dealing with secondary analyses should preferentially be reported with multi-site rather than single site data. However, site specific analyses and reports may be pursued if approved by the Governance Committee.

5.5. Submission of Proposals for Manuscripts, Abstracts, and invited presentations

The publication process of a SEARCH manuscript starts with the submission of a manuscript proposal. The written proposals serve to minimize overlap between papers and will follow a standard format, including a description of the hypotheses of the paper, a one or two page paper topic description including a list and description of variables, and the general statistical approach, as well as the list of writing group members. Abstracts and invited presentations that do not directly result from an approved paper proposal must follow the process outlined below as for manuscripts. Such abstracts and invited presentations should, with only rare exception, also lead to a published paper for SEARCH.

5.5.1. Prior to submission of a manuscript proposal, the originating author will review PP&A documentation regarding papers already proposed, and will communicate directly with the Topic Area Lead in the area of interest in order to avoid inappropriate overlap or inefficient use of study resources. Such communication is to be briefly documented on the formal manuscript proposal.

5.5.2. Prior to submission of a manuscript proposal, each site will be informed of the development of the manuscript topic. This notification can come either from the PP&A committee (in the case of group-authored or major papers that the PP&A may originate) or from the originating investigator (generally in the case of an "other" or ancillary study paper). The submitted manuscript proposal will include documentation that each site had opportunity to participate in the work. Each author named on the proposal (to include at least one representative from each site unless a site formally declines participation) will be provided a reasonable amount of time to review and comment on the proposal prior to submission to the PP&A committee.

5.5.3. The manuscript proposal will consist of the following information:

a) Manuscript title

b) Initiating investigator name and center, including contact information (and sponsor if a EIS officer or fellow)

c) Introduction/background

d) Hypothesis

e) Methods

f) Analysis Plan (including variables required)

g) Proposed timeline

The completed manuscript proposal shall be submitted electronically to the chairperson of the PP&A Committee for review.

5.5.4. The PP&A Committee will review the manuscript:

a) To ascertain that the formal manuscript proposal format has been followed.

b) To determine that a clear and accurate analysis plan is included in the proposal.

c) To determine if there is inappropriate overlap between the proposed manuscript and any other papers proposed or in progress. In such cases the investigator will be encouraged to collaborate on the existing proposal/manuscript.

d) To confirm that each site has had a reasonable opportunity to participate and that the proposed writing group is appropriate.

e) To assign a Liaison from among the PP&A committee members (excluding any PP&A committee member who may also be a writing group member). The assigned PP&A Liaison is the person through whom communications will occur regarding the manuscript.

5.6. Process for Approval of Proposal

5.6.1. Scheduling Review of Proposals. The PP&A Committee members will be given adequate time for review of each proposal. Therefore, proposals must be submitted a minimum of 3 business days prior to a scheduled PP&A call for the proposal to be considered on the call. The PP&A Chair and Committee as a whole reserves the right to defer discussion of a proposal if the upcoming agenda is full, or if it is obvious that the proposal will require further work prior to a productive discussion. The Writing Group Chair will be notified accordingly of when the proposal will be discussed by the full PP&A committee.

5.6.2. Review of Proposals. The Writing Group Chair will be invited to join the PP&A Committee call to briefly present the proposal, and to answer any questions posed by the Committee. The PP&A will ask the Writing Group Chair to leave the call, to allow for unbiased discussion of the proposal by the PP&A. Respect for all individuals is required at all times in these proceedings.

5.6.3. Actions on Proposals. Each member of the PP&A committee, except the PP&A Chair, will have one vote in the decision about a paper proposal. If a PP&A Committee member is the Writing Group Chair, they will rescue themselves from the vote. In the case of a tie vote, the PP&A Chair will cast a tie-breaking vote. The PP&A Committee will accept, reject, or ask for a resubmission with modifications for any manuscript proposal, and will inform the Writing Group chair of their decision and rationale for the decision. Requested modifications may relate to scope of work or Writing Group membership. Invited presentations must be approved as an *other* paper.

5.6.4. Upon approval by the PP&A Committee, the manuscript proposal shall be given a manuscript number and this information, along with a description of the proposed paper, will be entered in the Manuscript Tracking Database.

5.7. Responsibilities of Writing Group Members and Chairperson

The Writing Group Chair is responsible for all phases of manuscript preparation, from conception through publication. Responsibilities include:

5.7.1. Preparation of the paper proposal, paper outlines, the *identification* of data analyses needed from the Data Coordinating Center, interim status reports and their submission to the PP&A Committee.

5.7.2. Assignment of tasks to Writing Group members, *specification of* clear deadlines for completion of these tasks, *and ascertainment* that the tasks are completed on schedule.

5.7.3. Confirmation that the manuscript has approval of the Writing Group before submission of its Penultimate Draft to the PP&A Committee.

5.7.4. Determination of the order of authorship on the manuscript. A major criterion for this determination shall be the effort and contribute on made by the members of the Writing Group in preparation of the manuscript. Disagreements regarding author order will follow the Conflict Resolution process (Section 9 below).

5.7.5. Recommendation of a journal to which the manuscript should be submitted. Selection of the journal for initial submission of the manuscript is delegated to the Writing Group, with input from the PP&A Committee. For this decision, the

PP&A will obtain input as needed from the Lead on the topic area, and from the Governance Committee.

5.7.6. Correspondence with co-authors, communication with the Data Coordinating Center and the PP&A Committee, responses to the CDC clearance review, and to journal editors.

Members of the Writing Group are responsible for performance of tasks assigned by the Chairperson within the allotted time period. Each member is expected to actively participate in the preparation of the manuscript. If a Writing Group member does not accomplish the tasks assigned to him/her and has not contributed to the manuscript, he/she can be removed from the Writing Group. Writing group chairpersons will have the authority to measure the effort of the other writing group members contributions and remove non-contributing members from writing group membership, and thus from the final listing of contributing authors. If the writing group chair wishes to remove a writing group member, this process should begin with a discussion between the writing group chairperson and the writing group member. If the issue cannot be resolved in this manner, the PI overseeing the person to be removed will be contacted by the writing group chairperson. If resolution is not achieved, the Chair of PP&A is to be informed, and the Chair will proceed with steps towards conflict resolution as outlined in this document (Section 9).

5.8. Specific Roles and Responsibilities of PP&A, Writing Group Chairs, Topic Area Leads to Monitor and Facilitate Progress

5.8.1. The PP&A Committee has the authority and responsibility to rank the priority of papers for analysis. This will be done in consultation as needed with the Governance Committee, the Topic Area Lead and the writing group chairs of specific papers, as well as the Coordinating Center to take into account issues related to work load and efficiency.

5.8.2. The PP&A Committee has the authority and responsibility to monitor papers for progress over time, and to encourage progress, typically via the PP&A committee member assigned as Liaison for the specific paper. This will be done in consultation as needed with the Governance Committee, the Topic Area Lead and the writing group chairs of specific papers, as well as the Coordinating Center for issues related to work load and efficiency. If there are concerns regarding progress the PP&A will communicate this directly to the Writing Group chair, and as appropriate, to the Lead for the topic area.

5.8.3. The Topic Area Lead has the authority and responsibility to monitor progress on papers in his/her topic area and to encourage progress. If there are concerns regarding progress on a specific paper, the Topic Area Lead will communicate directly with writing group chair, and, if concerns persist, with PP&A.

5.8.4. The Writing Group Chair has the authority and responsibility to set interim deadlines for writing group members to encourage progress and completion of the work. Deadlines will be made in consultation with writing group members, and with the Coordinating Center (especially as relates to completion of the various steps of data analysis). The Writing Group Chair will communicate directly with the PP&A committee if difficulties arise in meeting interim deadlines to the extent that timely completion of the work is at risk.

5.8.5. The Writing Group Chair has the responsibility to communicate with the Topic Area Lead and with the PP&A committee if the scope of the manuscript (or related product; e.g., abstract or invited presentation) exceeds the originally proposed scope to a degree that may impinge unreasonably upon the scope of other work (whether formally proposed or not). It is understood that, once analyses begin, some additional work may be required to adequately address the scientific questions posed in the original manuscript proposal, which was not anticipated specifically in the original proposal. However, it is the responsibility of the Writing Group Chair to monitor this aspect of work and to avoid inappropriately expanding the work at hand in a way that creates inappropriate overlap with other efforts, or that inappropriately leads to the exclusion of other interested SEARCH investigators.

5.8.6. The PP&A Committee has the authority and responsibility to require limitations on the scope of work to reasonably reflect the original, approved proposal, should procedures outlined above (Section 5.9.5) not result in a mutually agreeable scope of work in the manuscript. Should conflict arise in this regard, the procedures outlined in Section 9 will be followed.

5.8.7. Authority to Modify Writing Groups

The PP&A Committee may propose change the composition of the Writing Groups, including the Writing Group Chair, that have failed to produce the required manuscript according to the schedule originally agreed upon by the Group and the PP&A Committee. If the PP&A Committee is considering such an action, the PP&A Chair will discuss this directly and privately with the Writing Group chair as a first step. If needed, the conflict resolution process described below (Section 9) will be followed. A formal proposal from PP&A Committee to remove or reassign the responsibility of Writing Group members will be reviewed and decided by the Governance Committee.

5.9. Final Approval Prior to Submission of Manuscript (or Abstracts that directly result from work on an Approved Manuscript proposal)

The PP&A Committee has the authority to approve the near final draft before submission to the Governing Committee for their review for factual accuracy and the CDC for clearance. If any author creates undue delay in the clearance process for publication, the Governance Committee can remove the author from the writing group. During the CDC clearance process, manuscripts go through Section Chief, Branch Chief, Division Associate Director of Science, and Editorial Review. This process normally takes four to six weeks. Manuscript final development can continue during the clearance process. Abstracts need to be submitted to the CDC for clearance ONLY if accepted for presentation or publication.

Principal Investigators are responsible for assuring that their personnel abide by these guidelines prior to presenting or publishing any data from the SEARCH study.

5.10. Submission of the Manuscript. The Coordinating Center has the responsibility to manage the logistics of manuscript submission and associated communications. The Writing Group Chair has the responsibility to provide any specific prose that may be needed for the submission cover letter, to respond (or coordinate a response) to reviewer comments, and to review publication galleys.

6. Abstracts and Presentations

The goal of the process for abstracts and presentations is to facilitate communication of SEARCH results to the scientific community in a timely fashion. It is understood that, due to abstract and presentation deadlines, flexibility in implementing this process may be required on occasion.

Many abstracts will, ideally, emerge from approved paper topics. For these, and any other abstracts, an Abstract Lead will communicate to each site, via the PI, and to the Coordinating Center and the CDC, to invite participation by each site, the Coordinating Center and the CDC. An abstract proposal will then by developed and each participating investigator will be given reasonable, clearly defined, time to contribute to this abstract proposal.

The abstract proposal will be submitted to the PP&A no later than 3 business days prior to a regularly scheduled PP&A call. If the Abstract Leader feels it necessary, he/she will make a specific request to the PP&A Chair for a shorter timeline, or an e-mail approval process.

Upon approval by the PP&A of the abstract proposal, a PP&A Liaison will be assigned to the abstract, who is not a member of the Abstract Writing Group. The Abstract Writing Group will submit a draft of the abstract to the Liaison for approval.

Upon the Liaison's approval, the final abstract will be distributed to the full PP&A committee for final approval, typically via e-mail within 48 hours. PP&A committee members who are unable to review and respond within the allotted time forfeit their right to vote on the abstract.

Upon approval of the abstract by the PP&A committee, the abstract will be posted for the full SEARCH investigative group to see. Members of the SEARCH investigative group, including Governance Committee members, may comment on the abstract but such comments are not binding.

The Abstract Lead will communicate specifically with the CoC to determine the most efficient submission process (generally choosing between the Abstract Lead and the CoC). The PP&A will be notified of the decision.

The Abstract Lead will provide reasonable time for members of the Abstract Writing Group to comment on the material to be presented. Slides, tables, and/or a presentation script must be sent to the PP&A Committee Liaison at least two weeks prior to the scheduled presentation for review and approval.

Local presentations for the purpose of recruitment and physician information do not require PP&A Committee approval.

7. Press Releases

In general, press releases about study findings will be prepared by the first author of the individual paper and reviewed by the PP&A committee prior to submission to the Governance Committee for final review prior to release. These press releases should be given to the media when interviews are requested to help ensure uniformity and accuracy in the information disseminated through the media. Press releases issued by or approved by the Governance Committee do not require CDC clearance. However, any press release issued by the CDC or NIDDK should be reviewed by the PP&A Committee and the Governance Committee prior to its release.

8. Media Interviews

To facilitate the dissemination of information to the public concerning the SEARCH study, while maintaining uniformity, accuracy, and scientific integrity or the research, members of the Governance Committee (Principal Investigators, CDC, NIH, Coordinating Center, and Central Laboratory) are authorized to discuss the purpose and objectives, methods (once the protocol is approved), and published or presented data, with reporters. Where media deadlines allow, written submission of questions and the investigator’s responses should be submitted to the Policy and Procedures Committee for review and approval. When this is not possible, Governance Committee members are allowed to answer media inquiries. The

Governance Committee member or their designee is responsible for notifying the Policy and Procedures Committee that an interview took place and with whom.

9. Conflict Resolution

It is the intent of the stated Publications and Presentations policies to ensure efficient and fair procedures for maximizing the scientific productivity of SEARCH. In particular, these policies are designed to avoid conflict in the areas of authorship and scientific overlap across publications and presentations.

It is recognized that conflict may arise regarding SEARCH publications or presentations. Should conflict arise that cannot be resolved by the interested parties themselves, this will be brought to the attention of the Chair of the PP&A Committee, who will determine the first step towards conflict resolution. In many cases, resolution will occur via facilitated discussions among the parties concerned. As needed, the issue will be brought before the PP&A committee for discussion and recommendations for resolution, relative to the stated PP&A goals and policies. If resolution is not achieved to the satisfaction of the parties, then the issue will be brought before the Governing Committee. In all cases, values of fairness and respect will be upheld.

4. Methods: Denominator Estimation and Case Ascertainment - Kaiser Permanente Southern California (Revised 021205)

4.1. DENOMINATOR ESTIMATION / SITE-SPECIFIC APPROACH

Number of Members

The number of children/youth in the denominator at the KPSC site was based on the KPSC membership database.

For the 2001 prevalence year, the criteria for being counted in the denominator was: birth date 1/1/1982-12/31/2001, member on 12/31/2001, usual source of care not San Diego.

For the 2002 incidence year, the criteria for being counted in the denominator was: birth date 1/1/1983-12/31/2002, member on 12/31/2002, usual source of care not San Diego.

Birth date and membership years were incremented for subsequent incidence years.

Usual source of medical care was determined based on a computer algorithm that assigns KPSC members to a usual source of care based on their utilization of outpatient services.

Number of Members by Race/Ethnicity

KPSC does not routinely collect information on race/ethnicity. Estimates of the number of members of each ethnicity (Hispanic; White, African-American; Asian/Pacific Islander; Native American) by age in single years by gender and gender (M/F) were estimated based on geocoding to the US Census data as follows. Information on the addresses information of members less than 20 years of age in KPSC in 2000 was linked to block-level data from the Census Bureau's PL94-17 file. This process returns the % distribution of race/ethnicity of persons in that block in the following categories--Hispanic, non-Hispanic white, African-American, Asian/Pacific Islander, Native American, two races, other. The average % distribution by race/ethnicity for KPSC members in 2000 by age (in single years) and gender was calculated from these data. These estimated percentages were applied to the actual number of members in 2001 and 2002 in each age (single year) and gender group to yield estimates of the number of members in the race-ethnicity categories for single years of age and gender. In each age/gender category, the estimated number of member categories as being two races or unknown race was distributed as all the known members in that age/gender group.

We have published an evaluation that shows geocoding at the block-level yields valid estimates of the distribution of race/ethnicity at the group level for the southern California Kaiser Permanente membership (Chen et al. 2004). Others have published similar results for geocoding at the group level.

This procedure assumes that the distribution of people by race/ethnicity in blocks that include KP members was unchanged between the 2000 census and 2001/2002.

4.2. CASE ASCERTAINMENT / SITE SPECIFIC APPROACH

4.2.1. Prevalent Cases

Methods

Ascertainment of 2001 prevalent cases of pediatric diabetes was based on linkage of computer-stored data from the Pharmacy Information Management System (PIMS), the Hospital Information Management System (HIMS), and the Laboratory Management/ Results Management Information System (LMS/RMS) into a Diabetes Case Identification Database. This database was begun in 1994 as a resource for research and quality improvement at KPSC. Members of KP included in the database in an earlier year were carried forward in subsequent years even if they did not meet criteria for inclusion as possible cases in subsequent years in order to maximize sensitivity in detecting cases of diabetes.

The next table shows the data sources for the Diabetes Case Identification Database, the starting dates for each source, and the criteria for inclusion in the database for each source.

Data Source	Starting Date	Inclusion Criteria
Prescription Information Management System	1/1/1992-12/31-200x (on-going)	Prescription for insulin or oral hypoglycemic agent (see next table)
Laboratory Management and Results Information System	1/1/1992-12/31/200x (ongoing)	HgbA1 >= 7.9% for 1/1/1992 – 2/28/1992 HgbA1c >= 6.7% for 3/1/1993 – 12/31/2001 fructosamine >= 285 for 1/1/1992-12/31/2001
Hospital Information Management System	1/1/1992/ 12/31/200x (ongoing)	Hospitalized with discharge diagnosis 250.xx

The following gives the drug classes used to identify possible cases in the Prescription Information Management System and the GPI codes associated with these drugs.

Drug class	AHFS Codes	GPI Codes
Insulins	682008	27-10-xx
Sulfonylureas	682020	27-20-xx
Glitazones		27-60-xx
Other oral agents	682092	All other 27-xx-xx

Drug codes used to define individuals included in this database are reviewed annually and new codes added when necessary to capture drugs used to treat diabetes.

Identification of duplicate cases

Possible duplicate cases in the Diabetes Case Identification Database were removed based KP medical record number, name (first, last), gender (M/F) and date of birth (Mo/Dy/Yr) as a match key.

When there were matches (potential duplicates) using the simple match key, information was reviewed by staff and compared with other information available in the KPSC membership database to determine if the matches represented duplicates or were unique children with diabetes who had the same name, gender and exact date of birth.

Eligibility by Membership

Children / youth were eligible as 2001 prevalent cases if they were members of KPSC on 12/31/2001 and had a source of usual medical care other than San Diego. Usual source of medical care was determined based on a computer algorithm that assigns KPSC members to a usual source of care based on their utilization of outpatient services.

4.2.2. Incident Cases

Methods

The primary source of identification of incident cases was referral to the study by KPSC pediatric endocrinologists at the time of diagnosis. These endocrinologists agreed to cooperate in the study by "reporting" the occurrence of new diabetes cases by e-mail or phone to the research department along with the date of diagnosis.

An additional source of ascertainment of incident cases was a quarterly update of the Diabetes Case Identification Database. As for prevalent cases, this update relied on linkage of computer-stored information from the Prescription Management Information System (PIMS), the Laboratory Management/Results Management Information System, and the Hospital Management Information System. Criteria were as described above for the year 2001--prescription for insulin or an oral hypoglycemic drug, a laboratory test for hemoglobin A1c >=6.7, or a hospitalization with a discharge diagnosis of diabetes (ICD-9-CM 250.xx). Specific drug codes are given above, updated annually to include newly introduced insulins and oral hypoglycemic agents.

For cases not already identified as incident cases, computer-stored membership information and medical record review was used to determine whether the cases reflected a new physician diagnosis of diabetes and was a valid case (described below).

Identification of duplicate cases

Possible duplicate cases were removed based KP medical record number, name (first, last), gender (M/F) and date of birth (Mo/Dy/Yr) as a match key.

When there were matches (potential duplicates) using the simple match key, information was reviewed by staff and compared with other information available in the KPSC membership database to determine if the matches represented duplicates or were unique children with diabetes who had the same name, gender and exact date of birth.

Eligibility by Membership

Incident cases were eligible for SEARCH if they were a member of KPSC at any time during the incidence year and were not assigned to SD as their usual source of care. Usual source of medical care was determined based on a computer algorithm that assigns KPSC members to a usual source of care based on their utilization of outpatient services.

4.2.3. Identification of Fatal Cases Missed by Other Case Identification Methods

Methods

Deaths among members of Kaiser Permanente are routinely ascertained by linking information about members with the California Death Index. This linkage covers members even after they have left the Health Plan. Availability of this linkage lags at least one year behind the current calendar year.

When an individual dies before discharge from the hospital, death is flagged in a field in the hospital discharge record; in these cases, the discharge diagnosis corresponds to the cause of death in most instances.

At the California SEARCH center, we sought to identify eligible DM cases that died but had not otherwise been identified by SEARCH methods as follows. First, members with birth dates in the eligibility range who had an underlying cause of death of diabetes (ICD-9 codes 250.xx; ICD-10 codes E10.x-E14.9) in MORTLINK in 2001 or 2002. Second, individuals with birth dates in the eligibility range who were identified as in-hospital deaths and had a discharge diagnosis of diabetes (ICD-9-CM code 250.xx) were identified using the hospital discharge database.

Deaths due to diabetes in individuals who were members in 2001 were included as prevalent cases. Deaths due to diabetes that reflected a new diagnosis of diabetes in individuals who were members in 2002 were included as 2002 incident cases.

At our center, only 2 additional DM cases were identified using these procedures for 2001 and 2002.

4.3. CASE VALIDATION / SITE-SPECIFIC METHODS

Children with a physician diagnosis of diabetes were considered to be validated cases of diabetes.

For 2001 prevalent cases, lists of children identified based on computer record linkage were reviewed by the Kaiser Permanente pediatric endocrinologist who had an appointment with the child in 2001. Cases that the pediatric endocrinologist confirms as true cases of diabetes were considered validated. The KP medical records of remaining possible cases were reviewed, including cases seen by a pediatric endocrinologist and not confirmed as diabetes and possible cases not seen by a pediatric endocrinologist.

Incident cases were considered validated if they are referred to the study by a pediatric endocrinologist in the KPSC network. Possible cases that were identified based on the quarterly update of the Diabetes Case Identification Database were considered validated if they had a physician diagnosis of diabetes recorded in the medical record and the diagnosis was made between 1/1/2002-12/31/200x (the index year).

Deaths with diabetes as the cause of death listed on the death certificate or the hospital discharge record were considered validated DM cases.

4. Methods: Case Ascertainment: Colorado – Western Registry of Diabetes in Youth

GOAL

To ascertain and validate all unique (non-duplicated) cases of diabetes in youth aged 0-19 years who reside in the Western Registry of Diabetes in Youth (WRDY) prevalence area in 2001, and all unique (non-duplicated) newly occurring cases of diabetes in youth aged 0-19 years who reside in the WRDY incidence area in 2002-2004. This will allow estimation of prevalence and incidence rates by age, gender, and ethnicity.

4.1. DENOMINATOR ESTIMATION

4.1.1. **Site - specific approaches**

The 2000 US Census non-institutionalized non-military resident population from which cases are present in the index year will be used as denominator. A "resident" is defined as a person with a permanent address within the defined geographic area at any time in the index year, who is not noted to be living elsewhere and only temporarily residing at the eligible address.

Military personnel and dependents are counted in the denominator for the county in which they currently reside. Military and dependents that have access to civilian medical facilities will be captured in the numerator. Those that use military facilities will be excluded. Firm estimates of the size of this bias are not available, though it appears they will be small. Starting with year 2002 Census data on socio-economic characteristics of population as well as counts of civilian and non-civilian individuals will be available. We will then be able to subtract military personnel from our denominators. There are 5 Colorado Springs Military Bases in Colorado: Fort Carson, Peterson Air Force Base, Schriver Air Force Base, the U.S. Air Force Academy, and NORAD, and one in Denver: Buckley Air Force Base.

Persons of Native American origin residing on eligible Native American reservations and counted in the census as on-reservation members are considered residents of the reservation, even if they live off-reservation for any period of time during the eligible time period. Children born on reservation during the index year will also be considered residents of the reservation.

4.1.2. **Denominators for prevalence**

Prevalence of diabetes in youth aged 0-19 will be estimated for the year 2001 in the following geographic areas:

Urban-suburban counties, including the Denver-Boulder metropolitan statistical area, (Denver, Adams, Arapahoe, Douglas, Jefferson, and Boulder).

Rural Colorado counties, including the San Luis Valley (Conejos, Costilla, Alamosa, Sauguache, Mineral, Rio Grande) in south-central Colorado, and Mesa county in western Colorado. Selection of these counties was based on several reasons: a) they expressed interest in participating in the registry; b) a network of collaborators, health care providers, hospitals, etc, has already been developed through several previous studies in the San Luis Valley region; and c) their participation will help investigators learn about the ascertainment process in these areas, patterns of access to different sources of cases, patient referral patterns, and issues of confidentiality in different populations and provider groups.

Native American tribes on reservations in Arizona and New Mexico that have expressed interest to participate:
a) Navajo Nation in Arizona and New Mexico
b) Gila River Pima Indian Reservation in Arizona
c) Apache Indian Reservations White Mountain (Fort Apache) and San Carlos in Arizona

These reservations were approached based on their size and on preliminary expression of interest.

