SEARCH for Diabetes in Youth

Protocol - Phase 2[1]

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Approved by the SEARCH for Diabetes in Youth Study Steering Committee
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SEARCH Phase 2 Protocol
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SEARCH Protocol
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 people with out diabetes.

Until recently, diabetes diagnosed in children and adolescents was almost entirely considered to be type 1, which is usually due to the autoimmune 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. The occurrence of what appears clinically to be type 2 diabetes in youth, particularly minority youth, has been increasingly documented in several studies. 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, either for research purposes, or for ongoing public health surveillance.

Data from European studies suggest that the incidence of diabetes in childhood is increasing, but data from the US are lacking. Tracking of trends in incidence of diabetes in youth, according to diabetes type, is needed. Information about the clinical course and evolution of diabetes in children and youth, particularly type 2, is limited. Finally, data related to processes and quality of health care, and the impact of health care services on the health and well-being of youth with diabetes is lacking.

The SEARCH for Diabetes in Youth study, funded by the CDC with support from the NIDDK, began in 2000. For the first five-year funding cycle, **SEARCH Phase 1, the study objectives** were:

<u>Primary Objectives</u>

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.

Secondary Objectives

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 Phase 1 aimed to develop system(s) to maintain contact with study participants in order to facilitate ancillary studies and long term follow-up, and to establish a repository for long-term storage of biologic specimens obtained as a part of SEARCH and establish processes for access to these specimens.

SEARCH was continued for a second five-year funding cycle (SEARCH Phase 2), beginning in October, 2005. **The primary Aims for SEARCH Phase 2 are to**:

AIM 1: Prospectively ascertain newly diagnosed (2006 - 2009) incident diabetes cases in youth less than 20 years of age, and collect data that permits estimation of temporal trends in diabetes incidence by age, gender, race/ethnicity, and diabetes type for the period 2002-2008.

AIM 2: Conduct longitudinal follow-up of 2002 - 2005 incident cases already recruited to SEARCH in order to:

1) Document the evolution of newly diagnosed diabetes according to clinical and biochemical factors

2) Characterize the evolution of key risk factors for diabetes complications, according to diabetes type and race/ethnicity.

AIM 3: Assess the impact of quality of diabetes care in youth on short- and long-term outcomes including quality of life by:

1) Completing analytic work initiated in SEARCH as described in the Quality of Care Roadmap

2) Expanding the scope of quality of care assessment in order to explore the interrelationships of patient characteristics with important domains of health care

outcomes, such as glycemic control, satisfaction with care, receipt of recommended services, complications, and quality of life.

AIM 4: Develop and validate simple and low-cost case definitions and classifications of diabetes types in youth that can be used for public health surveillance

1) Determine the best practical typing algorithm for public health surveillance, using available, already collected demographic, clinical, and biochemical information. Validate the algorithm against the "gold standard" biochemical diabetes type based on diabetes autoantibody (DA) and fasting C-peptide (FCP) measurements.

The SEARCH study brings together major and timely facets of childhood diabetes research: an epidemiologic component that assesses temporal trends in the incidence of diabetes in youth; a pathophysiologic component addressing the natural history of diabetes in youth; a health services research component to evaluate the processes and quality of care for youth with diabetes; and a public health perspective on case classification of diabetes in youth.

Methods

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

To date, diabetes cases that were prevalent in 2001 and cases incident from January 1, 2002 through December 31, 2004 have been identified. The study will continue to identify incident cases from January 1, 2005 through December 31, 2009. The approach to identification of prevalent cases varied 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.

SEARCH Phase 1

In SEARCH Phase 1, approximately 6,400 prevalent cases were identified. For 2002, 2003, and 2004, approximately 1300, 1200, and 1200 incident cases were identified, respectively. It is estimated that for 2005 and later, approximately 1,200 incident cases per year will be identified across the six SEARCH centers.

Data collection in SEARCH includes, at baseline, both for prevalent and incident 2002 - 2005 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 are also being asked to return annually for a follow-up visit at 12, 24 and 60 months under SEARCH 2.

The baseline surveys 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 are being 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 undergo a stimulated C-peptide test.

Medical record review gathers information to classify diabetes type.