The following table shows estimates of prevalence denominator by ethnicity, based on the 2000 US census

Age	NHW	African American	Hispanic	Asian	Pacific Islander	Native American	Total
0-19	564,465	42,251	105,217	14,848	3,712	132,265	862,758

4.1.3. **Denominators for incidence**

Incidence of diabetes in youth aged 0-19 years will be estimated in the years 2002, 2003, and 2004. The Colorado – WRDY site will expand the area and population to enhance the size of Native American and Hispanic participation in the study, and therefore, to include:

The entire state of Colorado (63 counties)
Other additional Native American tribes on reservations in Arizona and New Mexico. Tribes that will be approached to participate are:

a) Navajo Nation in Arizona and New Mexico
b) Gila River Pima Indian Reservation (Arizona)
c) Apache Indian Reservations White Mountain (Fort Apache) and San Carlos in Arizona

d) Colorado River Indian Tribes/La Paz County in Arizona
e) Salt River Indian Pima/Maricopa County in Arizona
f) Tohono O'odham/Pima County in Arizona
g) Fort Yuma Reservation in Arizona

The following table shows estimates of prevalence denominator by ethnicity, based on the 2000 US census.

Age	NHW	African American	Hispanic	Asian	Pacific Islander	Native American	Total
0-19	955,789	60,388	223,960	28,182	1,367	151,153	1,420,839

Projection of population changes that will occur after the 2000 census will be used for incidence denominator estimation for years 2002 and beyond. Age- gender-, and ethnic – specific denominators will be estimated by applying projections from the 2000 census data to the total population projections.

4.2. CASE ASCERTAINMENT

4.2.1. **Prevalent Cases**

4.2.1.1. Case finding site – specific approaches

Data sources

Cases will be identified in the SEARCH – WRDY area through multiple approaches, which are site and area dependent. These are tabled in **Appendix 1** for each of the areas included. In each area, multiple sources will be used to ensure that as few cases are missed as possible.

The types of data sources include: pediatric endocrine clinical computerized databases, HMO computerized diabetes registries, diabetes registries based on Diabetes Electronic Management System (DEMS), school based health clinics charts, primary care practices charts, private practices charts, computerized hospital discharge records, diabetes educators case records, Indian Health Service computerized hospital and ambulatory databases, NIH/NIDDK research databases, and death certificates.

In most situations, possible cases will be identified through database searches (see description in Appendix 1). Preliminary information suggests that we will be able to identify approximately 70% of all estimated WRDY prevalent cases from the Barbara Davis database. For cases older than 16 years of age the Kaiser Permanente and Denver Health databases will be the main sources of possible cases. Preliminary

diabetes registries based on Diabetes Electronic Management System (DEMS) will also be queried for possible case identification through Community Health Centers. Chart reviews, hospital discharge record reviews from selected hospitals identified through the Colorado Hospital to Association, letters and telephone surveys to primary care practices are other additional methods that will be used to ensure as a complete ascertainment of cases as possible.

In most instances, we will be able to identify potential cases without prior consent from the patient. If such consent is in fact requested by a health plan organization, two different approaches may be used on a site - specific basis: a) contact the potential case before it is a validated case via the primary care physician in order to obtain consent to search the database, and b) search the database for potential cases of diabetes without recording personal identifiers (e.g. name).

In all locations, IRB review and approval of procedures will occur before any case ascertainment begins. IRB approval will be requested from each institution involved in the study, from the Indian Health Service, and from each of the participating Native American tribes in Arizona.

Once cases are identified and validated they will be contacted by SEARCH – WRDY through their primary care physicians and permission to enroll in the study will be requested. If no primary care physician can be identified, potential cases will be contacted for validation.

Identification of duplicate cases

Removal of duplicates will occur manually. Once personal identifiers (name, gender, date of birth, ethnicity, zip code, etc) are obtained, cross-duplicates will be checked manually and eliminated. Cases that cannot be determined to be unduplicated will be marked for further data collection if possible, by contact with parent or case.

Case definition and eligibility

Prevalent cases will be defined as either: a) physician diagnosis of diabetes or b) parent or self-report of physician diagnosis.

Specific information about the geographic area of residence such as street address and zip code, as well as information about tribal affiliation, Native American ethnicity, and residence on-reservation is needed to determine eligibility and residence during the prevalence year.

4.2.2. **Incident Cases**

4.2.2.1.Case finding site – specific approaches

Cases will be identified in the SEARCH-WRDY areas through multiple approaches, which are site and area dependent. These are tabled in **Appendix 2** for each of the areas included. In each area, multiple sources will be used to ensure that as few cases are missed as possible.

In all locations, IRB review and approval of procedures will occur before any case ascertainment begins. IRB approval will be requested from each institution involved in the study, from the Indian Health Service, and from each of the participating Native American tribes in Arizona.

Incident cases will be identified within 0-6 months of onset to obtain typing data. A network of reporting clinics, physicians, diabetes educators, and other sources with access to newly diagnosed patients will be developed and used as a primary source of case identification. Providers will notify the WRDY of new cases as they occur, with periodic mail and telephone reminders. In most situations, hospital discharge records with personal identifiers will represent a secondary source of case finding. Hospitals that treat more than 10 eligible cases per year will be identified through the Colorado Hospital Association, and permission to review the discharge records will be requested from individual hospitals. Other administrative data sources (electronic databases, charts, etc.) and diabetes educators lists will be additional methods used to determine the completeness of ascertainment on an annual basis Vital record searches will be conducted every 2 years.

Case definition and eligibility

Incident cases will be defined as either: a) physician diagnosis of diabetes or b) parent or self-report of physician diagnosis.

Specific information about the geographic area of residence such as street address and zip code, as well as information about tribal affiliation, Native American ethnicity, and residence on-reservation is needed to determine eligibility and residence during the incidence year

4.3. CASE VALIDATION

4.3.1. **Site - specific methods**

The methods to be used by the Colorado – WRDY site are outlined in Appendices 1 and 2 for each source of cases. In addition, death certificate searches will be conducted, once for prevalent cases, and every 2 years for incident cases.

Permission to enroll in the study will only be requested for validated cases (definite cases). Further permission will be requested from participants enrolled for each method of data collection that will be used in the study: in-person visits, interviews, chart reviews, genetic analyses. The individual will be offered the possibility to participate in all or just in selected parts of the data collection process.

4.4. COMPLETENESS OF CASE ASCERTAINMENT

4.4.1. **Prevalent cases**

Capture-recapture methods will be used to calculate the completeness of case ascertainment. The best statistical methods will be used, incorporating multiple ascertainment sources, with adjustment for non-independence of data sources.

Data elements required for calculation of capture-recapture estimates:

a) Source of case record
b) Date of inclusion on data source
c) Record numbers to remove duplicates from same data source

Extensive case identification from primary care practice survey will be used to estimate the accuracy of case ascertainment and the capture-recapture estimates.

4.4.2. **Incident cases**

Capture-recapture methods will be used for incident cases as they were for prevalent cases. The primary source will be provider reported cases, and the secondary source will be hospital discharge records. Additional sources, such as diabetes educator's lists may also be used as a secondary source.

At 24 - month intervals medical databases will be queried for cases that were not reported by the network of providers during the onset period to increase completeness of case ascertainment. This will be done using the same methods as for prevalent cases

The primary care practice survey will also inform incident case identification.

Death certificate searches will be conducted every 2 years.

APPENDIX 1
Sources of prevalent cases SEARCH-WRDY

Colorado counties: Denver, Adams, Arapahoe, Douglas, Jefferson, Boulder. For capture-recapture estimates, each unduplicated case will record all the sources in the six counties where it was identified.

Source	**Type**	**Record system**	**Case finding**	**Validation**
Barbara Davis Center (BDC) for Childhood Diabetes	Pediatric Endocrinology	Computerized case records; includes Children's Hospital cases; many of KP cases up to age ~ 16; Denver Health cases	Search of clinical computerized database (excluding codes for "rule out" diabetes; sibling); ICD codes not used in database	Review of all possible cases by responsible BDC provider, using name, date of birth, and computerized record contents (visit content, current treatment, etc.); record review in selected cases.
Kaiser Permanente	HMO	Computerized diabetes registry based on validated (adult) algorithm	Diabetes registry using computer algorithm: [(Pharmacy: Hedis medications + Chemstrips minus glucagon prescriptions) plus (Inpatient and outpatient codes: ICD 250.XX) plus (Lab: none)]	Presence in BDC database or chart review KP validation results: Sens=93.3%, Spec=100%; Accuracy= 99.5%; PPV+=100%; PPV- = 99.5%
Denver Health	HMO/ Community Health Center	Computerized diabetes registry; not well studied	Diabetes registry using computer algorithm: ICD codes 250.XX. Exclude: gestational diabetes (648.8); hyperglycemia NOS (790.6),neonatal diabetes mellitus(775.1), nonclinical diabetes (790.2)	Presence in BDC database or Denver Health chart review
Pediatric endocrine practice:	Private practice	Chart	Chart review	Simultaneous chart review

Source	Type	Record system	Case finding	Validation
Bloch/Nayak				
Community Health Centers	Federally funded community health center for primary care	Preliminary diabetes registry based on Diabetes Electronic Management System (DEMS); not well studied	Diabetes registry with chart augmentation	Presence in BDC database or chart review
Denver School-based clinics	School-based health clinics	Chart	Chart review	Presence in BDC database or chart review
College health systems U of Colorado Univ of Denver Regis Univ	Clinic	Chart	Chart review	Presence in BDC database or chart review
Primary care practices Sampled from Colorado provider list by type of practice and geography	Primary care	Mixed manual and computerized	Initial letter and telephone survey seeking any cases	Presence in BDC database or chart review
Colorado Hospital Association	Hospitals in Colorado $\geq$ 50 beds; restricted to geographic area	Computerized hospital discharge records;	Identifiers available from individual hospitals; ICD code 250.xx	Chart review

Mesa County (Grand Junction area) For capture-recapture estimates, each unduplicated case will record all the sources in the county and in the BDC database where it was identified.

Source	Type	Record system	Case finding	Validation
Community Hospitals: St Mary's; Community Hospital	Hospital	ICD coded discharges	Discharge database using computer algorithm: ICD codes 250.XX; 362.0X Exclude: gestational diabetes (648.8); hyperglycemia NOS (790.6), neonatal diabetes mellitus(775.1), nonclinical diabetes (790.2)	Chart review
Primary Care practices No. unknown at present	Medical practice	Mixed manual and computerized registry of diabetes	Initial letter and telephone survey seeking any cases; detailed review in practices that see persons with diabetes Mixed chart and registry	Chart review
Diabetes educators	Clinician referral	Case records	Chart review	Parent or self report

Native American Sites

NAVAJO NATION

Source	Type	Record system	Case finding	Validation
Indian Health Service data base	Ambulatory care and hospitals	Computerized hospital and ambulatory record system; pharmacy in some areas	Data base ICD code 250.xx 93% sensitive in Phoenix area	Chart review

GILA RIVER - PIMA INDIANS

Source	Type	Record system	Case finding	Validation
Indian Health Service data base	Ambulatory care and hospital	Computerized hospital and ambulatory record system; pharmacy in some areas	ICD code 250.xx	Chart review
NIH study	Research study	Research data base	Research records	Chart review

WHITE MOUNTAIN AND SAN CARLOS APACHE

Source	Type	Record system	Case finding	Validation
Indian Health Service data base	Ambulatory care and hospitals	Computerized hospital and ambulatory record system; pharmacy in some areas	Data base ICD code 250.xx 93% sensitive in Phoenix area	Chart review

APPENDIX 2
Sources of incident cases SEARCH-WRDY

Colorado: For capture-recapture estimates, each unduplicated case will record all the sources in the counties where it was identified.

Source	**Type**	**Record system**	**Case finding**	**Validation**
Barbara Davis Center (BDC) for Childhood Diabetes	Pediatric Endocrinology	Computerized case records; includes Children's Hospital cases; many of KP cases up to age ~ 16; Denver Health cases	Rapid reporting network	Review of all possible cases by responsible BDC provider, using name, date of birth, and computerized record contents (visit content, current treatment, etc.); record review in selected cases.
Kaiser Permanente	HMO	Computerized diabetes registry based on validated (adult) algorithm	Rapid reporting network	Presence in BDC database or chart review at KP KP validation results: Sens=93.3%, Spec=100%; Accuracy= 99.5%; PPV+=100%; PPV- = 99.5%
Denver Health	HMO/ Community Health Center	Computerized diabetes registry; not well studied	Rapid reporting network	Presence in BDC database or Denver Health chart review
Pediatric endocrine practice: Bloch/Nayak	Private practice	Chart	Rapid reporting network	Simultaneous chart review
Community Health Centers	Federally funded community health center for primary care	Preliminary diabetes registry based on Diabetes Electronic Management System (DEMS); not well studied	Rapid reporting network	Chart review
Denver School-based clinics	School-based health clinics	Chart	Rapid reporting network	Chart review
College health	Clinic	Chart	Rapid reporting network	Chart review

Source	Type	Record system	Case finding	Validation
systems U of Colorado Univ of Denver Regis Univ				
Primary care practices Sampled from Colorado provider list by type of practice and geography	Primary care	Mixed manual and computerized	Rapid reporting network	Chart review
Diabetes educators	Clinician referral	Case records	Rapid reporting network	Parent/ self report
Colorado Hospital Association	Hospitals in Colorado $\geq$ 10 cases per year	Computerized hospital discharge records;	Identifiers available from individual hospitals ICD code 250.xx	Chart review

Native American Sites

(Navajo Nation, Apache Tribes, Colorado River Indian Tribes, Salt River Pima Indians, Tohono O'odham, Fort Yuma Reservation)

Source	Type	Record system	Case finding	Validation
Indian Health Service data base	Ambulatory care and hospitals	Computerized hospital and ambulatory record system; pharmacy in some areas	Rapid reporting network	Chart review or parent/self report

GILA RIVER - PIMA INDIANS

Source	Type	Record system	Case finding	Validation
Indian Health Service data base	Ambulatory care and hospital	Computerized hospital and ambulatory record system; pharmacy in some areas	Rapid reporting network	Chart review or parent/self report
NIH study	Research study	Research data base	Research records	Chart review or parent/self report

4. Methods: Case Ascertainment - Hawaii

GOAL

To ascertain and validate all unique (non-duplicated) cases of diabetes in youth aged 0-19 years in Hawaii. This will allow estimation of prevalence and incidence rates by age, gender, and ethnicity.

4.1. DENOMINATOR ESTIMATION

4.1.1. **Site specific approaches**

The denominator for the Hawaii SEARCH site is the combined, non-duplicated membership of three large health care plans, which collectively include approximately 90% of the state's population. These organizations specifically include:

Hawaii Medical Service Association (HMSA) – Hawaii's Blue Cross/Blue Shield carrier, membership of approximately 640,000 individuals. SEARCH Project Co-Investigator: Richard Chung, M.D.

Kaiser Permanente Hawaii – Approximately 210,000 members. Search Project Co-Investigator: Teresa Hillier, M.D.

Hawaii State Department of Human Services, Med-QUEST Division – Includes approximately 130,000 medicaid-eligible individuals, as well as other traditionally uninsured individuals. SEARCH Project Co-Investigator: Lynette Honbo, M.D.

Total unduplicated plan membership for ages 0-19 based on 1997 data was 300,786, with 48% in the 0-9 age group and 52% in the 10-19 age group. We assume approximately equal distribution for all race/ethnic groups.

Race/ethnicity data are not available from these health plans. To estimate the proportions of each category agreed upon for the SEARCH project (Caucasian, African-American, Hispanic, Asian, Pacific Islander, and Native American), we applied proportions based on the 2000 Census data for Hawaii. For the actual study time period, membership data from the health plans will either be geocoded to estimate race/ethnicity proportions and/or a survey of a random sample of members will be conducted to collect race/ethnicity information.

The use of health plan membership as the denominator for our site offers distinct advantages in terms of enhanced completeness of ascertainment. In addition, because these plans include a large percentage of the state's population, including state-wide geographic membership including urban and rural, private and publicly insured members, we anticipate that our findings will be generalizeable to the state of Hawaii as a whole.

Some limitations to this approach include the exclusion of uninsured cases and those insured by a number of smaller health insurance plans as well as the challenge of unduplicating the combined membership of multiple health plans in order to express the study denominator as a proportion of the state's census. One plan, affiliated with a women's and children's hospital, may be particularly valuable. It is likely that children with diabetes covered by this health plan will be seen by Dr. Sorrel Waxman, a Co-Investigators, affiliated with this hospital. The feasibility of including this health plan will be determined.

Virtually all children in Hawaii have access to health insurance although it should be noted that, at any given point in time, some uninsured children may be missed by this approach. Some forms of insurance require application and some families may be required to pay out of pocket premiums for coverage. Children may be uninsured for lack of an application or a reluctance or inability to pay even low premiums. We anticipate that the severity of diabetes symptoms, particularly in younger patients, will necessitate health care that will initiate the process of acquiring health insurance.

Lastly, only crude estimates currently exist regarding duplication across health plan members throughout the state. Arriving at more accurate estimations of dual coverage will be necessary to accurately describe incidence and prevalence. This will be a challenge for the study team to address.

In conclusion, we believe the advantages of this approach in terms of confidence in completeness of case ascertainment, generalizeability of results, and the availability of relevant data considerably outweigh the challenges this approach may impose.

4.1.2. **Denominators for prevalence**

For prevalence case ascertainment, the denominator includes individuals enrolled in any of the three partnering health care plans and residing on the island of Oahu during the year 2001 (Oahu residents comprise approximately 80% of the state's population).

	Caucasian	African American	Hispanic	Asian	Pacific Islander	Native American	Total
0 thru 9	26295	3310	13733	50754	20914	319	115325
10-19	28486	3585	14877	54984	22657	346	124935
	54781	6895	28610	105738	43571	665	240260

4.1.3. **Denominators for incidence**

For incident case ascertainment, the denominator will include individuals enrolled in any of these three health care plans throughout the entire state of Hawaii for the years 2002, 2003 and 2004.

	Caucasian	African American	Hispanic	Asian	Pacific Islander	Native American	Total
0 thru 9	32869	4137	17166	63443	26143	399	144157
10-19	35608	4482	18596	68730	28321	433	156170
	68477	8619	35762	132173	54464	832	300327

4.2. CASE ASCERTAINMENT

4.2.1. **Prevalent Cases**

4.2.1.1. Case finding site-specific approaches

Variation in data sources available from each of the three health plans comprising the Hawaii study population necessitates different approaches to initial case identification. In general, the strategy for initial case identification employed with each data source is inclusive and will potentially result in the identification of cases that upon verification will be found to be false positive cases. However, the primary objective at this stage is to maximize sensitivity, at the unavoidable expense of compromising specificity.

Using plan-specific case identification criteria, insurance claims and encounter data will be requested from each of the three plans to include complete data through the end of the year 2001.

Data sources

The table below summarizes the characteristics of the data available from each of these plans relevant to the task of diabetes case identification. Case specific identifying information such as name, date of birth, and address are available from all health plans.

Data Available for SEARCH Project

	HMSA	Kaiser	Med-QUEST
Inpatient ICD-9 and CPT codes	✔	✔	✔
Outpatient ICD-9 and CPT codes	✔		✔
Pharmacy	✔	✔	✔
Lab tests ordered	✔	✔	✔
Lab test results		✔	Kaiser only
Utilization data	✔	✔	✔

Identification of duplicate cases

Given the particular data sources we will use for this project, the identification and removal of duplicate cases must be performed for both identified cases

(numerator) and for membership data (denominator). In addition, it is possible that duplicate cases may exist within individual data sources. While the specific identifiers that will be available to us for the purposes of duplicate removal prior to case validation are subject to IRB approval, we anticipate receiving name, gender, date of birth, address (with zip code) and inpatient discharge dates for all cases identified initially through data selection criteria. Since there are likely to be approximately 500 cases, computerized matching on these variables followed by visual checking is expected to be sufficient to identify duplicate cases in numerator data. Questionable cases within the same health plan source data will be referred back to the health plan for verification. Questionable cases found in two or more health plan data sources will be referred back to the health plan to check membership data for dual coverage. Previous work with similar data has revealed very few individuals receiving care in more than one plan in a given year.

The unduplication of plan membership data (denominator) will pose more challenges. It is unlikely that the health care plans will share complete listings of members with identifying information. Shared information is subject to IRB approval. In past studies we received gender, date of birth, and zip code for insurance plan members finding an overlap in membership of less than 3%. We will request these data elements again, adding as many characters of last and first names as the health plans and IRBs will permit. An automated matching process for membership data will be used due to the large volume of cases. Questionable duplicates within health plan datasets will be referred back to the plan for verification. A special process will be developed with health plan collaborators to resolve questionable duplicates identified in more than one dataset that will involve communication between the plans.

Case definition and eligibility

Cases that are between the ages of 0 and 19.999 during the selected index year (2001) will be eligible for inclusion in the study. Geographic eligibility for the Hawaii study center for prevalent cases will be limited to members of the HMSA, Kaiser Permanente and Med-QUEST health plans who reside on the island of Oahu (Honolulu County). The population of Honolulu County includes approximately 80% of the population of the entire state. All data sources to be used for initial case identification include zip codes in their membership files and Oahu residents can be readily identified on the basis of zip code.

a) Case Definition 1: HMSA Data

Designed primarily for billing purposes, this data source is typical of insurance claims datasets with considerable administrative information and little clinical information. Specific algorithms have been developed for identification of diabetic individuals using similar and sensitive data. However, the relative accuracy of these methods for identifying children with diabetes is unknown. Given the potential for misdiagnosis of hyperglycemic episodes in children we

anticipate less specificity of this method in the identification of children. Anecdotal evidence suggests a reluctance among Hawaii practitioners to utilize oral hypoglycemic agents in children however, which may result in fewer false positive cases based on this criteria in Hawaii than in other sites.

The specific criteria for initial case identification from this source include any one of the following:

- At least one prescription for insulin or oral anti-diabetic agent included in HEDIS list for the identification of persons with diabetes during the index year.
- A principal or secondary inpatient discharge ICD-9-CM diagnosis of diabetes (250.xx) during the index year. Diagnosis code 648.0x for gestational diabetes will be excluded.
- In outpatient claims, one visit with a diagnosis of diabetes (250.xx) during index year. Diagnosis code 648.0x for gestational diabetes will be excluded
- From laboratory claims or utilization files, at least two glycohemoglobin or fructosamine tests done on separate dates during the index year (CPT-4 codes 83036 or 82985).

b) Case Definition 2: Kaiser Permanente Hawaii Data

Kaiser Permanente Hawaii maintains a registry of patients with diabetes, similar diabetes registries are in use in other Kaiser regions. Eligible patients listed in this registry during the study index year will be identified as initial cases. Inclusion in this registry is based on the identification of individuals with diabetes in other databases maintained by the health plan, including pharmacy records, lab results and inpatient discharge diagnosis records. The Diabetes Registry is updated quarterly and checked against a current membership file. Cases are included in the registry once they have met any one of the criteria listed below, and remain on the registry as long as they are Kaiser Permanente members.

- An inpatient discharge ICD-9-CM diagnosis of diabetes (250.xx) during the index year. Diagnosis code 648.0x for gestational diabetes will be excluded.
- A glycohemoglobin test result >= 7.
- The dispensing of an antidiabetic drug (GPI code 27xxxx).

c) Case Definition 3: Med-QUEST Data

The Med-QUEST Division of the Hawaii State Department of Human Services is not a direct provider of patient care but provides for services through contracts with six health care plans, including HMSA and Kaiser Permanente Hawaii. The Med-QUEST Division requires that all contracted plans submit a standard dataset reporting all services provided to patients insured by Med-QUEST. For purposes of identifying patients with diabetes, the MED-QUEST dataset includes all of the same data elements included in the criteria listed above for HMSA, with no

additional criteria that would be useful for case identification. For Med-QUEST patients electing to receive care by Kaiser Permanente, additional data will be available since these patients having diabetes would also be listed in the Kaiser Permanente Diabetes Registry. Therefore, the criteria for case identification for all Med-QUEST patients would include any one of the following:

At least one prescription for insulin or oral anti-diabetic agent included in HEDIS list for the identification of persons with diabetes during the index year.

- A principal or secondary inpatient discharge ICD-9-CM diagnosis of diabetes (250.xx) during the index year. Diagnosis code 648.0x for gestational diabetes will be excluded.
- In outpatient claims, at least two visits on separate dates with a diagnosis of diabetes (250.xx) during the index year. Diagnosis code 648.0x for gestational diabetes will be excluded.
- From laboratory claims or utilization files, at least two glycohemoglobin or fructosamine tests done on separate dates during the index year (CPT-4 codes 83036 or 82985).
- Inclusion in the Kaiser Permanente Diabetes Registry during the index year.

4.2.2. **Incident Cases**

4.2.2.1. Case finding site-specific approaches

The need to rapidly identify incident cases, ideally within 0-3 months of onset for the accuracy of case typing, necessitates a different approach to case finding than the method proposed for prevalent cases. The lag time associated with administrative data sets available for use in Hawaii is generally about six months, too long a period of elapsed time from diagnosis to enable accurate typing of cases.

A network of clinics, physicians, and diabetes educators is being developed, to rapidly identify incident cases during 2002 - 2003. In general, reporting of identifying information about incident cases to the SEARCH study team requires development and IRB approval of appropriate consent procedures enabling physicians to obtain consent from parents and patients for release of this information for study purposes. The goal for this network is to include all physicians in the state diagnosing children and youth with diabetes at onset. To achieve this goal, a core group of study investigators and practicing physicians has been assembled to facilitate the inclusion and participation of physicians throughout the state in this reporting network.

This core group currently includes:

Beatrice Rodriguez, M.D., Ph.D. – SEARCH Principal Investigator
Teresa Hillier, M.D. – SEARCH Co-Investigator, Kaiser Permanente Hawaii
Beth Waitzfelder, M.A. – SEARCH Co-Investigator

J. David Curb, M.D., MPH – SEARCH Co-Investigator
Richard Chung, M.D. – SEARCH Co-Investigator, HMSA
Lynette Honbo, M.D. – SEARCH Co-Investigator, Med-QUEST
Wilfred Y. Fujimoto, M.D. – SEARCH Co-Investigator
Sorrel Waxman, M.D. – Search Consultant, Kapiolani Medical Center
Greg Uramoto, M.D. – SEARCH Consultant, Kuakini Medical Center
Joseph Humphry, M.D. – SEARCH Consultant, HMSA

Co-Investigator Teresa Hillier, M.D., affiliated with Kaiser Permanente Hawaii and Kaiser Permanent Northwest, will play a major role in the development of a rapid reporting network within Kaiser Hawaii. We will actively enlist the support and participation of endocrinologists, and other physicians treating children and youth at onset of diabetes, within Kaiser for the SEARCH Project. Dr. Hillier will assist in identifying standard referral policies within this health system that would result in the diagnosis of new cases by a particular group of Kaiser physicians. In addition, we will utilize data between 1/1/99 to 6/30/01 from the Kaiser Diabetes Registry to identify physicians who treated children and youth with diabetes for inclusion in the network.

Dr. Greg Uramoto of the Kuakini Medical Center is the only pediatric endocrinologist in Hawaii and a consultant on the SEARCH Project. Dr. Uramoto will play an important role in the network core contributing newly diagnosed cases from his practice, pending IRB approval of appropriate consent procedures.

The Kapiolani Medical Center for Women and Children, a specialty hospital and clinic in Honolulu, provides inpatient and outpatient services to women and children. The PHRI has a history of partnership in collaborative studies with physicians and one or more representatives from this medical center, including Co-Investigator Dr. Sorrel Waxman. They will be included in the network core group to facilitate physician reporting at Kapiolani.

We will utilize administrative data from HMSA and the Med-QUEST health plans to identify additional physicians who are likely to initially diagnose children and youth with diabetes. SEARCH Co-Investigators Drs. Lynette Honbo of the Med-QUEST Program, and Richard Chung of HMSA, and consultant Dr. Joseph Humphry of HMSA, we assist in identifying physicians treating cases of children with diabetes state-wide, for inclusion in the broader reporting network.

An early task of the core network will be to identify ways to encourage the state-wide physician participation in reporting incident cases. As part of the ascertainment of typology, the provision of antibody testing is one incentive that will encourage participation. Other possible incentives and methods will be considered to encourage broad project participation. This group will also assist in the development of a standardized form for physicians to report cases and reporting processes (i.e., mail, phone, electronic reporting) to facilitate the process.

Case definition and eligibility

Cases that are between the ages of 0 and 19.999 during the selected index year (2002) with a clinical diagnosis between 1/1/2002 – 12/31/04 are eligible for study inclusion. Geographic eligibility for the Hawaii study center for incident cases will include members of the HMSA, Kaiser Permanente and Med-QUEST health plans who reside in the state of Hawaii.

4.3. CASE VALIDATION

4.3.1. **Site-specific methods**

Most, if not all, incident cases will be reported by physicians and therefore meet the study physician diagnosis validation criteria. However, medical record reviews will be performed for incident cases (with patient/parent consent). This review provides an opportunity for case validation through confirmation of diagnosis in the medical record.

We will use a multi-step process to validate prevalent cases in conjunction with our collaborating health plans.

Physician letters - Based on lists of initially identified cases, letters will be sent to individual physicians who treated identified patients during the index year. (Primary care physicians or the physician who the patient has seen most often will be used whenever possible). Physicians will be asked to verify the diagnosis of diabetes for each patient listed, and indicate the diabetes type.

Patient/parent letters - At the same time physicians are contacted, letters will be sent to identified patients or parents explaining the study. This letter will include a reply card asking for verification of physician diagnosis of diabetes and a telephone contact number for an interview. Patients/parents will be told that they will be called requesting an interview unless they specifically refuse (pending IRB approval).

This strategy of case validation will maximize the opportunity for case validation (through physician confirmation, chart review and/or self-report of physician diagnosis). In addition, this approach will facilitate the estimation of positive predictive value of each method of case identification and the development of efficient and accurate algorithms. Each initial indicator of diagnosis (inpatient and outpatient diagnosis codes, pharmaceutical data, laboratory data, self-report and primary physician confirmation) will be assessed individually and in combination for positive predictive value.

4.3.2. **Completeness of case ascertainment**

4.3.2.1. Prevalent cases

A distinct advantage of using health plan membership and a broad method of initial case identification as the study denominator, versus census data, is greater certainty of

complete ascertainment. However, a possibility exits that cases may be missed. A capture-recapture method will be used to verify the completeness of case ascertainment.

The primary method will be to identify all of the physicians who have treated validated cases. All physicians treating 3 or more validated cases will be sent a letter asking them to compare lists of validated study cases to their cases of eligible patients (within age range, diagnosed with diabetes and residing on Oahu). They will be requested to contact this group if cases are missed. We anticipate a small group of physicians seeing large numbers of children/youth with diabetes and certain offices will be better able to identify cases than others. Focus will be on practices with relatively larger numbers of cases and better information systems. We will request the health plan of missed cases as an indication of other health plans to be considered as supplemental data sources for inclusion in initial case finding.

A second method will be to utilize the Hawaii Health Information Corporation, which maintains a statewide list of all hospital discharges in the state. We will request a listing of all eligible patients with date of birth, date of discharge during index year, gender, health plan and zip code (names are not available). This list will be compared to initially identified cases from health plan data sources assessing whether cases have been missed. Again, this information will serve as an indication of other health plans to consider as supplemental data sources for inclusion in initial case finding.

In addition, we will contact diabetes educators and school nurses to determine if this method yields new cases meeting study criteria.

4.3.2.2. Incident cases

Administrative claims data and Kaiser Diabetes Registry data for the index year (2002) and the previous year (2001) will be used to ascertain completeness of network reporting. Theoretically, incident cases should appear in the index year and not in the previous year. All such cases will be compared to those obtained through network reporting. In conjunction with health plan Co-Investigators, treating physicians of patients appearing only in the index year of administrative data and not appearing on the network reporting list, will be contacted for confirmation as an incident case. It is anticipated these cases may include individuals who recently moved to Hawaii and prevalent cases having no health care utilization during the year prior to the index year. This process will enable estimation of the accuracy of using administrative data alone for the identification of incident cases.

4. Methods: Case Ascertainment - Children's Hospital Medical Center, Cincinnati, Ohio

Cincinnati Children's Hospital Medical Center (CCCHMC) is the only pediatric healthcare facility serving southwest Ohio, northern Kentucky, and southwest Indiana. As a result, children and adolescents with complex medical problems are referred almost exclusively to CCCHMC. The majority of patients served by CCCHMC are residents of one of eight counties surrounding the hospital. These eight counties make up the primary service area for the hospital.

GOAL

The goal in Cincinnati is to ascertain and validate all unique (non-duplicated) cases of diabetes in youth less than 20 years of age in the 8-county primary service area for CCCHMC. This will allow estimation of prevalence and incidence rates by age, gender, and race/ethnicity.

4.1. DENOMINATOR DETERMINATION

Prevalence of diabetes in youth less than 20 years of age was estimated for the year 2001 in the 8-county primary service area for CCCHMC. July 2001 age and gender specific projections derived from Census 2000 data for these 8 counties were used to determine the prevalence denominator. Since these 8 counties do not encompass any military installations, it was not necessary to adjust projections to compensate for military personnel in the denominator. Race data for the following racial/ethnic groups was based on the race-bridging modeling approach developed by the National Center for Health Statistics: Non-Hispanic White, African-American, Hispanic, Asian/Pacific Islander, and Native American/Alaska Native. In addition, zip code level geocoding was used to assign race to prevalent cases for whom race data was unknown (6).

4.1.1. Site specific approaches

The geographic area to be used as the denominator for the calculation of prevalence and incidence will include the 8-county primary service area for CCCHMC. These counties include:

Ohio – Butler, Clermont, Hamilton, and Warren Counties
Kentucky – Boone, Campbell, and Kenton Counties
Indiana – Dearborn County

4.1.2. Denominators for prevalence

The following tables summarize projections from Census 2000 data on July 1, 2001 for the 8-county primary service area of CCHMC. A race-bridging model and zip code level geocoding were used to arrive at the race/ethnicity specific totals.

Characteristic	Population Denominators (%)
Total population	549,356
Age group	
0 – 4 years	132,995
5 – 9 years	135,708
10 – 14 years	143,334
15 – 19 years	137,319

Gender	
Male	280,744
Female	268,612
Race/ethnicity	
Non-Hispanic White	445,009
African-American	86,296
Hispanic	8,204
Asian/Pacific Islander	8,659
American Indian	1,188

4.1.3. Denominators for incidence

Incidence of diabetes in youth less than 20 years of age will be estimated in the years 2002, 2003, and 2004 in the same 8-county primary service area used for prevalence calculations. Incidence denominators will be determined using projections for the index year based on Census 2000 data. Race/Ethnicity will be assigned using the same bridging and geocoding methods.

4.2. CASE ASCERTAINMENT

4.2.1. Prevalent Cases

4.2.1.1. Case finding site-specific approaches

Primary Source for Case Identification

The primary source for identification of prevalent cases was the Diabetes Database, maintained by the Division of Endocrinology at CCCHMC. In 1988 a clinical database of diabetes patients seen at CCCHMC since 1978 was established by review of their medical records. This database continues to be updated on a regular basis.

Patients who live in the 8-county primary service area of CCHMC were identified via their zip codes. All patients who met the eligibility criteria for prevalent cases were contacted to verify that they lived in the 8-county geographic area during the index year. Patients who attended college and lived outside the geographic area during the index year as indicated on IPS were excluded.

The following is a description of the components of the Diabetes Database:
All Diabetes patients both inpatient and outpatient

a) Demographics
medical record number, name, date of birth, gender, race/ethnicity, home address and home phone, and parents' names and work phones

b) Clinical information
type of diabetes, date of onset of diabetes, date of most recent diabetes visit to CCHMC, who provided care at each visit, HgbA1c, goals, severe blood sugar episodes and a description of the episode, whether a blood glucose record was kept, co morbidities, insulin or oral agent prescribed.

c) Physical examination
Date of visit, height, weight, BMI, blood pressure, presence of acanthosis, Tanner stage.

Expanded Sources for Case Identification

Expanded case identification was done to identify subjects who met the eligibility criteria, yet who have never been seen at CCHMC. We have established a network to identify these cases. The following sources yielded the most cases:

a) Endocrinologists:
There are a total of thirty-one endocrinologists who practice in our 8 county primary service area. Eight of these are pediatric endocrinologists and all eight are employed by CCHMC. Their patients are captured by data dumps from the CCHMC Diabetes Database. The other twenty-three endocrinologists are adult-focused representing fourteen practices. All of these practices were contacted. Two indicated that they do not see clients with diabetes; three do not see youth. Of the remaining practices, one indicated they were unable to generate a list, five provided a list, and three declined to participate.

b) Hospitals
After Endocrinologists, hospitals identified the largest number of valid, eligible cases. There are eighteen adult-focused hospitals located within the Cincinnati area. These hospitals include: Bethesda North, Christ, Deaconess, Dearborn County, Fort Hamilton, Good Samaritan, Jewish, McCullough-Hyde Hospital, Mercy Hospital Anderson, Mercy Franciscan Hospital Western Hills, Mercy Franciscan Hospital Mt. Airy, Mercy Hospital Clermont, Mercy Hospital Fairfield, Middletown Regional Hospital, St. Elizabeth, St. Luke Hospital East and West, and University Hospital. In addition, one pediatric hospital, Children's Medical Center in Dayton, OH, provides care for young people in our catchment area. Approval was received from 7 IRB's and 7 Oversight Committees. One IRB Services Agreement was signed. Initially, all hospitals were asked to identify all inpatients and outpatients born after 12/31/1981 who were assigned a diagnostic code of 250.xx and had a visit after January 1, 2000. Sixteen hospitals complied with our request. Two passively refused. One hospital services an older population and after querying their system did not have any cases that met our eligibility requirements. Once approvals were in place, lists were generated

on a regular basis adjusting the visit date to correspond to the date queried on the previous list.

c) Additional Secondary sources included:

Certified Diabetes Educators (CDE's)
Members of the Diabetes Educators of the Cincinnati Area, a local organization for diabetes educators, had agreed to participate in our network for the identification of cases. Their membership consists primarily of registered nurses and dietitians. Following the implementation of HIPAA, several of the educators contacted were reluctant to provide us with names of clients with diabetes. A small number of CDE's working in endocrine or primary care offices were contacted to aid with validation. A majority of the CDE's associated with hospital educational programs did provide the names of young people with diabetes for whom they provided services.

Private and Public Payors
Four major private insurance companies serve the majority of the Cincinnati area population. At the time of our original grant proposal, three of four companies had agreed to assist us in the identification of cases. After HIPAA was implemented, collecting data from these providers became more problematic. Anthem, Humana, United Health Care and Aetna were contacted. Of these payors, Anthem and Aetna provided data.

Four state or federally funded programs serve Cincinnati area clients. All four were contacted. The Bureau for Children with Medical Handicaps (BCMH) required Ohio Department of Health IRB approval. Approval was granted, however, we did not receive the requested information from BCMH. OH Medicare refused to release data. Caresource HMO (a version of Medicaid) did provide a list. Kentucky Medicaid did report cases based on ICD-9 code; however, we were unable to validate "new" cases, because charts were unavailable and provider name was omitted. The Kentucky Commission for Children with Special Health Care Needs was contacted, but reported that they did not provide services for children with diabetes.

City and State Health Departments
The City of Cincinnati Health Department and the Ohio Department of Human Services originally agreed to participate in our network to identify cases. We received IRB approval and the Cincinnati Health Department provided data. Chart reviews were completed to validate "new" cases and collect core information. The Boone County (KY) Health Department Diabetes Coordinator stated she rarely sees children or young adults and had no names to report.

Colleges and Universities
The health centers of the four universities with the largest enrollment in our catchment area were contacted about providing data. All four stated health forms were not a requirement, and therefore, unless students presented with a problem related to their diabetes or were frequent visitors with unrelated conditions and remembered by the staff, identification would be impossible. Miami University did agree to provide names and core data on students with diabetes know to them. The Medical director called each student and obtained individual authorization to release information to us. The head nurse at Northern Kentucky University's Health Center offered to explore the possibility of putting a notice in an on-line student newsletter. The University of Cincinnati agreed to post a flier and to ask students presenting with either a primary or secondary diagnosis of diabetes to complete an IPS.

Other Activities
In addition, we sent a mailing to a sample of primary care physicians (pediatrics, family practice, general practice, and internal medicine) to test the sensitivity of our case-finding methods utilizing our Diabetes Database and our network of partners. We asked this sample of physicians to indicate whether or not they had seen any diabetes patients who meet the eligibility criteria without making a referral to CCHMC or an adult endocrinologist. Since our sampling indicated a number of Family Practitioners treated their own clients with diabetes, we expanded our network and attempted to contact all Family Practitioners. We used the practice or office manager as the initial contact person in each practice.
We also publicized this study by attending diabetes walks and programs geared to school nurses. Fliers were distributed to school nurses.

Pursuing the sources listed under section c) was time consuming and yielded a very small number of "new", valid, eligible cases. Therefore, the decision was made to eliminate these sources from future case ascertainment efforts.

Expanded Sources Case Validation and Registration

In order to protect patient confidentiality, lists provided by network providers included the minimum amount of PHI required to de-duplicate cases and collect core data. Anticipating HIPAA issues, we obtained a waiver of individual authorization from the IRB at CCHMC prior to initiating requests for lists to expedite data collection from providers outside of the hospital. We were successful with most providers in using the provisions of 45 CRF §164.512(i) with regards to the use of one IRB approved waiver for covered entities in multisite projects. One of the hospitals did not have an internal IRB, and therefore required an IRB Services Agreement giving CCHMC's IRB authority for our project at their site.

We compared the information provided by outside providers to our Diabetes Database to identify new cases, as well as duplicates. If a medical record was available on a new case, it was reviewed either by a representative of the outside provider or by a SEARCH Study team member to validate and determine eligibility of the case. In situations where a record was not available such as an insurance provider, the physician of record was asked to validate the case.

Most of our network partners agreed to mail information about this study including an IPS to all newly identified cases. Before returning the completed survey, subjects were asked to check a box on the cover of the survey indicating whether or not they wished to be contacted with additional information on the study. They were contacted only if they indicated a desire to receive more information.

New cases were assigned a unique identification number. A limited amount of data including; date of birth, date of diagnosis, type of diabetes, race, gender, county and zip code was added to the SEARCH database under the ID number. Name was assigned as either Jane or John Doe depending on the gender. If the survey was returned, the subject's name and all contact information were added to the database.

The source(s) of each validated case was recorded, i.e. Diabetes Database within CCHMC, endocrinologist, insurance company, school nurse, etc. This information was then used to determine the capture-recapture estimates for completeness of ascertainment.

The IPS completion rate for sources identified outside of CCHMC was approximately 30%.

4.2.1.2. Identification of duplicate cases

The Diabetes Database was designed to prevent the entry of more than one record for any patient due to the uniqueness of the medical record number. Occasionally, however, a patient is mistakenly assigned more than one medical record number, thereby permitting a duplicate entry in the Diabetes Database. Each month a query is run to identify patients in the SEARCH database who have matching entries for medical record number or date of birth and last name. This method allows two opportunities to identify duplicate records. When duplicate records are identified, these records are reviewed to confirm that they are duplicates. True duplicate records are marked as duplicates in the SEARCH database.

For expanded sources of case identification, duplicates are identified by comparing our Diabetes Database to the lists provided by our network partners as described above. DOB duplication is investigated further to eliminate duplicate cases entered due to spelling errors or name changes or interchange of first and middle names. Duplicates are eliminated before cases are added to the SEARCH database.

4.2.1.3. Case definition and eligibility

Prevalent cases were defined as either: a) physician diagnosis of diabetes or b) parent or self-report of physician diagnosis. Prevalent cases include all cases less than 20 years of age who lived in the 8-county primary service area for CCHMC at anytime during the index year of 2001. College students were counted according to their reported residence location during 2001. Military personnel and institutionalized cases were excluded.

4.2.2. Incident Cases

4.2.2.1. Case finding site-specific approaches

Primary Source for Case Identification

The primary source for identification of incident cases is the Diabetes Database maintained by the Division of Endocrinology at CCHMC. In 1988 a database of diabetes patients seen at CCHMC since 1978 was established by review of their medical records. This database continues to be updated on a regular basis.

The investigators review the patient's medical record to confirm validity and to insure that the subject meets the eligibility criteria for an incident case.

Patients who live in the 8-county primary service area are identified via their zip codes. All patients who meet the eligibility criteria for incident cases are contacted to verify that they live in the 8-county geographic area. Patients who are attending college and live outside the geographic area are excluded.

Expanded Sources for Case Identification

Expanded case identification was done to identify subjects who meet the eligibility criteria, yet who have never been seen at CCHMC. The same network partners established to identify prevalent cases were used to assist us in identifying 2002 and 2003 incident cases: 1) endocrinologists, 2) diabetes educators, 3) insurance companies, 4) hospitals, 5) city and state health departments, and 6) primary care physicians who care young people with diabetes who meet the eligibility criteria without endocrinology referral. Due to low yield from expanded providers, efforts for 2004 were limited to the

most productive: 1) adult endocrinologists, 2) hospitals, 3) hospital based CDE's, and 4) The Cincinnati Health Department.

We return periodically to these network partners to request a list of newly identified cases. In order to protect patient confidentiality, these lists include the minimum amount of PHI required to de-duplicate cases and collect core data. We have obtained a waiver from the IRB at CCHMC to expedite data collection from providers outside of the hospital. We compare the information provided to our Diabetes Database to identify new cases, as well as duplicates. If a medical record is available on a new case, it is reviewed either by a representative of the outside provider or by a SEARCH Study team member to validate and determine eligibility of the case. In situations where a record is not available such as an insurance provider, the physician of record is asked to validate the case. Most of our network partners have agreed to mail information about this study including an IPS to all newly identified cases. Before returning the completed survey, subjects are asked to check a box on the cover of the survey indicating whether or not they wish to be contacted with additional information on the study. They are contacted only if they indicate a desire to receive more information. New cases will be assigned a unique identification number. A limited amount of data to include; date of birth, date of diagnosis, type of diabetes, race, gender, county and zip code will be added to the SEARCH database under the ID number. Name will be assigned as either Jane or John Doe depending on the gender. If the survey is returned, the subjects name and all contact information will be added to the database.

Case definition and eligibility

Incident cases are defined as either: a) physician diagnosis of diabetes or b) parent or self-report of physician diagnosis. Incident cases include all cases less than 20 years of age on 12/31 of the onset years of 2002, 2003, 2004 and who lived in the 8-county primary service area for CCHMC at the time of diagnosis. College students were counted according to their reported residence location at the time of onset. Institutionalized cases and military personnel were excluded.

4.3. CASE VALIDATION

4.3.1. Completeness of case ascertainment

4.3.1.1. Prevalent cases

All visits to the diabetes inpatient unit and the diabetes outpatient treatment center were entered into a clinical diabetes database. Each month using a unique medical record number these diabetes visits were compared to the SEARCH Database to

identify new cases. New cases with a diabetes diagnosis or with the diagnosis omitted are then downloaded from this clinical database to the SEARCH Database. All cases not previously included in the database are marked for further review. Medical records are then reviewed to confirm that the patient indeed has diabetes, to classify the type of diabetes, and to determine eligibility. Confirmed, eligible cases are then registered.

To capture young people seen by other CCHMC departments, an administrative report was requested regularly from the CCHMC billing database. This report included all inpatients and outpatients born after 12/31/1981 who were seen at CCHMC with either a primary or secondary 250.xx ICD-9 code and lived in one of the eligible counties as determined by zip code.

We used our network partners (endocrinologists, diabetes educators, insurance companies, hospitals, and city and state health departments) to maximize the sensitivity of our expanded case-finding outside CCHMC.

The source(s) of each validated case was recorded, i.e. Diabetes Database within CCHMC, endocrinologist, insurance company, school nurse, etc. This information was then be used to determine the capture-recapture estimates for completeness of ascertainment.

In addition, by comparing observed to expected ratios by age group and county and by confirming an increase in prevalence with age, face validity and consistency within the site was evaluated. Rate consistency among sites was reviewed and an explanation of any inconsistencies was pursued to justify disparities.

4.3.1.2. Incident cases

All visits to the diabetes inpatient unit and the diabetes outpatient treatment center are entered into a clinical diabetes database. Using a unique medical record number, these diabetes visits are compared monthly to the SEARCH Database to identify new cases. New cases with a diabetes diagnosis or with the diagnosis omitted are then downloaded from this clinical database to the SEARCH Database. All cases not previously included in the database are marked for further review. Medical records are then reviewed to confirm that the patient indeed has diabetes, to classify the type of diabetes, and to determine eligibility. Valid, eligible cases are then registered.

Additional cases seen at CCHMC but not by the Endocrinology Service are captured by a regularly requested CCHMC administrative report. This report is compared to the SEARCH database and a chart review is performed for all “new” cases to confirm validity and eligibility prior to registration.

Due to the low yield from many of the expanded sources pursued for prevalent, incident 2002, and incident 2003 case finding, we will use only the Diabetes database at CCHMC, the administrative report from CCHMC, Adult Endocrinologists, hospitals, hospital based CDE's, and the Cincinnati Health Department for future incident case finding.

The source(s) of each validated case will be recorded, i.e. Diabetes Database within CCHMC, endocrinologist, insurance company, school nurse, etc. This information will then be used to determine the capture-recapture estimates for completeness of ascertainment.

We will review observed to expected ratios by age group and county as a tool to evaluate face validity and consistency within the site. Consistency among sites will be evaluated and an explanation of any inconsistencies will be pursued to justify disparities.

4. Methodology of Case Ascertainment – South Carolina

SEARCH – South Carolina seeks to document the incidence and prevalence of diabetes among South Carolina children and adolescents. Incident cases will be identified by recording all youth newly diagnosed with diabetes in South Carolina aged 0-19 beginning 1/01/2002. To identify prevalent cases, SEARCH South Carolina will record all youth aged 0-19 with a diagnosis of diabetes in 2001 in the four South Carolina counties of Richland, Lexington, Orangeburg, and Calhoun.

GOAL

To ascertain and validate all unique (non-duplicated) cases of diabetes in youth aged 0-19 years in defined geographic areas in defined periods of time. This will allow estimation of prevalence and incidence rates by age, gender, and ethnicity.

4.1. DENOMINATOR ESTIMATION

4.1.1. Site specific approaches

The 2000 US Census non-institutionalized non-military (NI-NM) resident population from which cases are present in the index year will be used as the primary denominator in sites using geographic-based denominators such as South Carolina. Use of this denominator will most closely align the population at risk for all sites.

Special Populations

College students: Such individuals are counted in the Census in their residence location as of April 1 2000, usually the college/town where they attend school. They will be included in the NI-NM denominators. There are three large research universities (University of South Carolina, Clemson University, and the Medical University of Charleston) and nine teaching colleges and universities within the South Carolina geographic area of interest. South Carolina also has 22 independent and private colleges and universities. Contact with the school(s) health services will be made to determine the estimated number of known cases, and the school's willingness to participate.

Military personnel: Military personnel are counted in the Census for the county in which they currently reside/are based. Initial total population estimates include them, however, as the Census results are further refined, the military members are identified separately. Final denominator estimates will exclude military service members, though they will be included in less refined estimates. There are three large military bases in South Carolina: Fort Jackson Army Base, Shaw Air Force Base, and the US Marine Corps Recruiting Depot - Parris Island. Fort Jackson, located in Richland County, is the largest basic training facility for the army, graduating approximately 40,000 soldiers each year. Shaw Air Force Base,

located in Sumter County, supports approximately 6,500 military and civilian workers and 6,000 family members.

Native American Reservation residents: There are various Native American tribes residing in South Carolina. These include two federally recognized tribes: the Catawba and the Cherokee. The Catawba reservation lies within the South Carolina borders. Other non-federally recognized tribes include: the Lumbee (primarily North Carolina), the Pee Dee, the Chicora, the ChicoraWaccammaw, the Edisto, and the Santee. Census data will be used for identifying the number of Native Americans in general. From previous work with the Catawba, we expect to be able to determine tribal-specific rates for the Catawba Nation by using the Catawba tribal roles for denominator data. Whether the other nations keep accurate tribal roles for tribal specific rates is unclear.

Persons living in group settings: The group quarters population includes all people not living in households. Two general categories of people in group quarters are recognized:

a) The institutionalized population that includes people under formally authorized, supervised care or custody in institutions at the time of enumeration (such as correctional institutions, nursing homes, and juvenile institutions). These will be identified separately and removed from the denominator. b) Non-institutionalized population that includes all people who live in group quarters other than institutions (such as military quarters, and group homes.) These will be removed resulting in the non-institutionalized, non-military population used as the primary denominator for all geographic sites.

Denominator estimation by age, gender, ethnicity

Age categories (0-4, 5-9, 10-14, 15-19) from the 2000 census will be used to calculate rates**.** Gender (M, F) and ethnic categories from the 2000 census will also be used, and ethnic groups will be collapsed into more inclusive groups (e.g. Non-Hispanic White, Hispanic American, African American, Asian, Pacific Islander, Native American) using rules developed by the census.

4.1.2. Denominator for prevalence

Prevalence of diabetes in youth aged 0-19 will be estimated for the year 2001 in each of the geographic areas and populations included in the SEARCH registry project.

In most geographic areas, projections beyond 2000 will not be available for some time. Thus, for the initial prevalence estimate, year 2000 denominator data will be used. Once projections for the year 2001 are available, and population subsets (non-institutional, non-military) are made by the South Carolina Health and Demographics Section, Office of Research and Statistics, State Budget and Control Board, prevalence estimates will be updated.

4.1.2.1.Geographic area and population

SEARCH – SC will seek to identify and register all youth diagnosed with diabetes in the four counties of Richland, Lexington, Orangeburg, and Calhoun of South Carolina who were born between 01/01/1982 and 12/31/2001. At the time of the 2000 census, 169,880 youth under the age of 20 were living in this area. 46% were non-White, and 54% were White. The population distribution by race is provided in Appendix 1. Richland and Lexington counties are primarily urban and account for 81% of the youth in the four county region. Orangeburg and Calhoun counties are rural communities.

4.1.3. Denominator for incidence

Incidence of diabetes in youth aged 0-19 years will be estimated in the years 2002, 2003, and 2004 in all 46 counties in South Carolina.

For the geographic denominators, South Carolina will use projections of population changes that will occur after the 2000 census for years 2002 and beyond provided by the South Carolina Health and Demographics Section, Office of Research and Statistics, State Budget and Control Board. If population projections cannot be made using age-, gender-, and ethnic-specific subsets, these will be estimated by applying proportions from the 2000 census data to the total population projections.

4.1.3.1.Geographic area and population

SEARCH – SC will seek to identify and register all youth diagnosed with diabetes in all 46 counties of South Carolina whose date of birth is on or after 01/01/83 starting in the year 2002. Study participants for incident cases in 2002 will encompass all children and adolescents who were diagnosed with diabetes $\geq$ January 1, 2002 regardless of type, who were born between 1/1/1983 and 12/31/2002, who are aged 0 – 19.999 in the index year, and who are residents of the state of South Carolina. The birth date eligibility will be advanced one year for each subsequent year through the end of the study. See Appendix 2 for South Carolina statewide estimates.

4.2. CASE ASCERTAINMENT

4.2.1. Prevalent cases

4.2.1.1.Case finding site specific approaches

The goals of case finding are to identify all unique (non-duplicated) prevalent cases, and validate that every unique case is a true case in the eligible population of the four county areas of South Carolina (Richland, Lexington, Orangeburg, and Calhoun). Multiple sources will be used to identify prevalent cases.

Data sources

a) Pediatric endocrinologists: Drs. Howard Heinze and David Schwartz have the main pediatric endocrinology practice serving the midlands 13 county area which includes Richland, Lexington, Orangeburg and Calhoun counties. In addition, Dr. Steven Willi, a pediatric endocrinologist in Charleston, also sees a substantial number of children with diabetes during his weekly clinic in Orangeburg, South Carolina. All names will be personally reviewed and validated by one of the physicians to confirm diabetes status. For prevalent cases, a one-time thorough assessment of the patient databases will be conducted.

b) Adult endocrinologists: There are 13 adult endocrinologists in the Richland/Lexington county area. There is one endocrinologist in Orangeburg county and none in Calhoun county. For prevalent cases, a one-time thorough assessment of the patient databases will be conducted at each practice.

Table 3. Endocrinologists in the four county area of South Carolina

Practice	Institutional Affiliation	County
Howard Heinze	University of South Carolina Pediatric Endocrinologist	Richland
David Schwartz	University of South Carolina Pediatric Endocrinologist	Richland
Tu Lin	University of South Carolina endocrinology	Richland
Kay McFarland	University of South Carolina endocrinology	Richland
Robby Brennan	Laurel Endocrine Assoc.	Richland
Rita Jain	Laurel Endocrine Assoc.	Richland
Eric Horst	Laurel Endocrine Assoc.	Richland
Mary Lynn Kemick	Laurel Endocrine Assoc.	Richland
Leo Walker	None	Richland
Howard Nankin	None	Richland
Jura Osterman	University of South Carolina	Richland
Ronald Johnson	None	Richland
Edward Moore	None	Richland
Vagar Ahmad	Richland Memorial Hospital	Richland
Evelyn Runer	University of South Carolina	Richland
Frank Kohler	None	Orangeburg

c) Hospitals: The five hospitals serving Richland, Lexington, Orangeburg and Calhoun counties are Palmetto Richland, Palmetto Baptist, Providence, Lexington Medical Center, and The Regional Medical Center of Orangeburg. There is no hospital in Calhoun County. All five hospitals have in-patient facilities, emergency room facilities, and affiliated outpatient clinics.

All hospitals serving the four county area will be asked to participate in identifying patients who meet the criteria. Billing data will be used to identify any child/adolescent who had a diabetes related ICD-9 code recorded during a hospital visit, regardless of the purpose of visit. Billing data will represent all outpatient, inpatient and emergency room visits. We will request potential subject names, names of parents, all available contact information (phone numbers, address), county of residence, race, gender, date of birth, visit ID, patient ID, all ICD-9 codes recorded at each visit, admitting physician, consulting physician, and payor sources (all sources including Champus and Tricare.) This data will be reviewed to eliminate children who do not meet the eligibility criteria.

Table 4. Hospitals serving the four county area of South Carolina

Data Source	City	County	Available Services		
			In-Patient	Out -Patient	Emergency Room
Palmetto Richland Hospital	Columbia	Richland	X	X	X
Palmetto Baptist Hospital	Columbia	Richland	X	X	X
Providence Hospital	Columbia	Richland	X	X	X
Lexington Medical Center	West Columbia	Lexington	X	X	X
The Regional Medical Center of Orangeburg (TRMC)	Orangeburg	Orangeburg	X	X	X

d) Federally funded primary health care clinics: These include Eau Claire Pediatric Clinic, a non-profit pediatric clinic located in Lexington County, and Family and Health Centers, Inc, a non-profit organization located in Orangeburg County which includes 7 satellite clinics located in Orangeburg and Calhoun counties.

e) Outpatient clinics (hospital affiliated): There are three hospital-affiliated outpatient clinics in the four county area.

Table 5. Outpatient clinics (hospital affiliated) serving the four county area of South Carolina

Data Source	County
University of South Carolina Pediatric Clinic	Richland
University of South Carolina Family Practice Center	Richland
The Regional Medical Center of Orangeburg	Orangeburg

Other sources that may be utilized include:

a) Health services from the University of South Carolina, South Carolina State University, Columbia College, Benedict College, Allen University and Claflin University.

b) Certified Diabetic Educators: This approach has not been piloted but yields the potential of assessing completeness particularly in those children that are well covered in the health care system. SEARCH SC has established a close working relationship with the Diabetes Initiative of South Carolina (DSC), a group designed to develop and implement a comprehensive statewide plan of community outreach programs, health professional education, and diabetes surveillance.

c) There are several larger pediatric practices not addressed above that care for children with diabetes that we intend to query for lists of diabetic patients, including Drs. John Khoury and Debbie Greenhouse's practices.

Identification of duplicate cases

Given multiple record sources, duplicate cases must be removed. In addition, incident case reports must be compared to prevalent reports to determine if the case is actually incident. This involves establishing record matching procedures. The more demographic data that are available, the better the likelihood that duplicates will be recognized.

The following items are to be considered as possible matching variables for SEARCH-SC:

a) First name

b) Last name

c) Date of birth

In South Carolina, we feel confident that we will consistently receive first name, last name, and date of birth from each provider. These three variables will be the primary identifiers used for identification of duplicates. Use of these primary identifiers proved highly effective for identification of duplicates in the RLDR project. Reports that cannot be determined to be unduplicated based on these three variables will be further investigated on a case-by-case basis by using additional identifiers (e.g., phone numbers, addresses, zip code, gender, and race) or if possible by contact with a parent of a report.

Methods used to identify duplicate reports as described above may result in undercount of cases if two youth have the same first and last names and the same date of birth, which is deemed highly unlikely. Therefore, estimates of prevalence would not be greatly affected.

4.2.1.2.Case definition and eligibility

Prevalent cases will be identified via a) a physician diagnosis of diabetes or b) parent or self-report of physician diagnosis.

A "physician diagnosis" of diabetes is considered to have been identified if any of the following methods are used: a) record review for physician diagnosis of diabetes; b) direct verification of case status by knowledgeable physician (or other health care provider directly involved in care); or c) location in clinically verified database (where case has been verified by a clinician). In South Carolina, all initial contact with patients or their parents will be made through a physician, who has previously verified case status.

The following eligibility criteria will apply to all prevalent cases:

a. Index year: 2001

b. Birth year: 1/1/1982 – 12/31/2001

c. Age range: 0 – 19.999 in 2001

d. Geographic area: Richland, Lexington, Orangeburg, and Calhoun Counties in South Carolina.

e. Non-institutionalized, non-military resident/member of population from which cases are present in the index year

Military personnel: Such individuals are not part of the Census denominators for non-institutionalized, non-military (NI-NM) personnel. Fort Jackson Army base is the only major military installation in Richland, Lexington, Orangeburg, and Calhoun counties. Active duty personnel automatically receive medical care through Moncrief Army Community Hospital's (MACH) Family Health Center (FHC). Dependents of active military members who live on base or within a 30 minute driving radius also qualify for treatment through FHC. Those dependents who live outside the 30-minute radius plus all retirees and their dependents are referred to a Primary Care Manager (PCM) and receive their medical care from the surrounding community. We will not seek cases from Moncrief Army Community Hospital. Military members or military dependents will be identified at initial contact.

College students: College students are eligible, as they will be included in the non-institutionalized, non-military denominator. Contact with the school(s) health services will be made to determine the number of known cases, and to develop methods for further contact.

There are two large Universities and several smaller colleges within our geographic area of interest which include: The University of South Carolina, South Carolina State University, Columbia College, Benedict College, Allen University, Claflin University, and Columbia International University.

Estimated number of prevalent cases

Table 6. Estimated number of prevalent cases by age and ethnicity.

Age Group	White, NH/L[1]	Black or African American NH/L[1]	Hispanic or Latino	Asian, NH/L[1]	Hawiiian or Pacific Islander, NH/L[1]	Nat Amer or Alaskan Native, NH/L[1]	other [2], NH/L[1]	Total[3]
0-9 Years	46	40	1	0	0	0	0	87
10-19 Years	128	143	9	2	0	1	0	283
Total 0-19 years	174	183	10	2	0	1	0	370

[1] Not Hispanic or Latino
[2] Other, not Hispanic or Latino category, set to zero because of unavailability of rates
[3] Total based on non-rounded numbers

4.2.2. Incident cases

4.2.2.1.Case finding site-specific approaches

The goals of case finding are to identify all unique (non-duplicated) incident cases, and validate that every unique case is a true case in the eligible population of the state of South Carolina. Multiple sources will be used to identify incident cases.

Data sources

a) Pediatric endocrinologists: There are 7 pediatric endocrinologists in the state of South Carolina from whom we will request a list of all patients who meet the eligibility criteria. Information on the time lapse between a referral and when the patient is actually seen will be requested, as would current contact information. We will ask that all names be personally reviewed and validated by one of the endocrinologists to confirm diabetes status.

Table 7: Pediatric Endocrinologists-South Carolina

Name	Location	Affiliation
Dr. James A. Amrhein	Greenville	Greenville Hospital System
Dr. Howard Heinze	Columbia	USC
Dr. I. David Schwartz	Columbia	USC
Dr. Lester L. Key Jr.	Charleston	MUSC
Dr. Karen J. Loechner	Hollywood (Charleston Co.)	Unknown
Dr. Tarina M. Mendes	Florence	Unknown
Dr. Steven M. Willi	Charleston	MUSC

Name	**Location**	**Affiliation**
Dr. James A. Amrhein	Grenville	Greenville Hospital System
Dr. Howard Heinze	Columbia	USC
Dr. I. David Schwartz	Columbia	USC
Dr. Lester L. Key Jr.	Charleston	MUSC
Dr. Karen J. Loechner	Hollywood (Charleston Co.)	Unknown
Dr. Tarina M. Mendes	Florence	Unknown
Dr. Steven M. Willi	Charleston	MUSC

b) Adult endocrinologists: 61 adult endocrinologists in the state will be contacted. This should yield cases among older teenagers who may not see a pediatric endocrinologist. Checks at six-month intervals may be all that is necessary for case ascertainment.

Hospitals: There are 84 hospitals in the state of South Carolina. All hospitals serving the state will be asked to participate in identifying patients who meet the criteria. Billing data will be used to identify any child/adolescent who had a diabetes related ICD-9 code recorded during a hospital visit, regardless of the purpose of visit. Billing data will represent all outpatient, inpatient and emergency room visits. We will request potential subject names, names of parents, all available contact information (phone numbers, address), county of residence, race, gender, date of birth, visit ID, patient ID, all ICD-9 codes recorded at each visit, admitting physician, consulting physician, and payor sources (all sources including Champus and Tricare.) This data will be reviewed to eliminate children who do not meet the eligibility criteria.

c) University affiliated family practices and pediatric clinics: University affiliated family practice and pediatric clinics will be queried for eligible cases. This will be done on a case-by-case basis as the organizational and institutional structures may be quite different across South Carolina's Medical Schools (University of South Carolina Medical School, Medical University of South Carolina.)

d) Federally funded primary health care clinics: Billing data from federally funded primary health care clinics will be queried for eligible cases. These include 13 clinics in the South Carolina Primary Health Care Association and Eau Clair Pediatric Clinic.

e) Non-university affiliated pediatric practices: Billing data from a sample of non-university pediatric clinics will be queried for eligible cases. The practices will be selected based on prior information on referral patterns and caseload.

We will also query major medical centers near the state boundaries of North Carolina (Charlotte) and Georgia (Augusta) for eligible cases. Other sources that may be utilized include: school nurses, diabetes educators, family practitioners and pediatricians, university/college related health services, any of the larger practices known to care for children with diabetes.

Case definition and eligibility

Incident cases will be defined via a) a physician diagnosis of diabetes or b) parent or self-report of physician diagnosis.

A "physician diagnosis" of diabetes is considered to have been identified if any of the following methods are used: a) record review for physician diagnosis of diabetes; b) direct verification of case status by knowledgeable physician (or other health care provider directly involved in care); or c) location in clinically verified database (where case has been verified by a clinician). In South Carolina, all initial contact with patients or their parents will be made through a physician, who has previously verified case status.

The following eligibility criteria apply to all incident cases:

a. Diagnosed on or after 1/1/2002

b. Birth year: 1/1/1983 – 12/31/2002, advanced by one year for each subsequent incident period

c. Age range: 0 – 19.999

d. Geographic area: statewide

e. Non-institutionalized, non-military resident/member of population from which cases are present

Military personnel: Military personnel are counted in the Census for the county in which they currently reside/are based. Initial total population estimates include them, however, as the Census results are further refined, the

military members are identified separately. Final denominator estimates will exclude military service members, though they will be included in less refined estimates. We will not actively seek data on incident cases of diabetes from any military based hospitals in South Carolina.

College students: College students are eligible, as they will be included in the non-institutionalized, non-military denominator. Contact with the school(s) health services will be made to determine the number of known cases, and to develop methods for further contact.

Estimated number of incident cases

Table 8. Estimated number of incident cases by age and ethnicity per year

Age Group	White, NH/L[1]	Black or African American NH/L[1]	Hispanic or Latino	Asian, NH/L[1]	Hawiiian or Pacific Islander, NH/L[1]	Nat Amer or Alaskan Native, NH/L[1]	other [2], NH/L[1]	Total[3]
0-9 Years	45	30	1	0	0	0	0	77
10-19 Years	67	43	4	1	0	0	0	115
Total 0-19 years	112	73	5	1	0	0	0	192

[1] Not Hispanic or Latino
[2] Other, not Hispanic or Latino category, set to zero because of unavailability of rates
[3] Total based on non-rounded numbers

4.3. CASE VALIDATION

The goals of case validation are to a) determine whether cases meet the case definition; b) develop estimates of positive predictive value (PPV) by source and site; c) develop algorithms to balance efficiency and accuracy of case finding and degree of certainty.

4.3.1. Site-specific methods

Confirmation of case status will be accomplished as a result of our initial approach to the case, namely, contact with the potential case through their physician's office. Cases will initially be identified by health care providers from records/databases. Once a case report is identified, the health care provider will be encouraged to verify that the reported cases have diabetes and are eligible. Next a letter on the health care provider's letterhead containing their signature and co-signed by the SEARCH SC PI will be sent out inviting the patient to participate in the study. The letter will also contain the initial participant survey/module. The case will subsequently be called by phone and invited to participate in the study. If they agree, the process as described in the Measurement Protocol 4.6 will be initiated.

4.3.2. Completeness of case ascertainment

4.3.2.1. Prevalent cases

Capture-recapture

Capture-recapture methods will be used to calculate the completeness of case ascertainment. The best statistical methods will be used, incorporating multiple ascertainment sources, with adjustment for non-independence of data sources.

It is also recognized that the assumption of independence of source is violated to a considerable degree given the referral patterns and institutional and personnel interconnections in the health care system dealing with diabetes patients in this area. Data elements required to calculate capture-recapture estimates include: source of case record, date of inclusion on data source, record numbers to remove duplicates from same data source.

Random sample of primary care practices

A random sample of 10% of the family practices and pediatric practices will be selected. A database and/or chart review will be conducted to assess the completeness of ascertainment.

Death certificates

Full individual information on individuals meeting the SEARCH eligibility criteria and deceased with an underlying or contributing cause of death listed of diabetes will be requested from the South Carolina Department of Vital Statistics. These individuals will be matched against the SEARCH South Carolina database to identify potential missing cases. Any missing cases identified in this manner will be considered death-certificate-only cases (DCO).

4.3.2.2. Incident cases

Capture-recapture

Capture-recapture methods will be used to calculate the completeness of case ascertainment. The best statistical methods will be used, incorporating multiple ascertainment sources, with adjustment for non-independence of data sources.

It is also recognized that the assumption of independence of source is violated to a considerable degree given the referral patterns and institutional and personnel interconnections in the health care system dealing with diabetes patients in this area. Data elements required to calculate capture-recapture

estimates include: source of case record, date of inclusion on data source, record numbers to remove duplicates from same data source

Random sample of primary care practices

A random sample of 10% of the family practices and pediatric practices will be selected. A database and/or chart review will be conducted to assess the completeness of ascertainment.

Death certificates

Full individual information on individuals meeting the SEARCH eligibility criteria and deceased with an underlying or contributing cause of death listed of diabetes will be requested from the South Carolina Department of Vital Statistics. These individuals will be matched against the SEARCH South Carolina database to identify potential missing cases. Any missing cases identified in this manner will be considered death-certificate-only cases (DCO).

Appendices

Appendix 1: Census 2000 Summary File 1 (SF 1) PCT 12 H, I, J, K, L, M, N, O Richland, Lexington, Orangeburg, and Calhoun

	White alone, not Hispanic or Latino	Black or African American alone, not Hispanic or Latino	Hispanic or Latino	Asian alone, not Hispanic or Latino	Native Hawaiian and other Pacific Islander alone, not Hispanic or Latino	American Indian or Alaskan Native alone, not Hispanic or Latino	Other	Total	
under 5 years	21368	17654	1269	520	21	103	1029	41964	
5 to 9 years	23009	20144	1050	448	12	109	839	45611	
Subtotal 0-9 years	44377	37798	2319	968	33	212	1868		87575
10 to 14 years	23837	20061	933	449	10	121	683	46094	
15 to 17 yars	14249	12119	681	304	10	93	370	27826	
18 and 19 years	11411	10120	971	346	17	85	312	23262	
Subtotal 10-19 years	49497	42300	2585	1099	37	299	1365		97182
Total	93874	80098	4904	2067	70	511	3233	184757	

Appendix 2:

Census 2000 Summary File 1 (SF 1) PCT 12 H, I, J, K, L, M, N, O South Carolina

	White alone, not Hispanic or Latino	Black or African American alone, not Hispanic or Latino	Hispanic or Latino	Asian alone, not Hispanic or Latino	Native Hawaiian and other Pacific Islander alone, not Hispanic or Latino	American Indian or Alaskan Native alone, not Hispanic or Latino	Other	Total
under 5 years	155476	90112	9512	2459	84	1078	6133	264854
5 to 9 years	164178	105410	7634	2268	89	755	4734	285068
Subtotal 0-9 years	319654	195522	17146	4727	173	1833	10867	549922
10 to 14 years	168389	108756	6328	2235	89	1009	3673	290479
15 to 17 yars	97966	62769	4480	1451	53	648	1873	169240
18 and 19 years	74868	42809	5326	1280	60	460	1334	126137
Subtotal 10-19 years	341223	214334	16134	4966	202	2117	6880	585856
Total	660877	409856	33280	9693	375	3950	17747	1135778

4. Methods: Case Ascertainment - Puget Sound Region, Washington

4.1. GOAL

To ascertain and validate all unique (non-duplicated) cases of diabetes in youth aged 0-19 years in the Puget Sound Region of Washington. This region includes 5 counties: King, Kitsap, Pierce, Snohomish and Thurston Counties. This will allow estimation of prevalence and incidence rates by age, gender, and ethnicity.

4.2. DENOMINATOR ESTIMATION

4.2.1. **Site specific approach**

The 2000 US Census non-institutionalized, non-military resident population of the 5-county Puget Sound Region will be used. Projections beyond 2000 will be made by the WA State Office of Financial Management (OFM) that provides the executive branch, the legislature, and the public with estimates, forecasts, and reports on the state's population. Various public and private organizations rely on data developed and maintained by OFM for planning and assessment purposes. The agency also serves as a liaison with the federal Census Bureau.

4.2.2. **Special populations**

College students: An effort will be made to contact medical facilities affiliated with larger institutions in this region, e.g. University of Washington, to find cases since college students will be included in the denominator.

Military personnel: The pediatric endocrinology group affiliated with Madigan Army Medical Center has expressed interest in participating in SEARCH. If a significant number of cases are identified in this population, alternate denominators including military populations will be used to calculate rates that can be compared to those produced using the non-military, non-institutionalized population.

Native American residents: There are several Native American reservations in the Puget Sound region (including Swinomish, Tulalip, S'Klallam Port Gamble, Port Madison, Puyallup, Muckleshoot, Nisqually Indian Reservations) as well as many urban, non-reservation based American Indians. Given the large percentage of urban Indians in our area and likely referral of American Indian youth with diabetes to non-reservation based clinical sites, local case ascertainment will not focus on reservation-based youth.

4.2.3. **Denominators for prevalence**

For the initial prevalence estimate, the 2000 US Census will be used for the 5-county Puget Sound Region. Once projections based on the 2000 US Census are updated by the

WA State OFM, prevalence estimates will be updated. The estimated populations residing in the Puget Sound Region is summarized in Table 1.

Table 1. Estimated prevalence denominators by age group and ethnicity*

Age Group	Caucasian	African-American	Hispanic	Asian/PI	Native American	Total
0-4	181,272	15,990	12,775	19,884	3,811	233,732
5-9	202,115	16,456	13,592	23,143	3,972	259,278
10-14	200,586	15,295	12,933	22,884	4,119	255,817
15-19	179,879	14,042	11,546	24,550	4,076	234,093

*Based on 2000 census estimates [WA State Office of Financial Management]

4.2.4. **Denominators for incidence**

Population projections made by the WA State OFM based on the 2000 US Census for the subsequent years of incident case ascertainment will be used.
The same 5-county Puget Sound geographic region will be used for prevalent and incident case ascertainment. The estimated populations residing in the Puget Sound Region are summarized below in Table 2 (same numbers as prevalence table).

Table 2. Estimated incidence denominators by age group and ethnicity*

Age Group	Caucasian	African-American	Hispanic	Asian/PI	Native American	Total
0-4	181,272	15,990	12,775	19,884	3,811	233,732
5-9	202,115	16,456	13,592	23,143	3,972	259,278
10-14	200,586	15,295	12,933	22,884	4,119	255,817
15-19	179,879	14,042	11,546	24,550	4,076	234,093

*Based on 2000 census estimates [WA State Office of Financial Management]

4.3. CASE ASCERTAINMENT

4.3.1. **Prevalent Cases**

4.3.1.1. **Case finding site-specific approaches**

Data sources

A combination of clinical and non-clinical or administrative data sources will be used to identify prevalent cases.

a) Pediatric endocrinologists

There are 5 pediatric endocrinology groups in the Puget Sound region. Patients with diabetes seen by these groups will probably represent a majority of the prevalent cases in the region. They have all agreed to participate in this study. Potential cases

will be identified by the endocrinology groups and evaluated to determine whether they meet the case definition.

- Children's Hospital Pediatric Endocrinology, Seattle
- Woodinville Pediatrics
- Group Health Eastside
- Pediatrics Northwest, Tacoma
- Madigan Army Medical Center

b) Adult endocrinologists

Each adult endocrinology group in the Puget Sound region likely sees a few older adolescents with diabetes. In order to assess the extent to which adult endocrinologists are caring for patients < 20 years of age, these practices will be surveyed or contacted to discuss this issue. If the number of potential cases is significant at certain practices, these groups will be included in our case ascertainment plan. Potential cases will be identified by these endocrinology groups and evaluated to determine whether they meet the case definition.

c) Hospital records

Two major pediatric hospitals serve the 5-county Puget Sound area:

- Children's Hospital and Regional Medical Center (CHRMC)
- Mary Bridge Children's Hospital (MBCH)

Combined these two pediatric hospitals represent 47% of all pediatric hospitalizations for diabetes (30% CHRMC, 17% MBCH) in Washington State.

Other area hospitals with a history of providing care to youth with diabetes will be included in providing data for prevalent cases. This list of hospitals will be obtained by examining hospitalization data for youth with diabetes residing in the 5 counties from 1987-1999.

Billing data will be used to identify any youth who had a diabetes-related ICD-9 code (250.xx) recorded during a hospital visit, regardless of the purpose of visit. Potential subject names, names of parents, all available contact information (phone numbers, address), race/ethnicity, gender, date of birth and all ICD-9 codes recorded at each visit will be requested. It is likely that the extent of this information will vary by hospital depending on their institution's IRB approval. This data will be reviewed to eliminate children who do not meet eligibility criteria.

Each hospital will provide the following variables as permitted by IRB:

- Name
- DOB

- ICD-9 codes
- Patient ID or medical record number
- Any/all parental contact information
- Address and county of residence
- Gender
- Race/ethnicity

If the hospitals are unwilling to share direct identifiers (e.g. name, parental contact information), indirect identifiers (e.g. date of birth, gender, residential zipcode, date of diagnosis) will be used to assess completeness of case ascertainment from the clinical non-hospital based sites.

d) Primary care clinics

It is likely that a number of general pediatricians in the region care for their own diabetes patients (primarily type 1) with or without limited subspecialist involvement. Similarly, family practitioners are likely to care for older adolescents with type 2 diabetes without referral to an endocrinologist.

Primary care clinics in the Puget Sound region will be surveyed to evaluate the yield of cases not captured by other methods and to assess referral patterns for patients with type 1 or type 2 diabetes. If a significant number of cases are found exclusively through primary care clinics, a primary care network will be established for prevalent case ascertainment.

A targeted effort to find cases may involve direct contact with practices in more rural areas (farther away from referral centers) and practices serving geographic areas where more ethnic minorities live (populations at greater risk for type 2).

e) Community Diabetes Registry

The Community Diabetes Initiative (CDI) is a partnership involving the Community Health Plan of Washington and the Washington State Department of Health Diabetes Control Program. The collaboration is implemented at all eight of the federally qualified community health centers in King County, plus clinics run by the Seattle-King County Department of Public Health. The participating health centers are the 45th St. Clinic, Community Health Centers of King County, Country Doctor Community Health Centers, International Community Health Services, Pike Market Medical Clinic, Puget Sound Neighborhood Health Centers, Sea Mar Community Health Centers, and the Seattle Indian Health Board.

The CDI is focusing on three areas of care for people with diabetes: resources, self-management support, and a clinical database called Diabetes Electronic Management System (DEMS). DEMS is a clinical management tool developed by the WA State Department of Health Diabetes Control Program and is designed to assist health care providers and management to track the quality of care provided to patients with

diabetes. Demographics, clinical information, laboratory results, and outcomes can be tracked through the DEMS database. While many clinics use DEMS solely as a management tool, the CDI clinics have shared their data in a registry. There are approximately 4000 patients in their database and approximately 50 prevalent cases that are <20 years of age. The medical directors in the CDI network will be approached for permission to obtain information from the database and to be a source for prevalent cases.

A pediatric version of DEMS is being developed and will be shared with practices who choose to participate in our local surveillance network. Backup data entry of known diabetes cases in their clinics will assist ascertainment for prevalent cases.

f) Group Health Diabetes Registry

Prevalent cases of diabetes will also be identified through the Group Health Diabetes Registry. This registry has been available at Group Health Cooperative of Puget Sound, a not-for-profit HMO that serves more than 400,000 enrollees in Western Washington, since 1995-1996. Patients with diabetes are identified from administrative databases by pharmacy (insulin or diabetes medications), laboratory (elevated fasting or random blood glucose levels or elevated HgbA1c levels) or hospital discharge data (ICD-9 codes for diabetes mellitus). Utilization and laboratory data are added regularly to keep this registry database current. [Ref McCullough DK et al. A Population-Based Approach to Diabetes Management in a Primary Care Setting. Effective Clinical Practice. 1998;1:12-22]

g) Washington State Comprehensive Hospital Abstract Reporting System (CHARS)

A secondary data source that will be used for identification of hospitalized diabetes cases is the Washington State Comprehensive Hospital Abstract Reporting System (CHARS). While CHARS will not be used to identify prevalent cases, it will be used to identify hospitals that admit youth with diabetes and to assess the comprehensiveness of case ascertainment.

CHARS will be used to retrospectively examine first time hospitalizations (new diagnoses) for diabetes (ICD-9 CH 250.xx) among youth aged less than 20 years. In a preliminary examination of CHARS data for incident cases of diabetes in youth under age 20, 30% of the hospitalizations took place at CHRMC, 17% at MBCH. Every other hospital in the state provided the initial admission for less than 5% of the incident cases of diabetes in youth less than 20 years of age. It is estimated that 70% of incident cases of type 1 diabetes in the youth (particularly the very young and those with severe diabetic ketoacidosis) are managed in the inpatient setting and thus captured through hospital-based admissions/discharge data sources. Youth with severe diabetic ketoacidosis and very young children are generally admitted to the pediatric tertiary-care hospitals, CHRMC or MBCH. These data can be evaluated for the Puget Sound region counties of study and compared to the known cases from the clinical sites.

h) Insurance administrative data

As part of an AHRQ funded grant (RO1-09948-01A1) to study features of managed care that are associated with quality of care for children (0-20 years old) with chronic medical problems, a consortium of health plans in Washington state has been created. Members of the consortium have agreed to share administrative data on all their children, not only those with the conditions under study. Diabetes is one of the conditions focused on in this study. Administrative data from the following plans are available and will be used to create analysis files as needed for SEARCH:

1) Group Health Cooperative (GHC) of Puget Sound. GHC is a 530,000-member staff model HMO. It has frequently served as a collaborator in University of Washington sponsored, claims based research. (46,000 eligible children)
2) Medicaid Managed Care and fee-for-service (FFS). Washington State Medicaid includes both a managed care plan ("Healthy Options") and children who have been exempted from it and remain in a fee-for-service system. Exempted children tend to have chronic or complex medical conditions. (330,000 eligible children)
3) PREMERA Blue Cross. This is the second largest private health insurance carrier in Washington with over 600,000 commercial enrollees in a range of coverage options including: network HMO, Point of Service (POS), and Preferred Provider Organization (PPO). (420,000 eligible children)
4) Regence Blue Shield. This is the largest private health insurance carrier in Washington with over 900,000 commercial enrollees with similar coverage options to PREMERA. (490,000 eligible children)

Complete data sets are available from June1997-June 2001. Data tapes arrive annually making identification of incident cases infeasible.

Fields to be extracted from claims databases:

Product Table – 1 record for each plan product
Carrier ID
Product ID (will link to the 2 product fields in the enrollment database)
Product type (e.g., fee-for-service, preferred provider organization, point-of-service, and staff-model health maintenance organization)

Enrollment Table – 1 record for each enrollee
ID code for linking to claims data
Date of birth
Gender
Race/Ethnicity (where available)
Enrollment date
Disenrollment date

Claims Table – 1 record for each line item of a claim
ID code for linking to other claims and to enrollment database
Claim number
Zip code of residence (county code, if zip code is unavailable)
First and last dates of service
Type of provider
Performing (billing) Provider ID
Provider specialty
All diagnosis codes
All procedure codes (CPT, HCPCS, or other)
Admission date
Discharge date
Prescription fills (National drug codes)
Dollar amounts (billed, allowed, paid by plan, paid by other 3rd party insurer, paid by Medicare, co-pay, co-insurance, deductible, discounted by provider, etc.)
Location of service

4.3.2. **Identification of prevalent cases**

Based on previous studies with the above-described set of administrative data, the optimal method for identification of children with type 1 diabetes is a combination of ICD-9 codes and prescription fills for insulin. The addition of pharmacy data increases specificity dramatically and obviates the problem of a single diagnosis for diabetes representing a "rule out." For type 2 diabetes, similar criteria will be used substituting oral hypoglycemic agents for insulin fills. Again, the use of adjunct pharmacy data should increase the specificity of the diagnosis. The fifth digit (of ICD-9 codes) (0 or 1) has not been found to reliably distinguish type 1 from type 2 diabetes.

	Criteria
Diabetes	Any ICD-9 code of 250 + at least one pharmacy fill for insulin OR Any ICD-9 code for 250 + at least one pharmacy fill for any oral hypoglycemic agent (based on NDC codes)

As with the hospitalization data, as much identifying information as possible will be obtained. If the plans are unwilling to share direct identifiers (e.g. name, SSN, parental contact information), indirect identifiers (e.g. date of birth, gender, residential zipcode, diagnosis) will be used to assess completeness of case ascertainment from the clinical sites.

These data may also be used to identify primary care providers that manage patients with diabetes. The feasibility of identifying primary care providers is being explored.

Additional sources

Additional data sources considered to identify prevalent cases include:
a) Certified Diabetes Educators
b) School nurses
Working relationships with these groups are currently being explored.

Identification of duplicate cases

The following items are to be considered as possible matching variables, depending on the information available from different sources:

- Name
- Gender
- Date of birth
- Race/ethnicity
- Geographical information – address and/or ZIP code
- Social security number
- Medical record numbers
- Telephone number(s)
- Admission date of hospitalization(s)
- Parent's name, mothers' maiden name, and mother's date of birth
- Partial name matches

All sources used to identify cases (e.g. clinical records, hospital records, registries, etc.) will be recorded. We anticipate that most cases will be identified by at least 2 distinct sources (e.g. clinic and hospital record). We will use a combination of manual, deterministic, and probabilistic record linkage methods to remove duplicates.

Case definition and eligibility

a) Prevalence: index year = 2001

b) "Onset of diabetes" is the date of first clinical diagnosis of diabetes in a non-pregnant state.

c) Birth year: 1/1/82 – 12/31/2001 (for 2001 prevalence year).

d) Age range: 0 – 19.999 in the index year.

e) Geographic area: 5-county Puget Sound Region, Washington (King, Kitsap, Pierce, Snohomish and Thurston Counties)

f) Resident of population: Non-institutionalized, non-military resident or member of population from which cases are present in the index year.

g) Military personnel: Active duty military personnel will be excluded to align with the denominator. If such persons can be identified with high sensitivity, they can be used in alternate estimates of prevalence that also count military personnel in the denominator. Military dependents that have access to civilian medical facilities will be identified as cases in the numerator and will be included in the non-military denominator.

h) College students: College students are eligible, as they will be included in the non-institutionalized, non-military denominator. An effort will be made to contact medical facilities affiliated with larger institutions in this region, e.g. University of Washington.

4.3.3. **Incident Cases**

4.3.3.1. **Case finding site-specific approaches**

Data sources

A combination of clinical and non-clinical or administrative data sources will be used to identify incident cases.

a) Pediatric endocrinologists

The 5 pediatric endocrinology groups in the Puget Sound Region will be a source for incident cases. Patients with diabetes seen by these groups will likely represent a majority of the incident cases in the region. They have all agreed to participate in this study. Potential cases will be identified by the endocrinology groups and evaluated to determine whether they meet the case definition.

b) Adult endocrinologists

Adult endocrinology groups found to see youth with diabetes in the prevalence case ascertainment plan will be included in the active surveillance network for incident cases. Potential cases will be identified by these endocrinology groups and evaluated to determine whether they meet the case definition.

c) Hospital records

The two children's hospitals serving the 5-county Puget Sound area:

- Children's Hospital and Regional Medical Center (CHRMC)
- Mary Bridge Children's Hospital (MBCH)

will be a part of the active surveillance network. The hospitals will be contacted on a regular (e.g. monthly) basis by SEARCH for new cases of diabetes.

Other area hospitals with a history of providing care to youth with diabetes will be included in the network for incident cases.

Billing data will be used to identify any youth who had a diabetes related ICD-9 code (250.xx) recorded during a hospital visit, regardless of the purpose of visit. Potential subject names, names of parents, all available contact information (phone numbers, address), race/ethnicity, gender, date of birth and all ICD-9 codes recorded at each visit will be requested. It is likely that the extent of this information will vary by hospital depending on their institution's IRB approval. This data will be reviewed to eliminate children who do not meet eligibility criteria.

Each hospital will provide the following variables as permitted by IRB:
- Name
- DOB
- ICD-9 codes
- Patient ID or medical record number
- Any/all parental contact information
- Address and county of residence
- Gender
- Race/ethnicity

If the hospitals are unwilling to share direct identifiers (e.g. name, SSN, parental contact information), indirect identifiers (e.g. date of birth, gender, residential zipcode, date of diagnosis) will be used to assess completeness of case ascertainment from the clinical non-hospital based sites.

d) Primary care clinics

Primary care practices found to care for youth with diabetes independently of endocrinologists will be included in the surveillance network for incident case ascertainment.

A targeted effort to find cases may involve direct contact with practices in more rural areas (farther away from referral centers) and practices serving geographic areas where more ethnic minorities live (populations at greater risk for type 2).

e) Community Diabetes Registry

Refer to section 4.2.1.1(e) for discussion on DEMS and the CDI. Medical directors in the CDI network will be approached for permission to be a source for incident cases.

f) Group Health Diabetes Registry

Refer to section 4.2.1.1 (f) for discussion on the Group Health diabetes registry. This registry is updated daily and will be used to identify incident cases. The registry will be queried monthly for new cases. Primary care providers for these cases will be contacted to determine if they are new diagnoses or new enrollees with diabetes and to establish case validation.

Additional sources

Additional data sources considered to identify incident cases include:

- Certified Diabetes Educators
- School nurses

Working relationships with these groups are currently being explored.

Case definition and eligibility

Incident diagnosis years will begin in 2002 and continue for the period of the project. Cases are eligible to be counted as incident when diagnosed from January 1 through December 31 of that year.

a) "Onset of diabetes" is the date of first clinical diagnosis of diabetes in a non-pregnant state.

b) Age range: 0 – 19.999 in the onset year

c) Resident of population defined for incident cases: 5-county Puget Sound Region, Washington (King, Kitsap, Pierce, Snohomish and Thurston Counties.

4.4. CASE VALIDATION

4.4.1. **Site-specific methods**

The majority of prevalent cases will be validated by physician verification since cases will primarily be identified and approached through the primary care or endocrinology practices. Cases found from DEMS or Group Health Diabetes Registry will fall in the category of a clinically verified database. For cases consenting to medical record review, secondary confirmation of case status will occur during chart review.

Since the majority of incident cases will be reported through a rapid reporting system from a knowledgeable health care provider, they meet the primary criteria for validation, as used for prevalent cases. For those cases identified from record systems or other methods, validation is required. Validation sources may include:

- Record review for physician diagnosis of diabetes
- Direct verification of case status by knowledgeable physician (or other health care provider directly involved in care)
- Location in clinically verified database (where case has been verified by a clinician)
- Interview of parent(s) or self-report (among older subjects) of physician diagnosis of diabetes

4.4.2. **Completeness of case ascertainment**

4.4.2.1. **Prevalent cases**

Capture-recapture
Capture-recapture methods will be used to calculate the completeness of case ascertainment. The best statistical methods will be used, incorporating multiple primary ascertainment sources (e.g. endocrinologist, primary care provider, CHARS, etc.), with adjustment for non-independence of data sources. Cases from Group Heath will be excluded from capture-recapture methodology given the non-independence of data sources from that institution.

Data elements required to calculate capture-recapture estimates:
- Source of case record
- Date of inclusion on data source
- Record numbers to remove duplicates from same data source.

Random sample of primary care practices
Extensive case identification from a random sample of primary care practice will also be used to estimate the completeness of case ascertainment.

Death certificates
Information from death certificates on individuals with diabetes listed as cause of death will be requested from the state department of Vital Statistics. This information

will be matched against local SEARCH database to further assess completeness of case ascertainment. Cases identified using only death certificates will be classified as death-certificate-only cases.

4.4.2.2.**Incident cases**

Capture-recapture
Capture-recapture methods will be used for incident cases as they were for prevalent cases in those sites where they can be used. Each source of a case report will be recorded to allow these calculations.

CHARS and the administrative data from the health plans will be used to assess the completeness of case ascertainment from clinical sites. These databases will be accessed annually to obtain counts (plus indirect identifiers) of youth with diabetes; i.e. these numbers would serve as a "denominator" for all potential youth with diabetes. Cases enrolled in SEARCH who have given consent for review of medical records/databases will be matched using these indirect identifiers to those found in the databases.

Random sample of primary care practices
Extensive case identification from a random sample of primary care practice will also be used to estimate the completeness of case ascertainment.

Death certificates
Information from death certificates on individuals with diabetes listed as cause of death will be requested from the state department of Vital Statistics. This information will be matched against local SEARCH database to further assess completeness of case ascertainment. Cases identified using only death certificates will be classified as death-certificate-only cases.

Table V – 1. Estimated Number of Prevalent Cases Type 1 Based on Incidence * Denominator Except for Hawaii

	Non-Hispanic White			African American			Hispanic			Asian			Pacific Islander			Native American			ALL
Age	Rate	Denom	N	Rate	Denom	N	Rate	Denom	N	Rate	Denom	N	Rate	Denom	N	Rate	Denom	N	
0 thru 9																			
California[1]	1	170740	170	1	32621	32	0.5	100294	50	0.1	28997	2	1	7249	7	0.01	1742	0	261
Colorado[2]	1	302760	302	1	22787	22	0.5	56145	28	0.1	7558	0	1	1890	1	0.01	64853	0	353
Hawaii[3]	1	26295	26	1	3310	3	0.5	13733	6	0.3	50754	15	2	20914	41	0.01	319	0	91
Ohio[4]	1	235,458	235	1	31,556	31	0.5	0	0	0.1	0	0	1	0	0	0.01	0	0	266
Seattle[5]	1	383,387	383	1	32446	32	0.5	26367	13	0.1	34422	3	1	8605	8	0.01	7783	0	439
S Carolina[6]	1	44377	44	1	37798	37	0.5	2319	1	0.1	968	0	1	33	0	0.01	212	0	82
10 thru 19																			
California[1]	2.2	179361	394	2.2	34269	75	1.8	105359	189	0.8	30461	24	2.5	7615	19	0.01	1742	0	701
Colorado[2]	2.2	261705	575	2.2	19464	42	1.8	49072	88	0.8	7290	5	2.5	1822	4	0.01	67412	0	714
Hawaii[3]	2.2	28486	62	2.2	3585	7	1.8	14877	26	1.6	54984	87	3	22657	67	0.01	346	0	249
Ohio[4]	2.2	249,921	549	2.2	33,495	73	1.8	0	0	0.8	0	0	2.5	0	0	0.01	0	0	622
Seattle[5]	2.2	380465	837	2.2	29337	64	1.8	24479	44	0.8	37947	30	2.5	9487	23	0.01	8195	0	998
S Carolina[6]	2.2	49497	108	2.2	42300	93	1.8	2585	4	0.8	1099	0	2.5	37	0	0.01	299	0	205
Total		***2312452***	***3685***		***322968***	***511***		***395230***	***449***		***254480***	***166***		***80309***	***170***		***152903***	***0***	***4981***

Table V – 2. Estimated Number of Prevalent Cases Type 2 Based on Incidence * Denominator Except for Hawaii

	Non-Hispanic White			African American			Hispanic			Asian			Pacific Islander			Native American			ALL
Age	Rate	Denom	N	Rate	Denom	N	Rate	Denom	N	Rate	Denom	N	Rate	Denom	N	Rate	Denom	N	
0 thru 9																			
California[1]	0.05	170740	8	0.05	32621	1	0.13	100294	13	0.1	28997	2	0.11	7249	0	0.4	1742	0	24
Colorado[2]	0.05	302760	15	0.05	22787	1	0.13	56145	7	0.1	7558	0	0.11	1890	0	0.4	64853	25	48
Hawaii[3]	0.05	26295	1	0.05	3310	0	0.13	13733	1	0.2	50754	10	0.2	20914	4	0.4	319	0	16
Ohio[4]	0.05	235,458	11	0.05	31,556	1	0.13	0	0	0.1	0	0	0.11	0	0	0.4	0	0	12
Seattle[5]	0.05	383,387	19	0.05	32446	1	0.13	26367	3	0.1	34422	3	0.11	8605	0	0.4	7783	3	29
S Carolina[6]	0.05	44377	2	0.05	37798	1	0.13	2319	0	0.1	968	0	0.11	33	0	0.4	212	0	3
10 thru 19																			
California[1]	0.39	179361	69	1.18	34269	40	1.46	105359	153	0.78	30461	23	1.07	7615	8	1.7	1742	2	295
Colorado[2]	0.39	261705	102	1.18	19464	22	1.46	49072	71	0.78	7290	5	1.07	1822	1	1.7	67412	114	315
Hawaii[3]	0.39	28486	11	1.18	3585	4	1.46	14877	21	1.8	54984	98	2	22657	45	1.7	346	0	179
Ohio[4]	0.39	249,921	97	1.18	33,495	39	1.46	0	0	0.78	0	0	1.07	0	0	1.7	0	0	136
Seattle[5]	0.39	380465	148	1.18	29337	34	1.46	24479	35	0.78	37947	29	1.07	9487	10	1.7	8195	13	269
S Carolina[6]	0.39	49497	19	1.18	42300	49	1.46	2585	3	0.78	1099	0	1.07	37	0	1.7	299	0	71
Total		**2312452**	**502**		**7**	**193**		**395230**	**307**		**254480**	**170**		**80309**	**68**		**152903**	**157**	**1397**

TOTALS

Estimated Prevalent Cases

		TOTAL
California[1]		1281
Colorado[2]		1430
Hawaii[3]		535
Ohio[4]		1036
Seattle[5]		1735
S Carolina[6]		361
		6378

Rates are per 1,000

[1] California (KPSC) - all but SD

[2] Colorado - urban Denver counties, other selected CO counties, Pima, Apache, and Navaho in Arizona, NM

[3] Hawaii - members of 3 major health plans residing on Oahu

[4] Ohio (Cincinnati) - Cincinnati and 8 urban counties

[5] Seattle - 5 counties

[6] S Carolina - 4 counties

Table V – 3. Estimated Number of Prevalent Cases All Types Based on Incidence Plus Denominator Except for Hawaii

	Non-Hispanic White			African American			Hispanic			Asian			Pacific Islander			Native American			ALL
Age	Rate	Denom	N	Rate	Denom	N	Rate	Denom	N	Rate	Denom	N	Rate	Denom	N	Rate	Denom	N	
0 thru 9																			
California[1]	1	170740	178	1	32621	33	0.5	100294	63	0.1	28997	4	1	7249	7	0.01	1742	0	285
Colorado[2]	1	302760	317	1	22787	23	0.5	56145	35	0.1	7558	0	1	1890	1	0.01	64853	25	401
Hawaii[3]	1	26295	27	1	3310	3	0.5	13733	7	0.3	50754	25	2	20914	45	0.01	319	0	107
Ohio[4]	1	235,458	246	1	31,556	32	0.5	0	0	0.1	0	0	1	0	0	0.01	0	0	278
Seattle[5]	1	383,387	402	1	32446	33	0.5	26367	16	0.1	34422	6	1	8605	8	0.01	7783	3	468
S Carolina[6]	1	44377	46	1	37798	38	0.5	2319	1	0.1	968	0	1	33	0	0.01	212	0	85
10 thru 19																			
California[1]	2.2	179361	463	2.2	34269	115	1.8	105359	342	0.8	30461	47	2.5	7615	27	0.01	1742	2	996
Colorado[2]	2.2	261705	677	2.2	19464	64	1.8	49072	159	0.8	7290	10	2.5	1822	5	0.01	67412	114	1029
Hawaii[3]	2.2	28486	73	2.2	3585	11	1.8	14877	47	1.6	54984	185	3	22657	112	0.01	346	0	428
Ohio[4]	2.2	249,921	646	2.2	33,495	112	1.8	0	0	0.8	0	0	2.5	0	0	0.01	0	0	758
Seattle[5]	2.2	380465	985	2.2	29337	98	1.8	24479	79	0.8	37947	59	2.5	9487	33	0.01	8195	13	1267
S Carolina[6]	2.2	49497	127	2.2	42300	142	1.8	2585	7	0.8	1099	0	2.5	37	0	0.01	299	0	276
Total		***2312452***	***4187***		***322968***	***704***		***395230***	***756***		***254480***	***336***		***80309***	***238***		***152903***	***157***	***6378***

Table V – 4. Estimated Annual Number of Incident Cases Type 1

	Non-Hispanic White			African American			Hispanic			Asian			Pacific Islander			Native American			ALL
Age	Rate	Denom	N	Rate	Denom	N	Rate	Denom	N	Rate	Denom	N	Rate	Denom	N	Rate	Denom	N	
0 thru 9																			
California	13.5	170740	23	9.5	32621	3	7	100294	7	0.9	28997	0	12.7	7249	0	0	1742	0	33
Colorado	13.5	504413	68	9.5	32685	3	7	121224	8	0.9	14948	0	12.7	725	0	0	74453	0	79
Hawaii	13.5	32869	4	9.5	4137	0	7	17166	1	4	63443	2	15	26143	3	0	399	0	10
Ohio	13.5	235,458	31	9.5	31,556	2	7	0	0	0.9	0	0	12.7	0	0	0	0	0	33
Seattle	13.5	383,387	51	9.5	32446	3	7	26367	1	0.9	34422	0	12.7	8605	1	0	7783	0	56
S Carolina	13.5	319645	43	9.5	195522	18	7	17146	1	0.9	4727	0	12.7	173	0	0	1833	0	62
10 thru 19																			
California	16.7	179361	29	13.1	34269	4	11.4	105359	12	3.2	30461	0	14	7615	1	0	1742	0	46
Colorado	16.7	451376	75	13.1	27703	3	11.4	102736	11	3.2	13234	0	14	642	0	0	76700	0	89
Hawaii	16.7	35608	5	13.1	4482	0	11.4	18596	2	4	68730	2	16	28321	4	0	433	0	13
Ohio	16.7	249,921	41	13.1	33,495	4	11.4	0	0	3.2	0	0	14	0	0	0	0	0	45
Seattle	16.7	380465	63	13.1	29337	3	11.4	24479	2	3.2	37947	1	14	9487	1	0	8195	0	70
S Carolina	16.7	341223	56	13.1	214334	28	11.4	16134	1	3.2	4966	0	14	202	0	0	2117	0	85
Total		**3284466**	**489**		**672587**	**71**		**549501**	**46**		**301875**	**5**		**89162**	**10**		**175397**	**0**	**621**

Table V – 5. Estimated Annual Number of Incident Cases Type 2

	Non-Hispanic White			African American			Hispanic			Asian			Pacific Islander			Native American			ALL
Age	Rate	Denom	N	Rate	Denom	N	Rate	Denom	N	Rate	Denom	N	Rate	Denom	N	Rate	Denom	N	
0 thru 9																			
California	0.7	170740	1	5	32621	1	1.8	100294	1	2.07	28997	0	3.3	7249	0	4.7	1742	0	3
Colorado	0.7	504413	3	5	32685	1	1.8	121224	2	2.07	14948	0	3.3	725	0	4.7	74453	3	9
Hawaii	0.7	32869	0	5	4137	0	1.8	17166	0	2.07	63443	1	5	26143	1	4.7	399	0	2
Ohio	0.7	235,458	1	5	31,556	1	1.8	0	0	2.07	0	0	3.3	0	0	4.7	0	0	2
Seattle	0.7	383,387	2	5	32446	1	1.8	26367	0	2.07	34422	0	3.3	8605	0	4.7	7783	0	3
S Carolina	0.7	319645	2	5	195522	9	1.8	17146	0	2.07	4727	0	3.3	173	0	4.7	1833	0	11
10 thru 19																			
California	2.9	179361	5	7.2	34269	2	9.5	105359	10	13.9	30461	4	11.3	7615	0	21.3	1742	0	21
Colorado	2.9	451376	13	7.2	27703	1	9.5	102736	9	13.9	13234	1	11.3	642	0	21.3	76700	16	40
Hawaii	2.9	35608	1	7.2	4482	0	9.5	18596	1	13.9	68730	9	22	28321	6	21.3	433	0	17
Ohio	2.9	249,921	7	7.2	33,495	2	9.5	0	0	13.9	0	0	11.3	0	0	21.3	0	0	9
Seattle	2.9	380465	11	7.2	29337	2	9.5	24479	2	13.9	37947	5	11.3	9487	1	21.3	8195	1	22
S Carolina	2.9	341223	9	7.2	214334	15	9.5	16134	1	13.9	4966	0	11.3	202	0	21.3	2117	0	25
Total		**3284466**	**55**		**672587**	**35**		**549501**	**26**		**301875**	**20**		**89162**	**8**		**175397**	**20**	**164**

Estimated Incident Cases	
	TOTAL
California	103
Colorado	217
Hawaii	42
Ohio	89
Seattle	151
S Carolina	183
	785
Rates are per 100,000	

Table V – 6. Estimated Annual Number of Incident Cases All Types

	Non-Hispanic White			African American			Hispanic			Asian			Pacific Islander			Native American			ALL
Age	Rate	Denom	N	Rate	Denom	N	Rate	Denom	N	Rate	Denom	N	Rate	Denom	N	Rate	Denom	N	
0 thru 9																			
California	0.7	170740	24	5	32621	4	1.8	100294	8	2.07	28997	0	3.3	7249	0	4.7	1742	0	36
Colorado	0.7	504413	71	5	32685	4	1.8	121224	10	2.07	14948	0	3.3	725	0	4.7	74453	3	88
Hawaii	0.7	32869	4	5	4137	0	1.8	17166	1	2.07	63443	3	5	26143	4	4.7	399	0	12
Ohio	0.7	235,458	32	5	31,556	3	1.8	0	0	2.07	0	0	3.3	0	0	4.7	0	0	35
Seattle	0.7	383,387	53	5	32446	4	1.8	26367	1	2.07	34422	0	3.3	8605	1	4.7	7783	0	59
S Carolina	0.7	319645	45	5	195522	27	1.8	17146	1	2.07	4727	0	3.3	173	0	4.7	1833	0	73
10 thru 19																			
California	2.9	179361	34	7.2	34269	6	9.5	105359	22	13.9	30461	4	11.3	7615	1	21.3	1742	0	67
Colorado	2.9	451376	88	7.2	27703	4	9.5	102736	20	13.9	13234	1	11.3	642	0	21.3	76700	16	129
Hawaii	2.9	35608	6	7.2	4482	0	9.5	18596	3	13.9	68730	11	22	28321	10	21.3	433	0	30
Ohio	2.9	249,921	48	7.2	33,495	6	9.5	0	0	13.9	0	0	11.3	0	0	21.3	0	0	54
Seattle	2.9	380465	74	7.2	29337	5	9.5	24479	4	13.9	37947	6	11.3	9487	2	21.3	8195	1	92
S Carolina	2.9	341223	65	7.2	214334	43	9.5	16134	2	13.9	4966	0	11.3	202	0	21.3	2117	0	110
Total		**3284466**	**544**		**672587**	**106**		**549501**	**72**		**301875**	**25**		**89162**	18		**175397**	**20**	**785**

Table V - 7. Prevalence (per 1000) of Diabetes by Age, Type and Ethnicity: Rates Based on the Published Literature and Unpublished Data Available to SEARCH Investigators

	NHW	*AA*	*Asian*	*PI*	*NA*	*Hispanic*
Type 1						
Age 0-9	1.00	1.00	0.10	1.00	0.01	0.50
Age 10-19	2.20	2.20	0.80	2.50	0.01	1.80
Type 2						
Age 0-9	0.05	0.05	0.10	0.11	0.40	0.13
Age 10-19	0.39	1.18	0.78	1.07	1.70	1.46

NHW = non-Hispanic white, AA = African American, PI = Pacific Islander, NA = Native American

Table V – 8. Estimated Incidence (per 100,000 per year) of Diabetes by Age, Type and Ethnicity: Rates Based on the Published Literature and Unpublished Data Available to SEARCH Investigators

	NHW	*AA*	*Asian*	*PI*	*N A*	*Hispanic*
Type 1						
Age 0-9	13.5[a]	9.5[c]	0.9[h]	12.7[j]	0	7.0[a]
Age 10-19	16.7[a]	13.1[d]	3.2[h]	14.0[j]	0	11.4[a]
Type 2						
Age 0-9	0.7[b]	5.0[e]	2.07[i]	3.3[k]	4.7[g]	1.8[b]
Age 10-19	2.9[b]	7.2[f]	13.9[i]	11.3[k]	21.3[g]	9.5[b]

NHW = non-Hispanic white, AA = African American, PI = Pacific Islander, NA = Native American

[a] using 1978-1988 Colorado incidence rates

[b] estimated from [a] using type1/type 2 prevalence rates

[c] estimated based on data from Libman et al. Diabetes Care 21:1278, 1998

[d] estimated from [f] using type1/type2 prevalence rates

[e] using S. Carolina Pilot registry data supplied by E. Mayer-Davies

[f] using data from Pinhas-Hamiel et al. J Pediatr 128: 608, 1996

[g] using Pima Indian data from NIDDK, J. Krakoff

[h] averaged using data from Asians in Hawaii (Patrick et al. Diabetes Care 20: 983, 1997) and from China and Japan (Karvonen et al. Diabetes Care 23:1516, 2000)
[I] using data from Kitagawa et al. Diabetes Res Clin Pract 24 (Suppl.): S7, 1994 and Clin Pediatr 37: 111, 1998
[j] estimated from Karvonen et al. Diabetes Care 23:1516, 2000
[k] estimated from [j] using type1/type 2 prevalence rates

* Rates for Asians and Pacific Islanders in Hawaii are based on unpublished actual counts of cases of diabetes available in Hawaii

Table V - 9. Estimated Prevalence Denominators by Center, Age Group, and Ethnicity[a]

Estimated Number of Prevalent Cases Type 1

Age	NHW	AA	Hispanic	Asian	PI	Nat.Am.	Total
0 thru 9							
California	170740	32621	100294	28997	7249	1742	341,643
Colorado	302760	22787	56145	7558	1890	64853	455,993
Hawaii	26295	3310	13733	50754	20914	319	115,325
Ohio	235,458	31,556	0	0	0	0	267,014
Seattle	383,387	32446	26367	34422	8605	7783	493,010
S Carolina	44377	37798	2319	968	33	212	85,707
10 thru 19							
California	179361	34269	105359	30461	7615	1742	358,807
Colorado	261705	19464	49072	7290	1822	67412	406,765
Hawaii	28486	3585	14877	54984	22657	346	124,935
Ohio	249,921	33,495	0	0	0	0	283,416
Seattle	380465	29337	24479	37947	9487	8195	489,910
S Carolina	49497	42300	2585	1099	37	299	95,817

[a] Incidence denominators are estimated from the 2000 census for geographic-based centers (Cincinnati, Colorado, Seattle, S. Carolina, and from 2000 membership data for member-based centers (Hawaii and S. California. NHW = non-Hispanic white, AA = African American, PI = Pacific Islander, NA = Native American
* *Totals do not add due to rounding*

Table V - 10. Estimated Incidence Denominators by Center, Age Group, and Race/Ethnicity[a]

Age	NHW	AA	Hispanic	Asian	PI	NA	Total
0 thru 9							
California	170740	32621	100294	28997	7249	1742	341,643
Colorado	504413	32685	121224	14948	725	74453	748,448
Hawaii	32869	4137	17166	63443	26143	399	144,157
Ohio	235,458	31,556	0	0	0	0	267,014
Seattle	383,387	32446	26367	34422	8605	7783	493,010
S Carolina	319645	195522	17146	4727	173	1833	539,046
10 thru 19							
California	179361	34269	105359	30461	7615	1742	358,807
Colorado	451376	27703	102736	13234	642	76700	672,391
Hawaii	35608	4482	18596	68730	28321	433	156,170
Ohio	249,921	33,495	0	0	0	0	283,416
Seattle	380465	29337	24479	37947	9487	8195	489,910
S Carolina	341223	214334	16134	4966	202	2117	578,976
Total	**3284466**	**672587**	**549501**	**301875**	**89162**	**175397**	**5,072,988**

[a] Incidence denominators are estimated from the 2000 census for geographic-based centers (Cincinnati, Colorado, Seattle, S. Carolina, and from 2000 membership data for member-based centers (Hawaii and S. California. NHW = non-Hispanic white, AA = African American, PI = Pacific Islander, NA = Native American

* *Totals do not add due to rounding*

Appendix VI
Diabetes Definitions and Other Specific Types of Diabetes

Table 1 provides a list of diabetes definitions used throughout the protocol.

Table 1. Definitions of Types of Diabetes

Term	Definition	Comment
Type 1	The destruction of the beta cells leading to an absolute deficiency of insulin resulting in diabetes.	
Type 1a: general	The autoimmune destruction of the beta cells leading to an absolute deficiency of insulin resulting in diabetes.	
Type 1a: biochemical	Identified by the presence of diabetes and any one of 4 specific diabetes autoantibodies (DAA) and fasting c-peptide < 3.7 ng/ml. (See Diabetes Autoantibody below)	
Type 1: clinical	The presence of either diabetes onset < 10 years of age AND 1. weight < the 25th percentile for chronological age OR 2. BMI < 50th percentile for chronological age and gender	• measured within one year of diagnosis • measured within one year of diagnosis
Type 2 – general	The presence of insulin resistance and beta cell dysfunction resulting in diabetes	
Type 2: biochemical	The presence of diabetes and insulin resistance and the absence of autoimmune markers	
Type 2: clinical	The presence of diabetes and a) duration of diabetes > 1 years and no insulin therapy for > 1 month without an episode of diabetic ketoacidosis or b) duration of diabetes > 6 months and never treated with insulin.	
Other Types of Diabetes	The presence of a disease or the administration of a drug that results in beta cell destruction or dysfunction or inhibits the action of insulin resulting in diabetes.	See information below for details of specific diseases
Hybrid diabetes	Biochemical evidence of more than one type of diabetes.	Biochemical evidence of both autoimmunity and insulin resistance.

Gestational Diabetes	• Glucose intolerance first recognized during pregnancy
	• Six-weeks after the pregnancy ends, the women should be reclassified as
	  ○ diabetic
	  ○ impaired fasting glucose
	  ○ impaired glucose tolerance
	  ○ normoglycemic	

Term	Definition	Comment
Autoimmunity	1. cytoplasmic islet cell antibodies (ICA) 2. glutamic acid decarboxulase (GAD) 3. insulin autoantibodies 4. IA-II	▪ Plasma specimen ▪ Insulin autoantibodies must be performed within 10 days of initiation of exogenous insulin therapy or the presence of insulin autoantibodies ▪ The frequency of immune markers decreases with increased duration of disease with 65% of Type 1a persons having $\geq$ 1 positive immune markers with duration of disease of 10 years.
Insulinopenia	A fasting plasma c-peptide < 0.8 ng/ml	Obtained when the person is metabolically stable – defined as no episode of DKA for 1 month prior to laboratory testing. This concentration of c-peptide was chosen for the following reasons: ▪ In the Diabetes Control and Complications Trial, type 1A patients had c-peptide < 0.6 ng/ml ▪ In the Bogalusa Heart Study, the 5th percentile for fasting plasma c-peptide concentration was 0.8 ng/ml ▪ In health, non-diabetic Swedish subjects (7 to 34 years old) the 2.5th percentile was 0.7 ng/ml
Insulin Resistance	Fasting plasma c-peptide $\geq$ 3.7 ng./ml	This c-peptide was chosen because, in non-diabetic, health adolescents, the 95th percentile for fasting plasma c-peptide was $\geq$ 3.7 ng/ml

Other Specific Types of Diabetes

Other Specific Types of Diabetes is defined as the presence of a disease or the administration of a drug that results in beta cell destruction or dysfunction or inhibits the action of insulin resulting in diabetes. Autoimmune destruction of the beta cells is excluded from this category.

Other Specific Types of Diabetes are identified by the presence of:

- Diabetes

  AND

- a well defined disease or drug that results in destruction or dysfunction of the beta cells or inhibits the action of insulin.

Specific examples are:

Genetic defects of beta cell function.

- MODY 1: HNF 4 alpha
- MODY 2: Glucokinase
- MODY 3: HNF 1 alpha
- MODY 4: Insulin Promoter Factor 1
- MODY 5: HNF 1 beta
- Mitochondrial DNA
- Other

Genetic defects in insulin action

- Type A insulin resistance
- Leprechanism
- Rabson-Mendanhall Syndrome
- Lipotrophic diabetes
- Other

Disease of the exocrine Pancreas

- Pancreatitis
- Trauma/pancreatectomy
- Neoplaisa
- Cystic fibrosis
- Hemochromatosis
- Fibrocalaulus pancreatectomy
- Uncommon forms of immune-mediated diabetes
- "Stiff Man" Syndrome
- Anti-insulin receptor antibodies

Other genetic syndromes sometimes associated with diabetes

- Down's Syndrome
- Klinefelter's syndrome
- Turner's syndrome
- Wolfram's syndrome
- Fredreich's ataxia
- Huntington's Chorea
- Laurence-Moon-Biedl Syndrome
- Myotonic dystrophy
- Prophyria
- Prader-Willi syndrome
- Other

Drugs Potentially Causing Diabetes

- Vacor
- Petamindine
- Nicotinic acid
- Glucocorticoids
- Thyriod hormone
- Diazoxide
- Beta-adrenergis agents
- Thiazides
- Dilantin
- Gamma interferon

Appendix VIIa
Model Consents for Stimulated C-peptide Test
Incident Cases, Defined Cases of Diabetes: Insulin Production Test

1. Title and Introductory Paragraph

Title: SEARCH for Diabetes

We invite you (or your child) to take part in a research study to figure out how many children and teenagers in the United States have diabetes and to better figure out what type of diabetes you/your child has.

The reason for giving you the following information is to help you to decide if you would like to take part in this research study.

First, we want you to know four things that apply to all research at the [Name of Institute].
1. Taking part in the study is entirely voluntary, that is, by your choice.
2. You may not get any personal benefit from participation, but we may learn things that will benefit others.
3. Your decision or refusal to take part will not affect what medical care you/your child receives or how you/your child receives the medical care.
4. You may stop taking part in the study at any time without penalty or loss of benefits to which you are otherwise entitled.

If you have personal, religious, cultural, or ethical beliefs that you think might limit the types of tests you would agree to receive, please discuss them fully with your physicians or appropriate members of the research team before entering this study.

This consent form may contain some words that are not familiar to you. Please discuss any questions you have about this study with the research staff members.

2. Objectives of the Study

Diabetes is the third most common life-long disease in people under 20 years of age. The total number of cases of diabetes in this age group is increasing. Also, types of diabetes that have not been seen in young people are now being seen. These changes have resulted in gaps in knowledge about the total number of cases and types of diabetes in the United States, the type of care young people with diabetes receive, and the effect diabetes has on their lives. This research study will gather information to answer these questions.

You/your child have been asked to take part in this study because you/your child has diabetes. The purpose of the study is to learn in individuals under 20 years of age:
A) how many cases of diabetes there are in the United States;
B) more about the characteristics of each type of diabetes;

C) what medical care is being given;
D) how diabetes is affecting the lives of individuals with diabetes.

3. Procedures

You/your child have been asked to return for a test that measures how much insulin your/your body makes in over to learn more about how much insulin certain types of diabetes make over time.

The test to measure how much insulin your/your child's body makes will be done in the following way. A member of the research team will set yup an early morning appointment. You/your child will come to the appointment after not having anything but water to eat or drink for 10 hours. A small plastic needle will be placed in your/your child's forearm. You/your child will drink a liquid meal and blood will be drawn through the plastic needle every 30 minutes for 2 hours. Upon completion of the test, you/your child will be given breakfast.

Test results

A member of the research team will tell you the results of any information that is collected or tests that are done that may be important to your/your child's health or health care.

The research team will also tell the physicians who are taking care of you/your child the results of any tests that affect your/your child's health care.

☐ I agree to have the results shared with my physician. _____ initials

☐ I do not agree to have the results shared with my physician. _____ initials

4. Risks, Discomforts and Precautions

The risks from drawing blood from a vein in the lower arm include mild pain, bruising at the site of the blood draw, and occasionally fainting. To lower the possibility of these risks, blood will be drawn by experienced medical staff and a local numbing medicine may be placed on the skin before the blood is drawn to decrease any pain. The total amount of blood that will be obtained is between two teaspoonsful (10 cc) and 3 tablespoonsful (45cc).

The blood tests require that you/your child not eat any food overnight. In order to prevent low or high blood sugars, you/your child's blood sugar will be checked by finger-stick and your diabetes medication will be given as needed to control you/your child's blood sugar.

Some of the tests will look for the presence or risk of developing of the complications of diabetes. If these tests identify complications of diabetes or risk of developing the complications, the results may make you/your child anxious. If this happens, you/your child will be referred to local mental health professionals for evaluation and treatment.

Add institutional compensation statement, e.g., "You understand that if you believe you/your child have been injured as a result of participation in biomedical or behavior research, you are to

contact Dr. ….. at (add phone number). (Institution's name) follows a policy of making all decisions concerning compensation and/or medical treatment for physical injuries occurring during or caused by participation in biomedical or behavior research on an individual basis."

5. Benefits

There are no direct benefits from taking part in this study. However, this study may more clearly tell your/your child's type of diabetes and whether you/your child has any of the complications of diabetes. If you agree, this information will be shared with your health care professionals. This may allow them to change how your/your child's diabetes is taken care of and any complications that may be present.

There are also potential benefits to society from participation in this study. This is a large study being carried out at six major medical centers across the United States. The information obtained in this study will give a very good picture of how often young people develop diabetes and its complications and the effect of diabetes on their lives. This information will be important for planning the type of medical care young people with diabetes will need in the future.

6. Alternatives of Care

Whether you/your child decides to take part or declines to take part in this study, your decision will not affect your/your child's medical care.

7. Confidentiality of Records

The research team will keep the information collected, test done, and samples stored strictly private to the extent permitted by law. Any publication resulting from taking part in this study will not identify you/your child by name.

Upon entry into the study, a special number will be given to you/your child. The number will be used to identify the information and laboratory tests that will be done during this study. The special number and the information collected during this study will be sent to Wake Forest University in order to study the information. The list containing the special number assigned to you/your child will be kept in a locked file in the office of Dr. ……. Thus, no one other than Dr. ….. and his/her research team will be able to link any of the information collected to you/your child.

8. Availability of Information

As the results from the information gathered in this study become available, the results will be shared with you/your child and the meaning of the results explained. If you agree, the information will be shared with your/your child's health care professionals. If any questions come up about this study, you/your child can call Dr. (principal investigators name) at (principal investigator's phone number). For information about your rights as a research subject, you can call Dr. (name of the head of the local IRB) at (phone number of the local IRB).

9. The Right to Withdraw

You/your child may leave from this study at any time by writing a letter to Dr. (PI of the site) telling Dr. (PI) that you want to leave the study. If you/your child leave this study, you/your child can ask Dr. (PI) that any information collected be removed from the research file. Leaving study will have no effect on your/your child's ability to get medical care nor will it have any effect on the standard of care your/your child's health care professionals are giving.

10. Additional Elements of Consent

People who are under 18 years of age will receive a $20 gift certificate for taking part in the study. People who are greater than 18 years of age will receive $20 for taking part in the study.

11. Witnessing and Signatures

Based on the information provided above and having had the opportunity to discuss any concerns with the investigator or his designee, you voluntarily consent to take part in this research study**.**

_____
Subject's Signature

_____
Parent/Guardian's Signature (if Participant < 18 Years Of Age)

_____
Witness As To Voluntary Signature

_____
Investigator

_____
Date

Rev (date), Approved (date)

Model Consents for Stimulated C-peptide Test
Incident Case, undefined type of diabetes: Mixed meal challenge

1. Title and Introductory Paragraph

Title: SEARCH for Diabetes

We invite you (or your child) to take part in a research study to figure out how many children and teenagers in the United States have diabetes and to better figure out what type of diabetes you/your child has.

The reason for giving you the following information is to help you to decide if you would like to take part in this research study.

First, we want you to know four things that apply to all research at the [Name of Institute].
1. Taking part in the study is entirely voluntary, that is, by your choice.
2. You may not get any personal benefit from participation, but we may learn things that will benefit others.
3. Your decision or refusal to take part will not affect what medical care you/your child receives or how you/your child receives the medical care.
4. You may stop taking part in the study at any time without penalty or loss of benefits to which you are otherwise entitled.

If you have personal, religious, cultural, or ethical beliefs that you think might limit the types of tests you would agree to receive, please discuss them fully with your physicians or appropriate members of the research team before entering this study.

This consent form may contain some words that are not familiar to you. Please discuss any questions you have about this study with the research staff members.

2. Objectives of the Study

Diabetes is the third most common life-long disease in people under 20 years of age. The total number of cases of diabetes in this age group is increasing. Also, types of diabetes that have not been seen in young people are now being seen. These changes have resulted in gaps in knowledge about the total number of cases and types of diabetes in the United States, the type of care young people with diabetes receive, and the effect diabetes has on their lives. This research study will gather information to answer these questions.

You/your child have been asked to take part in this study because you/your child has diabetes. The purpose of the study is to learn in individuals under 20 years of age:
- A) how many cases of diabetes there are in the United States;
- B) more about the characteristics of each type of diabetes;
- C) what medical care is being given;
- D) how diabetes is affecting the lives of individuals with diabetes.

3. Procedures

You/your child have been asked to return for a mixed meal challenge test (a test that measures how much insulin your/your body makes) because the information collected during earlier visits was not enough to figure out what type of diabetes you/your child has. Measuring the amount of insulin your/your child's body makes will help to figure out what type of diabetes you/your child has.

The test to measure how much insulin your/your child's body makes will be done in the following way. A member of the research team will set up an early morning appointment. You/your child will come to the appointment after not having anything but water to eat or drink for 10 hours. A small plastic needle will be placed in your/your child's forearm. You/your child will drink a liquid meal and blood will be drawn through the plastic needle every 30 minutes for 2 hours. Upon completion of the test, you/your child will be given breakfast.

Test Each Year

You/your child will return each year for up to three years to see how much insulin your/your child's body makes.

Test results

A member of the research team will tell you the results of any information that is collected or tests that are done that may be important to your/your child's health or health care.

The research team will also tell the physicians who are taking care of you/your child the results of any tests that affect your/your child's health care.

☐ I agree to have the results shared with my physician. _____ initials

☐ I do not agree to have the results shared with my physician. _____ initials

4. Risks, Discomforts and Precautions

The risks from drawing blood from a vein in the lower arm include mild pain, bruising at the site of the blood draw, and occasionally fainting. To lower the possibility of these risks, blood will be drawn by experienced medical staff and a local numbing medicine may be placed on the skin before the blood is drawn to decrease any pain. The total amount of blood that will be obtained is between two teaspoonsful (10 cc) and 3 tablespoonsful (45cc).

The blood tests require that you/your child not eat any food overnight. In order to prevent low or high blood sugars, you/your child's blood sugar will be checked by finger-stick and your diabetes medication will be given as needed to control you/your child's blood sugar.

Some of the tests will look for the presence or risk of developing of the complications of diabetes. If these tests identify complications of diabetes or risk of developing the complications, the results may make you/your child anxious. If this happens, you/your child will be referred to local mental health professionals for evaluation and treatment.

Add institutional compensation statement, e.g., "You understand that if you believe you/your child have been injured as a result of participation in biomedical or behavior research, you are to contact Dr. ….. at (add phone number). (Institution's name) follows a policy of making all decisions concerning compensation and/or medical treatment for physical injuries occurring during or caused by participation in biomedical or behavior research on an individual basis."

5. Benefits

There are no direct benefits from taking part in this study. However, this study may more clearly tell your/your child's type of diabetes and whether you/your child has any of the complications of diabetes. If you agree, this information will be shared with your health care professionals. This may allow them to change how your/your child's diabetes is taken care of and any complications that may be present.

There are also potential benefits to society from participation in this study. This is a large study being carried out at six major medical centers across the United States. The information obtained in this study will give a very good picture of how often young people develop diabetes and its complications and the effect of diabetes on their lives. This information will be important for planning the type of medical care young people with diabetes will need in the future.

6. Alternatives of Care

Whether you/your child decides to take part or declines to take part in this study, your decision will not affect your/your child's medical care.

7. Confidentiality of Records

The research team will keep the information collected, test done, and samples stored strictly private to the extent permitted by law. Any publication resulting from taking part in this study will not identify you/your child by name.

Upon entry into the study, a special number will be given to you/your child. The number will be used to identify the information and laboratory tests that will be done during this study. The special number and the information collected during this study will be sent to Wake Forest University in order to study the information. The list containing the special number assigned to you/your child will be kept in a locked file in the office of Dr. ……. Thus, no one other than Dr. ….. and his/her research team will be able to link any of the information collected to you/your child.

8. Availability of Information

As the results from the information gathered in this study become available, the results will be shared with you/your child and the meaning of the results explained. If you agree, the information will be shared with your/your child's health care professionals. If any questions come up about this study, you/your child can call Dr. (principal investigators name) at (principal

investigator's phone number). For information about your rights as a research subject, you can call Dr. (name of the head of the local IRB) at (phone number of the local IRB).

9. The Right to Withdraw

You/your child may leave from this study at any time by writing a letter to Dr (PI of the site) telling Dr. (PI) that you want to leave the study. If you/your child leave this study, you/your child can ask Dr. (PI) that any information collected be removed from the research file. Leaving study will have no effect on your/your child's ability to get medical care nor will it have any effect on the standard of care your/your child's health care professionals are giving.

10. Additional Elements of Consent

People who are under 18 years of age will receive a $20 gift certificate for taking part in the study. People who are greater than 18 years of age will receive $20 for taking part in the study.

11. Witnessing and Signatures

Based on the information provided above and having had the opportunity to discuss any concerns with the investigator or his designee, you voluntarily consent to take part in this research study**.**

_____
Subject's Signature

_____
Parent/Guardian's Signature (if Participant <18 Years of Age)

_____
Witness As To Voluntary Signature

_____
Investigator

_____
Date

Rev (date), Approved (date)

Model Consents for Stimulated C-peptide Test
Prevalent case, undefined type of diabetes: Insulin Production Test

1. Title and Introductory Paragraph

Title: SEARCH for Diabetes

We invite you (or your child) to take part in a research study to figure out how many children and teenagers in the United States have diabetes and to better figure out what type of diabetes you/your child has.

The reason for giving you the following information is to help you to decide if you would like to take part in this research study.

First, we want you to know four things that apply to all research at the [Name of Institute].
1. Taking part in the study is entirely voluntary, that is, by your choice.
2. You may not get any personal benefit from participation, but we may learn things that will benefit others.
3. Your decision or refusal to take part will not affect what medical care you/your child receives or how you/your child receives the medical care.
4. You may stop taking part in the study at any time without penalty or loss of benefits to which you are otherwise entitled.

If you have personal, religious, cultural, or ethical beliefs that you think might limit the types of tests you would agree to receive, please discuss them fully with your physicians or appropriate members of the research team before entering this study.

This consent form may contain some words that are not familiar to you. Please discuss any questions you have about this study with the research staff members.

2. Objectives of the Study

Diabetes is the third most common life-long disease in people under 20 years of age. The total number of cases of diabetes in this age group is increasing. Also, types of diabetes that have not been seen in young people are now being seen. These changes have resulted in gaps in knowledge about the total number of cases and types of diabetes in the United States, the type of care young people with diabetes receive, and the effect diabetes has on their lives. This research study will gather information to answer these questions.

You/your child have been asked to take part in this study because you/your child has diabetes. The purpose of the study is to learn in individuals under 20 years of age:
A) how many cases of diabetes there are in the United States;
B) more about the characteristics of each type of diabetes;
C) what medical care is being given;
D) how diabetes is affecting the lives of individuals with diabetes.

3. Procedures

You/your child have been asked to return for a test that measures how much insulin your/your body makes because the information collected during earlier visits was not enough to figure out what type of diabetes you/your child has. Measuring the amount of insulin your/your child's body makes will help to figure out what type of diabetes you/your child has.

The test to measure how much insulin your/your child's body makes will be done in the following way. A member of the research team will set up an early morning appointment. You/your child will come to the appointment after not having anything but water to eat or drink for 10 hours. A small plastic needle will be placed in your/your child's forearm. You/your child will drink a liquid meal and blood will be drawn through the plastic needle every 30 minutes for 2 hours. Upon completion of the test, you/your child will be given breakfast.

Test results

A member of the research team will tell you the results of any information that is collected or tests that are done that may be important to your/your child's health or health care.

The research team will also tell the physicians who are taking care of you/your child the results of any tests that affect your/your child's health care.

☐ I agree to have the results shared with my physician. _____ initials

☐ I do not agree to have the results shared with my physician. _____ initials

4. Risks, Discomforts and Precautions

The risks from drawing blood from a vein in the lower arm include mild pain, bruising at the site of the blood draw, and occasionally fainting. To lower the possibility of these risks, blood will be drawn by experienced medical staff and a local numbing medicine may be placed on the skin before the blood is drawn to decrease any pain. The total amount of blood that will be obtained is between two teaspoonsful (10 cc) and 3 tablespoonsful (45cc).

The blood tests require that you/your child not eat any food overnight. In order to prevent low or high blood sugars, you/your child's blood sugar will be checked by finger-stick and your diabetes medication will be given as needed to control you/your child's blood sugar.

Some of the tests will look for the presence or risk of developing of the complications of diabetes. If these tests identify complications of diabetes or risk of developing the complications, the results may make you/your child anxious. If this happens, you/your child will be referred to local mental health professionals for evaluation and treatment.

Add institutional compensation statement, e.g., "You understand that if you believe you/your child have been injured as a result of participation in biomedical or behavior research, you are to contact Dr. ….. at (add phone number). (Institution's name) follows a policy of making all

decisions concerning compensation and/or medical treatment for physical injuries occurring during or caused by participation in biomedical or behavior research on an individual basis."

5. Benefits

There are no direct benefits from taking part in this study. However, this study may more clearly tell your/your child's type of diabetes and whether you/your child has any of the complications of diabetes. If you agree, this information will be shared with your health care professionals. This may allow them to change how your/your child's diabetes is taken care of and any complications that may be present.

There are also potential benefits to society from participation in this study. This is a large study being carried out at six major medical centers across the United States. The information obtained in this study will give a very good picture of how often young people develop diabetes and its complications and the effect of diabetes on their lives. This information will be important for planning the type of medical care young people with diabetes will need in the future.

6. Alternatives of Care

Whether you/your child decides to take part or declines to take part in this study, your decision will not affect your/your child's medical care.

7. Confidentiality of Records

The research team will keep the information collected, test done, and samples stored strictly private to the extent permitted by law. Any publication resulting from taking part in this study will not identify you/your child by name.

The special number has been given to identify the information and laboratory tests that will be done during this study. The special number and the information collected during this study will be sent to Wake Forest University in order to study the information. The list containing the special number assigned to you/your child will be kept in a locked file in the office of Dr. ……. Thus, no one other than Dr. ….. and his/her research team will be able to link any of the information collected to you/your child.

8. Availability of Information

As the results from the information gathered in this study become available, the results will be shared with you/your child and the meaning of the results explained. If you agree, the information will be shared with your/your child's health care professionals. If any questions come up about this study, you/your child can call Dr (principal investigators name) at (principal investigator's phone number). For information about your rights as a research subject, you can call Dr. (name of the head of the local IRB) at (phone number of the local IRB).

9. The Right to Withdraw

You/your child may leave from this study at any time by writing a letter to Dr (PI of the site) telling Dr. (PI) that you want to leave the study. If you/your child leave this study, you/your child can ask Dr. (PI) that any information collected be removed from the research file. Leaving study will have no effect on your/your child's ability to get medical care nor will it have any effect on the standard of care your/your child's health care professionals are giving.

10. Additional Elements of Consent

People who are under 18 years of age will receive a $20 gift certificate for taking part in the study. People who are 18 years of age or older will receive $20 for participating in this study.

11. Witnessing and Signatures

Based on the information provided above and having had the opportunity to discuss any concerns with the investigator or his designee, you voluntarily consent to take part in this research study**.**

_____
Subject's Signature

_____
Parent/Guardian's Signature (if Participant <18 Years of Age)

_____
Witness As To Voluntary Signature

_____
Investigator

_____
Date

Rev (date), Approved (date)

Appendix VIIb
Model Consents for In-Person Module
Incident Case: In-person Visit

1. Title and Introductory Paragraph

Title: SEARCH for Diabetes

We invite you (or your child) to take part in a research study to figure out how many children and teenagers in the United States have diabetes and to better figure out what type of diabetes you/your child has.

The reason for giving you the following information is to help you to decide if you would like to take part in this research study.

First, we want you to know four things that apply to all research at the [Name of Institute].
1. Taking part in the study is entirely voluntary, that is, by your choice.
2. You may not get any personal benefit from participation, but we may learn things that will benefit others.
3. Your decision or refusal to take part will not affect what medical care you/your child receives or how you/your child receives the medical care.
4. You may stop taking part in the study at any time without penalty or loss of benefits to which you are otherwise entitled.

If you have personal, religious, cultural, or ethical beliefs that you think might limit the types of tests you would agree to receive, please discuss them fully with your physicians or appropriate members of the research team before entering this study.

This consent form may contain some words that are not familiar to you. Please discuss any questions you have about this study with the research staff members.

2. Objectives of the Study

Diabetes is the third most common life-long disease in people under 20 years of age. The total number of cases of diabetes in this age group is increasing. Also, types of diabetes that have not been seen in young people are now being seen. These changes have resulted in gaps in knowledge about the total number of cases and types of diabetes in the United States, the type of care young people with diabetes receive, and the effect diabetes has on their lives. This research study will gather information to answer these questions.

You/your child have been asked to take part in this study because you/your child has diabetes. The purpose of the study is to learn in individuals under 20 years of age:
- A) how many cases of diabetes there are in the United States;
- B) more about the characteristics of each type of diabetes;
- C) what medical care is being given;
- D) how diabetes is affecting the lives of individuals with diabetes.

3. Procedures

You understand that this study is made up of three parts: an in-person visit, a written series of questions, and a review your/your child's medical records to get all the information needed about your/your child's diabetes to answer the questions of this study. You also understand that you/your child will return each year for up to 3 years for an in-person visit that will include a personal and family medical history, a physical examination, a blood and urine sample, and a series of written and verbal questions.

In-person visit

A research team member will set up an appointment for you/your child. The appointment will be in the early morning. You/your child will come to the appointment after not having anything to eat or drink other than water for 10 hours. You/your child will not take your usual diabetes medicines until after you/your child has been given breakfast.

When you/your child arrives, blood will be taken from your/your child's arm to measure blood sugar, hemoglobin A1c (a measure of long-term blood sugar control), c-peptide (a measure of your/your child's own insulin production), different types of cholesterol (fat), and islet cell antibodies (markers in the blood for type 1 diabetes). A urine sample will also be obtained and tested to see if diabetes is affecting your/your child's kidneys. After these tests are done, you/your child will be given breakfast.

After breakfast, you/your child will take your usual diabetes medicine and have your personal and family medical history and a physical examination done by trained medical staff. The physical examination will include height, weight, waist measurement, heart rate, blood pressure, and examination of the skin of the neck.

Test results

A member of the research team will tell you the results of any information that is collected or tests that are done that may be important to your/your child's health or health care.

The research team will also tell the physicians who are taking care of you/your child the results of any tests that affect your/your child's health care.

☐ I agree to have the results shared with my physician. _____ initials

☐ I do not agree to have the results shared with my physician. _____ initials

Written Series of Questions

After the medical and family history and physical examination are done, you/your child will complete a written series of questions. The written series of questions will collect information about the effect that diabetes has had on your/your child's life, your social and income level, types of diabetes education you/your child have received, diabetes self-care habits you/your child do, and who takes care of your/your child's diabetes and general medical care. You/your child will also be sent a written series of questions every 12 months asking for information about your/your child's use of the health care system.

IF you/your child is 10 years of age or older, you/your child will be asked to answer a separate written series of questions dealing with the following health issues – physical activity, smoking, eating and sleeping patterns, and depression. If your child is between 10 and 17 years of age, this information will not be shared with you unless health issues are identified that need to be treated. The reason why the information will not be shared with you is to increase the likelihood that your child will answer the questions more accurately.

☐ I agree to have my child complete this series of questions. _____ Initials

☐ I do not agree to have my child complete this series of questions. _____ Initials

Medical Record Review

You/your child's medical records may also be reviewed to get information about your/your child's diagnosis and diabetes care since diagnosis. Specific information that will be recorded from your/your child's medical records at the time of diagnosis includes age, symptoms, laboratory tests and physical examination recorded. Information that will be recorded since diagnosis includes what medical care was done, what type and how often diabetes education was done, and how often tests for the complications of diabetes (high blood sugar, eye, kidney, cholesterol, and thyroid tests) were done.

Saving of blood and urine

Blood and urine will be saved for the duration of the study and used in the future as new tests are developed to learn more about the type of diabetes and when someone has or is at risk to get the complications of diabetes. If the results of the new tests affect your/your child's health, you will be informed of the test results.

☐ I agree to have my/my child's blood and urine saved for the duration of the study and used in the future for new tests as they are developed to learn more about the types of diabetes and the risk of developing the complications of diabetes. _____ Initials

☐ I do not agree to have my/my child's blood and urine saved for the duration of the study and used in the future for new tests as they are developed to learn more about the types of diabetes and the risk of developing the complications of diabetes. _____ Initials

Saving of DNA

DNA is found in all of your cells. DNA makes up your genes (the "blue print" for all inherited traits). Your genes decide how tall you are, what color hair you have, and all other body traits. The DNA in each person's body is different from every other person's DNA (except identical twins or triplets who have the same DNA). The differences may be why some people are more likely to get certain diseases like diabetes. DNA will be saved and used in the future as new tests are developed to tell your/your child's type of diabetes and the risk of developing the complications of diabetes, insulin resistance (insulin is not working as well as it should), and obesity. If the results of the new tests affect your/your child's health, you will be informed of the test results.

☐ I agree to have my/my child's DNA saved for the duration of the study and used in the future as new tests are developed to tell the type of diabetes and the risk of developing the complications of diabetes, insulin resistance (insulin is not working as well as it should), and obesity. _____ initials

☐ I do not agree to have my/my child's DNA saved for the duration of the study and used in the future as new tests are developed to tell the type of diabetes and the risk of developing the complications of diabetes, insulin resistance (insulin is not working as well as it should), and being overweight. _____ initials

Other tests

The information obtained at the in-person visit will be used to tell the type of diabetes you/your child has. In some cases the information will not be enough to tell the type of diabetes. If you/your child's type of diabetes cannot be clearly established, you/your child will be asked to have a test done that will measure how much insulin your/your child's body makes. The details of this test will be explained and you will be asked to complete a separate consent form at the time of these tests. Some individuals whose type of diabetes is clearly defined may also be asked to come back for these tests in order to better define how much insulin the different types of diabetes make.

Test Each Year

You/your child will come back each year for up to three years for an in-person visit, series of written and verbal questions, and other tests as described above. This information will be used to better tell your/your child's type of diabetes and follow changes in the type and care of diabetes over time.

Contact in the future

The researchers will call you as new studies are developed in the future to let you know about new studies and ask you/your child to take part in these studies. As with this study, taking part in any future study is voluntary. Taking part in the present study does not mean that you are agreeing to take part in any future study.

☐ I agree to be called in the future. _____ initials

☐ I do not agree to be called in the future. _____ initials

4. Risks, Discomforts and Precautions

The risks from drawing blood from a vein in the lower arm include mild pain, bruising at the site of the blood draw, and occasionally fainting. To lower the possibility of these risks, blood will be drawn by experienced medical staff and a local numbing medicine may be placed on the skin before the blood is drawn to decrease any pain. The total amount of blood that will be obtained is between two teaspoonsful (10 cc) and 3 tablespoonsful (45cc).

The blood tests require that you/your child not eat any food overnight. In order to prevent low or high blood sugars, you/your child's blood sugar will be checked by finger-stick and your diabetes medication will be given as needed to control you/your child's blood sugar.

Some of the tests will look for the presence or risk of developing of the complications of diabetes. If these tests identify complications of diabetes or risk of developing the complications, the results may make you/your child anxious. If this happens, you/your child will be referred to local mental health professionals for evaluation and treatment.

Add institutional compensation statement, e.g., "You understand that if you believe you/your child have been injured as a result of participation in biomedical or behavior research, you are to contact Dr. ….. at (add phone number). (Institution's name) follows a policy of making all decisions concerning compensation and/or medical treatment for physical injuries occurring during or caused by participation in biomedical or behavior research on an individual basis."

5. Benefits

There are no direct benefits from taking part in this study. However, this study may more clearly tell your/your child's type of diabetes and whether you/your child has any of the complications of diabetes. If you agree, this information will be shared with your health care professionals. This may allow them to change how your/your child's diabetes is taken care of and any complications that may be present.

There are also potential benefits to society from participation in this study. This is a large study being carried out at six major medical centers across the United States. The information obtained in this study will give a very good picture of how often young people develop diabetes and its complications and the effect of diabetes on their lives. This information will be important for planning the type of medical care young people with diabetes will need in the future.

6. Alternatives of Care

Whether you/your child decides to take part or declines to take part in this study, your decision will not affect your/your child's medical care.

7. Confidentiality of Records

The research team will keep the information collected, tests done, and samples stored strictly private to the extent permitted by law. Any publication resulting from taking part in this study will not identify you/your child by name.

Upon entry into the study, a special number will be given to you/your child. The number will be used to identify the information and laboratory tests that will be done during this study. The special number and the information collected during this study will be sent to Wake Forest University in order to study the information. The list containing the special number assigned to you/your child will be kept in a locked file in the office of Dr. …….. Thus, no one other than Dr. ….. and his/her research team will be able to link any of the information collected about you/your child.

8. Availability of Information

As the results from the information gathered in this study become available, the results will be shared with you/your child and the meaning of the results explained. If you agree, the information will be shared with your/your child's health care professionals. If any questions come up about this study, you/your child can call Dr (principal investigators name) at (principal investigator's phone number). For information about your rights as a research subject, you can call Dr. (name of the head of the local IRB) at (phone number of the local IRB).

9. The Right to Withdraw

You/your child may leave from this study at any time by writing a letter to Dr (PI of the site) telling Dr. (PI) that you want to leave the study. If you/your child leave this study, you/your child can ask Dr. (PI) that any information collected be removed from the research file and any blood, urine or DNA saved be destroyed and this will be done. Leaving study will have no effect on your/your child's ability to get medical care nor will it have any effect on the standard of care your/your child's health care professionals are giving.

10. Additional Elements of Consent

People who are under 18 years of age will receive a $20 gift certificate for taking part in the study. People who are greater than 18 years of age will receive $20 for taking part in the study. The parent who accompanies their child to the in-person visit will also receive $20.

11. Witnessing and Signatures

Based on the information provided above and having had the opportunity to discuss any concerns with the investigator or his designee, you voluntarily consent to take part in this research study**.**

_____
Subject's Signature

_____
Parent/Guardian's Signature (If Participant <18 Years of Age)

_____
Witness As To Voluntary Signature

_____
Investigator

_____
Date

Rev (date), Approved (date)

Model Consents for In-Person Module
Prevalent Case: In-person Visit

1. Title and Introductory Paragraph

Title: SEARCH for Diabetes

We invite you (or your child) to take part in a research study to figure out how many children and teenagers in the United States have diabetes and to better figure out what type of diabetes you/your child has.

The reason for giving you the following information is to help you to decide if you would like to take part in this research study.

First, we want you to know four things that apply to all research at the [Name of Institute].
1. Taking part in the study is entirely voluntary, that is, by your choice.
2. You may not get any personal benefit from participation, but we may learn things that will benefit others.
3. Your decision or refusal to take part will not affect what medical care you/your child receives or how you/your child receives the medical care.
4. You may stop taking part in the study at any time without penalty or loss of benefits to which you are otherwise entitled.

If you have personal, religious, cultural, or ethical beliefs that you think might limit the types of tests you would agree to receive, please discuss them fully with your physicians or appropriate members of the research team before entering this study.

This consent form may contain some words that are not familiar to you. Please discuss any questions you have about this study with the research staff members.

2. Objectives of the Study

Diabetes is the third most common life-long disease in people under 20 years of age. The total number of cases of diabetes in this age group is increasing. Also, types of diabetes that have not been seen in young people are now being seen. These changes have resulted in gaps in knowledge about the total number of cases and types of diabetes in the United States, the type of care young people with diabetes receive, and the effect diabetes has on their lives. This research study will gather information to answer these questions.

You/your child have been asked to take part in this study because you/your child has diabetes. The purpose of the study is to learn in individuals under 20 years of age:
- A) how many cases of diabetes there are in the United States;
- B) more about the characteristics of each type of diabetes;
- C) what medical care is being given;
- D) how diabetes is affecting the lives of individuals with diabetes.

3. Procedures

You understand that this study is made up of three parts: an in-person visit, a written series of questions, and a review your/your child's medical records to get all the information needed about your/your child's diabetes to answer the questions of this study.

In-person visit

A research team member will set up an appointment for you/your child. The appointment will be in the early morning. You/your child will come to the appointment after not having anything to eat or drink other than water for 10 hours. You/your child will not take your usual diabetes medicines until after you/your child has been given breakfast.

When you/your child arrives, blood will be taken from your/your child's arm to measure blood sugar, hemoglobin A1c (a measure of long-term blood sugar control), c-peptide (a measure of your/your child's own insulin production), different types of cholesterol (fat), and islet cell antibodies (markers in the blood for type 1 diabetes). A urine sample will also be obtained and tested to see if diabetes is affecting your/your child's kidneys. After these tests are done, you/your child will be given breakfast.

After breakfast, you/your child will take your usual diabetes medicine and have your personal and family medical history and a physical examination done by trained medical staff. The physical examination will include height, weight, waist measurement, heart rate, blood pressure, and examination of the skin of the neck.

Test results

A member of the research team will tell you the results of any information that is collected or tests that are done that may be important to your/your child's health or health care.

The research team will also tell the physicians who are taking care of you/your child the results of any tests that affect your/your child's health care.

☐ I agree to have the results shared with my physician. _____ initials

☐ I do not agree to have the results shared with my physician. _____ initials

Written Series of Questions

After the medical and family history and physical examination are done, you/your child will complete a written series of questions. The written series of questions will collect information about the effect that diabetes has had on your/your child's life, your social and income level, types of diabetes education you/your child have received, diabetes self-care habits you/your child do, and who takes care of your/your child's diabetes and general medical care. You/your child will also be sent a written series of questions every 12 months asking for information about your/your child's use of the health care system.

If you/your child is 10 years of age or older, you/your child will be asked to answer a separate written series of questions dealing with the following health issues – physical activity, smoking, eating and sleeping patterns, and depression. If your child is between 10 and 17 years of age, this information will not be shared with you unless health issues are identified that need to be treated. The reason why the information will not be shared with you is to increase the likelihood that your child will answer the questions more accurately.

☐ I agree to have my child complete this series of questions. _____ initials

☐ I do not agree to have my child complete this series of questions. _____ initials

Saving of blood and urine

Blood and urine will be saved for the duration of the study and used in the future as new tests are developed to learn more about the types of diabetes and when someone has or is at risk to get the complications of diabetes. If the results of the tests affect your/your child's health, you will be informed of the test results.

☐ I agree to have my/my child's blood and urine saved and used in the future for new tests as they are developed to learn more about the types of diabetes and the risk of developing the complications of diabetes. _____ initials

☐ I do not agree to have my/my child's blood and urine saved and used in the future for new tests as they are developed to learn more about the types of diabetes and the risk of developing the complications of diabetes. _____ initials

Saving of DNA

DNA is found in all of your cells. DNA makes up your genes. Your genes decide how tall you are, what color hair you have, and all other body traits. The DNA in each person's body is different from every other person's DNA (except identical twins or triplets who have the same DNA). The differences may be why some people are more likely to get certain diseases like diabetes. DNA will be saved and used in the future as new tests are developed to tell your/your child's type of diabetes and the risk of developing the complications of diabetes, insulin resistance (insulin is not working as well as it should), and being overweight.

☐ I agree to have my/my child's DNA stored for the duration of the study and used in the future as new tests are developed to define the type of diabetes and the risk of developing the complications of diabetes, insulin resistance (insulin is not working as well as it should), and obesity. _____ initials

☐ I do not agree to have my/my child's DNA stored for the duration of the study and used in the future as new tests are developed to define the type of diabetes and the risk of developing the complications of diabetes, insulin resistance (insulin is not working as well as it should), and obesity. _____ initials

Insulin Production Test (how much insulin your body makes)

The information obtained at the in-person visit will be used to tell the type of diabetes you/your child has. In some cases the information will not be enough to tell the type of diabetes. If you/your child's type of diabetes cannot be clearly established, you/your child will be asked to have a test done that will measure how much insulin your/your child's body makes. The details of this test will be explained and you will be asked to complete a separate consent form at the time of the test.

Contact in the future

The researchers will call you as new studies are developed in the future to let you know about new studies and ask you/your child to take part in these studies. As with this study, taking part in any future study is voluntary. Taking part in the present study does not mean that you are agreeing to take part in any future study.

☐ I agree to be called in the future. _____ initials

☐ I do not agree to be called in the future. _____ initials

4. Risks, Discomforts and Precautions

The risks from drawing blood from a vein in the lower arm include mild pain, bruising at the site of the blood draw, and occasionally fainting. To lower the possibility of these risks, blood will be drawn by experienced medical staff and a local numbing medicine may be placed on the skin before the blood is drawn to decrease any pain. The total amount of blood that will be obtained is between two teaspoonsful (10 cc) and 3 tablespoonsful (45cc).

The blood tests require that you/your child not eat any food overnight. In order to prevent low or high blood sugars, you/your child's blood sugar will be checked by finger-stick and your diabetes medicine will be given as needed to control your/your child's blood sugar.

Some of the tests will look for the presence or risk of developing of the complications of diabetes. If these tests identify complications of diabetes or risk of developing the complications, the results may make you/your child anxious. If this happens, you/your child will be referred to local mental health professionals for evaluation and treatment.

Add institutional compensation statement, e.g., "You understand that if you believe you/your child have been injured as a result of participation in biomedical or behavior research, you are to contact Dr. ….. at (add phone number). (Institution's name) follows a policy of making all decisions concerning compensation and/or medical treatment for physical injuries occurring during or caused by participation in biomedical or behavior research on an individual basis."

Benefits

There are no direct benefits from participating in this study. However, this study may more clearly define your/your child's type of diabetes and the presence or absence of some of the complications of diabetes. With your permission, this information will be shared with your

health care professionals and may allow them to change the management of your/your child's diabetes and any complications that may be present.

There are also potential benefits to society from participation in this study. This is a large study being carried out at six major medical centers across the United States. The information obtained in this study will give a very good picture of the frequency of diabetes and its complications and the effect of diabetes on the lives of individuals under 20 years of age. This information will be important in the planning of the distribution of medical and financial resources for the care of young people with diabetes in the future.

Alternatives of Care

Whether you/your child decides to take part or declines to take part in this study, your decision will not affect your/your child's medical care.

Confidentiality of Records

The research team will keep the information collected, tests done, and samples stored strictly private to the extent permitted by law. Any publication resulting from taking part in this study will not identify you/your child by name.

Upon entry into the study, a special number will be given to you/your child. The number will be used to identify the information and laboratory tests that will be done during this study. The special number and the information collected during this study will be sent to Wake Forest University in order to study the information. The list containing the special number assigned to you/your child will be kept in a locked file in the office of Dr. ……. Thus, no one other than Dr. ….. and his/her research team will be able to link any of the information collected about you/your child.

Availability of Information

As the results from the information gathered in this study become available, the results will be shared with you/your child and the meaning of the results explained. If you agree, the information will be shared with your/your child's health care professionals. If any questions come up about this study, you/your child can call Dr. (principal investigators name) at (principal investigator's phone number). For information about your rights as a research subject, you can call Dr. (name of the head of the local IRB) at (phone number of the local IRB).

5. The Right to Withdraw

You/your child may leave from this study at any time by writing a letter to Dr. (PI of the site) telling Dr. (PI) that you want to leave the study. If you/your child leave this study, you/your child can ask Dr. (PI) in a letter to remove from the research file any information collected or any saved blood, urine or DNA and this will be done. Leaving study will have no effect on your/your child's ability to get medical care nor will it have any effect on the standard of care your/your child's health care professionals are giving.

6. Additional Elements of Consent

People who are under 18 years of age will receive a $20 gift certificate for taking part in the study. People who are greater than 18 years of age will receive $20 for taking part in the study. The parent who accompanies their child to the in-person visit will also receive $20.

7. Witnessing and Signatures

Based on the information provided above and having had the opportunity to discuss any concerns with the investigator or his designee, you voluntarily consent to take part in this research study**.**

_____
Subject's Signature

_____
Parent/Guardian's Signature (If Participant <18 Years of Age)

_____
Witness As To Voluntary Signature

_____
Investigator

_____
Date

Rev (date), Approved (date)

Appendix VIIc
Model Consents for Medical Record Module
Medical Record Module

1. Title and Introductory Paragraph

Title: SEARCH for Diabetes

We invite you (or your child) to take part in a research study to figure out how many children and teenagers in the United States have diabetes and to better figure out what type of diabetes you/your child has.

The reason for giving you the following information is to help you to decide if you would like to take part in this research study.

First, we want you to know four things that apply to all research at the [Name of Institute].
1. Taking part in the study is entirely voluntary, that is, by your choice.
2. You may not get any personal benefit from participation, but we may learn things that will benefit others.
3. Your decision or refusal to take part will not affect what medical care you/your child receives or how you/your child receives the medical care.
4. You may stop taking part in the study at any time without penalty or loss of benefits to which you are otherwise entitled.

If you have personal, religious, cultural, or ethical beliefs that you think might limit the types of tests you would agree to receive, please discuss them fully with your physicians or appropriate members of the research team before entering this study.

This consent form may contain some words that are not familiar to you. Please discuss any questions you have about this study with the research staff members.

2. Objectives of the Study

Diabetes is the third most common life-long disease in people under 20 years of age. The total number of cases of diabetes in this age group is increasing. Also, types of diabetes that have not been seen in young people are now being seen. These changes have resulted in gaps in knowledge about the total number of cases and types of diabetes in the United States, the type of care young people with diabetes receive, and the effect diabetes has on their lives. This research study will gather information to answer these questions.

You/your child have been asked to take part in this study because you/your child has diabetes. The purpose of the study is to learn in individuals under 20 years of age:

A) how many cases of diabetes there are in the United States;
B) more about the characteristics of each type of diabetes;

C) what medical care is being given;
D) how diabetes is affecting the lives of individuals with diabetes.

3. Procedures

You understand that this study consists of a review of your/your child's medical records.

Medical Record Review
You/your child's medical records may be reviewed to get information about your/your child's diagnosis and diabetes care since diagnosis. Specific information that will be recorded from your/your child's medical records at the time of diagnosis includes age, symptoms, laboratory tests and physical examination recorded. Information that will be recorded since diagnosis includes what medical care was done, what type and how often diabetes education was done, and how often tests for the complications of diabetes (high blood sugar, eye, kidney, cholesterol, and thyroid tests) were done.

Test results
A member of the research team will tell you the results of any information that is collected or tests that are done that may be important to your/your child's health or health care.

The research team will also tell the physicians who are taking care of you/your child the results of any tests that affect your/your child's health care.

☐ I agree to have the results shared with my physician. _____ initials

☐ I do not agree to have the results shared with my physician. _____ initials

Future contact
The researchers will call you as new studies are developed in the future to let you know about new studies and ask you/your child to take part in these studies. As with this study, taking part in any future study is voluntary. Taking part in the present study does not mean that you are agreeing to take part in any future study.

☐ I agree to be called in the future. _____ initials

☐ I do not agree to be called in the future. _____ initials

4. Risks, Discomforts and Precautions

There are no known risks associated with the review of your/ your child's medical records.

Add institutional compensation statement, e.g., "You understand that if you believe you/your child have been injured as a result of participation in biomedical or behavior research, you are to contact Dr. ….. at (add phone number). (Institution's name) follows a policy of making all

decisions concerning compensation and/or medical treatment for physical injuries occurring during or caused by participation in biomedical or behavior research on an individual basis.

5. Benefits

There are no direct benefits from taking part in this study. However, this study may more clearly identify your/your child's type of diabetes and whether you/your child has any of the complications of diabetes. If you agree, this information will be shared with your health care professionals. This may allow them to change how your/your child's diabetes is taken care of and any complications that may be present.

There are also potential benefits to society from participation in this study. This is a large study being carried out at six major medical centers across the United States. The information obtained in this study will give a very good picture of how often young people develop diabetes and its complications and the effect of diabetes on their lives. This information will be important for planning the type of medical care young people with diabetes will need in the future.

6. Alternatives of Care

Whether your/your child decides to take part or not take part in this study, this decision will not affect you/your child's medical care.

7. Confidentiality of Records

The research team will keep the information collected, test done, and samples stored strictly private to the extent permitted by law. Any publication resulting from taking part in this study will not identify you/your child by name.

Upon entry into the study, a special number will be given to you/your child. The number will be used to identify the information that will be obtained during this study. The special number and the information collected during this study will be sent to Wake Forest University in order to study the information. The list containing the special number assigned to you/your child will be kept in a locked file in the office of Dr. ……. Thus, no one other than Dr. ….. and his/her research team will be able to link any of the information collected about you/your child.

8. Availability of Information

As the results from the information gathered in this study become available, the results will be shared with you/your child and the meaning of the results explained. If you agree, the information will be shared with your/your child's health care professionals. If any questions come up about this study, you/your child can call Dr (principal investigators name) at (principal investigator's phone number). For information about your rights as a research subject, you can call Dr. (name of the head of the local IRB) at (phone number of the local IRB).

9. The Right to Withdraw

You/your child may leave from this study at any time by writing a letter to Dr. (PI of the site) telling Dr. (PI) that you want to leave the study. If you/your child leave this study, you/your child can ask Dr. (PI) that any information collected be removed from the research file and this will be done. Leaving the study will have no effect on your/your child's ability to get medical care nor will it have any effect on the standard of care your/your child's health care professionals are giving.

10. Additional Elements of Consent

None.

11. Witnessing and Signatures

Based on the information provided above and having had the opportunity to discuss any concerns with the investigator or his designee, you voluntarily consent to take part in this research study**.**

_____
Subject's Signature

_____
Parent/Guardian's Signature (if Participant <18 Years of Age)

_____
Witness As To Voluntary Signature

_____
Investigator

_____
Date

Rev (date), Approved (date)

Model Consents for Medical Record Module
Survey Module

1. Title and Introductory Paragraph

Title: SEACRH for Diabetes

We invite you (or your child) to take part in a research study to figure out how many children and teenagers in the United States have diabetes and to better figure out what type of diabetes you/your child has.

The reason for giving you the following information is to help you to decide if you would like to take part in this research study.

First, we want you to know four things that apply to all research at the [Name of Institute].
1. Taking part in the study is entirely voluntary, that is, by your choice.
2. You may not get any personal benefit from participation, but we may learn things that will benefit others.
3. Your decision or refusal to take part will not affect what medical care you/your child receives or how you/your child receives the medical care.
4. You may stop taking part in the study at any time without penalty or loss of benefits to which you are otherwise entitled.

If you have personal, religious, cultural, or ethical beliefs that you think might limit the types of tests you would agree to receive, please discuss them fully with your physicians or appropriate members of the research team before entering this study.

This consent form may contain some words that are not familiar to you. Please discuss any questions you have about this study with the research staff members.

2. Objectives of the Study

Diabetes is the third most common life-long disease in people under 20 years of age. The total number of cases of diabetes in this age group is increasing. Also, types of diabetes that have not been seen in young people are now being seen. These changes have resulted in gaps in knowledge about the total number of cases and types of diabetes in the United States, the type of care young people with diabetes receive, and the effect diabetes has on their lives. This research study will gather information to answer these questions.

You/your child have been asked to take part in this study because you/your child has diabetes. The purpose of the study is to learn in individuals under 20 years of age:
A) how many cases of diabetes there are in the United States;
B) more about the characteristics of each type of diabetes;
C) what medical care is being given;
D) how diabetes is affecting the lives of individuals with diabetes.

3. Procedures

You understand that this study consists of a series of written questions and a review of your/your child's medical records. The questionnaires will be done either in-person, over the phone, or in written questionnaires.

Series of written questions
You/your child will complete an in-person, phone or written series of questions that will get the following information: age, gender, date of diagnosis, ethnic background, age at diagnosis, symptoms at diagnosis, laboratory tests to confirm the diagnosis of diabetes, personal and family medical history, type of diabetes, type of diabetes care, who delivered the diabetes care, laboratory tests performed to monitor the diabetes care, and any complications associated with the management of the diabetes.

Test results
A member of the research team will tell you the results of any information that is collected or tests that are done that may be important to your/your child's health or health care.

The research team will also tell the physicians who are taking care of you/your child the results of any tests that affect your/your child's health care.

☐ I agree to have the results shared with my physician. _____ initials

☐ I do not agree to have the results shared with my physician. _____ initials

Contact in the future
The researchers will call you as new studies are developed in the future to let you know about new studies and ask you/your child to take part in these studies. As with this study, taking part in any future study is voluntary. Taking part in the present study does not mean that you are agreeing to take part in any future study.

☐ I agree to be called in the future. _____ initials

☐ I do not agree to be called in the future. _____ initials

4. Risks, Discomforts and Precautions

There are no known risks to participating in this research study.

Add institutional compensation statement, e.g., "You understand that if you believe you/your child have been injured as a result of participation in biomedical or behavior research, you are to contact Dr. ….. at (add phone number). (Institution's name) follows a policy of making all decisions concerning compensation and/or medical treatment for physical injuries occurring during or caused by participation in biomedical or behavior research on an individual basis.

5. Benefits

There are no direct benefits from taking part in this study. However, this study may more clearly identify your/your child's type of diabetes and whether you/your child has any of the complications of diabetes. If you agree, this information will be shared with your health care professionals. This may allow them to change how your/your child's diabetes is taken care of and any complications that may be present.

There are also potential benefits to society from participation in this study. This is a large study being carried out at six major medical centers across the United States. The information obtained in this study will give a very good picture of how often young people develop diabetes and its complications and the effect of diabetes on their lives. This information will be important for planning the type of medical care young people with diabetes will need in the future.

6. Alternatives of Care

Whether your/your child decides to take part or not take part in this study, this decision will not affect you/your child's medical care.

7. Confidentiality of Records

The research team will keep the information collected, test done, and samples stored strictly private to the extent permitted by law. Any publication resulting from taking part in this study will not identify you/your child by name.

Upon entry into the study, a special number will be given to you/your child. The number will be used to identify the information that will be obtained during this study. The special number and the information collected during this study will be sent to Wake Forest University in order to study the information. The list containing the special number assigned to you/your child will be kept in a locked file in the office of Dr. ……. Thus, no one other than Dr. ….. and his/her research team will be able to link any of the information collected to you/your child.

8. Availability of Information

As the results from the information gathered in this study become available, the results will be shared with you/your child and the meaning of the results explained. If you agree, the information will be shared with your/your child's health care professionals. If any questions come up about this study, you/your child can call Dr (principal investigators name) at (principal investigator's phone number). For information about your rights as a research subject, you can call Dr. (name of the head of the local IRB) at (phone number of the local IRB).

9. The Right to Withdraw

You/your child may leave from this study at any time by writing a letter to Dr. (PI of the site) telling Dr. (PI) that you want to leave the study. If you/your child leave this study, you/your child can ask Dr. (PI) that any information collected be removed from the research file and this

will be done. Leaving the study will have no effect on your/your child's ability to get medical care nor will it have any effect on the standard of care your/your child's health care professionals are giving.

10. Additional Elements of Consent

None.

11. Witnessing and Signatures

Based on the information provided above and having had the opportunity to discuss any concerns with the investigator or his designee, you voluntarily consent to take part in this research study**.**

_____
Subject's Signature

_____
Parent/Guardian's Signature (if Participant <18 Years of Age)

_____
Witness As To Voluntary Signature

_____
Investigator

_____
Date

Rev (date), Approved (date)

Appendix VIId
Model for Active, Passive & Phone Consent
Active Consent for Information About the Study

Parent/patient
Name
Address
Date

Dear parent/young adult:

I am sending you this letter because you/name of child has diabetes and to let you know about an important, new, national research study that you/name of child may want to join.

The purpose of this study is to learn in individuals under 20 years of age:

A) how many cases of diabetes there are in the United States;
B) more about the characteristics of each type of diabetes;
C) what medical care is being provided;
D) how diabetes is affecting the lives of individuals with diabetes.

The study is taking place at six centers (Hawaii, Seattle, Los Angeles, Denver, Cincinnati, South Carolina) across the United States. I have enclosed a brochure that has more information about the study.

Please compete and return this form in the enclosed self-addressed, stamped envelope. By stating that you wish to be contacted you are only agreeing that a member of the research team can contact you. You are not agreeing to participate in the study.

I hope that you will choose to receive more information about this important study and ultimately agree to participate in the study.

Sincerely,

Third party contact

☐ I do wish to be contacted by a member of the research team
_____ Initials _____ Date

☐ I do not wish to be contacted by a member of the research team
_____ Initials _____ Date

Model for Active, Passive & Phone Consent
Passive Consent for Information About the Study

Parent/patient
Name
Address
Date

Dear parent/young adult:

I am sending you this letter because you/name of child has diabetes and to let you know about an important, new, national research study that you/name of child may want to join.

The purpose of this study is to learn in individuals under 20 years of age:

A) how many cases of diabetes there are in the United States;
B) more about the characteristics of each type of diabetes;
C) what medical care is being provided;
D) how diabetes is affecting the lives of individuals with diabetes.

The study is taking place at six centers (Hawaii, Seattle, Los Angeles, Denver, Cincinnati, South Carolina) across the United States. I have enclosed a brochure that has more information about the study.

In two weeks a member of the research team from (put in local site name) will be contacting you to provide further information about the study. If you do not wish to be contacted please sign below and return this letter to the research team in the enclosed envelope.

I hope you will choose to participate in this important study.

Sincerely,

Third party contact

☐ I do not wish to be contacted by a member of the research team
_____ Initials _____ Date

Model for Active, Passive & Phone Consent
Verbal Consent – Telephone Interview

SEARCH for Diabetes in Youth

INTRODUCTORY TELEPHONE SCRIPT

A. Hello, I'm _____ (interviewer name). I'm calling from_____ (interviewer site). Did you receive the letter from us about the "SEARCH for Diabetes in Youth" study?

1 _____ Yes **(DO YOU HAVE QUESTIONS ABOUT THE SURVEY?** Address questions.
_____ No **(GO TO B or C)**

2 _____ No, letter not received ➜**(READ ALTERNATE INTRODUCTION)**

ALTERNATE INTRODUCTION:

Kaiser Permanente is conducting a study about diabetes in youth. We are asking you to participate in this study because our records indicate that your child may have diabetes <<sites need to explain how their cases are *ascertained*>>. We hope that you and your child choose to participate in this important study by answering some questions about [you] [your child]. Answering these questions will take about 15 minutes. The questions are about how the diagnosis of diabetes was, treatments medications, and any other illnesses that [you] [your child] may have. There are no direct benefits from completing this survey. There is a risk of loss of confidentiality. However, every effort will be made to ensure that all the information you provide for this study will be kept confidential and protected to the fullest extent of the law. Information you provide will be used in scientific reports and publications, but your individual identity will not be revealed. The information will not become a part of your medical record. If you do not complete the survey, your medical care will not be affected in any way. At any time during the interview you may choose not to answer a question. You may also end the interview at any time.

B. Is this a good time for you to to complete a 15 minute telephone survey?
1 _____ Yes **(GO TO QUESTION #1)**
2 _____ No **(CONTINUE)**

C. I can call you back at a time more convenient for you if you are willing to be interviewed. Is there a time that would be more convenient for you?
1 _____ Yes **(SCHEDULE CALLBACK)**
2 _____ No **(GO TO D. AND THEN COUNT AS REFUSAL)**

Appendix VIIe – Model Assent
CHILDREN'S HOSPITAL AND REGIONAL MEDICAL CENTER
and
UNIVERSITY OF WASHINGTON (if appropriate)

ASSENT FORM

SEARCH for Diabetes
Incident cases

Investigator's name, position, department and telephone number.
Co-investigators' and associates' names, positions, departments and telephone numbers.
24-hour emergency number. (Include area code with each phone number.)

To be read to children younger than age seven, and to be read and signed by children ages 7 to 12

It was recently discovered that you have diabetes. There are different kinds of diabetes and the treatment for each kind is different. We want to learn more about the types of diabetes children and teenagers have. We also want to find out how many children and teenagers have diabetes in your area. We want to learn more about your health, and how diabetes affects you and your family.

We will ask you to do the things which have a check√ in the box:

- □ We want to take some blood from your arm with a needle and do some special tests on the blood that tell us about your diabetes. It may hurt a little and you may have a bruise on your arm. We will let you know what we learn about your diabetes after the tests are done.

- □ We will take some blood from your arm with a needle and look at some of the genes that we know have something to do with diabetes. A sample from this blood will be kept in a freezer until we do tests on it.

- □ We will take some blood from your arm with a needle, and leave the needle in the vein. You will then drink a milkshake-like drink over a short period of time. Then, every 30 minutes for the next 2 hours, we will take some blood from the needle that is in your arm. Once the needle is in your arm, drawing the blood should not hurt you at all. A total of 4 blood samples will be drawn and the whole test should take about 2 hours.

- □ We want to measure you and check your blood pressure. This will be a lot like the measurements you get at your doctor's office.

- We want to ask you questions about how you take care of your diabetes. You and your parents/caretakers will answer the questions. If you are over 10 years old, you will have some extra questions to answer about exercise, the foods you eat, and your sleeping habits. This will take about an hour

If you don't want to do something, tell us and we will stop.

Do you have any questions? Is this OK with you? If this is OK with you, please sign your name below.

Signature of child_____ Date_____

Signature of parent _____ Date_____