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

SEARCH Phase 2

In SEARCH Phase 2, for 2006 - 2009 incident cases, the data collection protocol is similar. The minor differences from the data collection process in SEARCH Phase 1 are the following: a focus on an expanded initial survey to capture information about diabetes diagnosis and health care received; a limited in-person visit to obtain laboratory information and the brief physical examination; these cases will not be followed prospectively except for brief annual update of contact information. Beginning in 2007, a time based sampling approach will be implemented for the incident cases. Incident cases will only be invited to participate in a Typology visit every other year. On alternating years, only the IPS will be collected. To allow for study of monogenic diabetes, children diagnosed with diabetes at less than 2 years of age may be asked to participate in the limited Typology visit regardless of their year of diagnosis. (03/07)

In addition, quality of care data collection is enhanced in SEARCH Phase 2, including an additional survey of incident 2002 - 2005 cases during their 24 and 60 month follow up visit, and of prevalent cases at one time point. Finally, during SEARCH Phase 2, incident 2002-2005 cases will be followed, in person, at 12, 24, and 60 months, rather than annually.

SEARCH Protocol - Section 1
Study Objectives

1. SEARCH Study Objectives

1.1. GOALS

Current aims of Phase 2 of the SEARCH for Diabetes in Youth Study (2005 - 2010) build upon the findings of the first five years of the study (2000 - 2005).

The SEARCH for Diabetes in Youth study was initiated in 2000 to: estimate the population prevalence and incidence of diabetes by type, age, gender, and ethnicity; develop practical approaches to classification of diabetes type; and describe the clinical course of diabetes in youth. This national multi-center study conducted population-based ascertainment of existing (prevalent) cases of diabetes in youth <20 years of age in 2001, and of all newly diagnosed (incident) cases of diabetes in youth <20 years of age in 2002 - 2005 in defined geographic areas.

The first five year phase of SEARCH ended in September 2005, with on-going collection of 2005 incident cases. DM cases were considered valid if diagnosed by a health care provider. Prior to SEARCH, there were no comprehensive population-based estimates of diabetes rate among youth of diverse racial/ethnic backgrounds. In the SEARCH population, the incidence of diabetes is higher than had been expected based on estimates from previous diabetes registries. To accurately assess temporal trends, study investigators will monitor diabetes incidence in youth for a longer period of time using consistent methodology for case ascertainment and classification, as developed by SEARCH. In addition, it is increasingly evident that diabetes in youth is a heterogeneous condition. Some patients not only exhibit the clinical features of Type 2 diabetes but also have positive diabetes autoantibodies. This finding demonstrates the limits of the current diabetes classification scheme in youth and the need to better understand the natural history and long-term evolution of diabetes in youth, especially those with features of both Type 1 and Type 2 diabetes. In 1997 the ADA put forth an approach to classifying diabetes into distinct disease states based on underlying etiology. Accordingly, SEARCH devoted considerable resources towards operationalizing this classification approach in order to develop the framework for future study of natural history of diabetes in youth, including evolution of clinical and pathophysiologic characteristics and changes in the risk-factor profile for diabetes-related complications. Finally, there is a need to better understand the quality of care and its impact on the quality of life of youth. To address these needs, the second five-year phase of SEARCH will address the following specific research aims:

AIM 1: Prospectively ascertain newly diagnosed (2006 - 2009) incident diabetes cases in youth less than 20 years of age, and collect data that permits estimation of temporal trends in diabetes incidence by age, gender, race/ethnicity, and diabetes type for the period 2002 - 2008.

AIM 2: Conduct longitudinal follow-up of 2002 - 2005 incident cases already recruited to SEARCH in order to:

1) Document the evolution of newly diagnosed diabetes according to clinical and biochemical factors
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AIM 3: Assess the impact of quality of diabetes care in youth on short- and long-term outcomes including quality of life by:

1) Completing analytic work initiated in SEARCH as described in the Quality of Care Roadmap
2) Expanding the scope of quality of care assessment in order to explore the interrelationships of patient characteristics with important domains of health care outcomes, such as glycemic control, satisfaction with care, receipt of recommended services, complications, and quality of life.

AIM 4: Develop and validate simple and low-cost case definitions and classifications of diabetes types in youth that can be used for public health surveillance

1) Determine the best practical typing algorithm for public health surveillance, using available, already collected demographic, clinical, and biochemical information. Validate the algorithm against the “gold standard” biochemical diabetes type based on diabetes autoantibody (DA) and fasting C-peptide (FCP) measurements.

The SEARCH study brings together major and timely facets of childhood diabetes research: an epidemiologic component that assesses temporal trends in the incidence of diabetes in youth; a pathophysiologic component addressing the natural history of diabetes in youth; a health services component; and a public health perspective on case classification of diabetes in youth.

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Background and Significance
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2. Background and Significance

2.1. RISK FACTORS AND TRENDS IN THE INCIDENCE OF TYPE 1 DIABETES

Virtually all epidemiological data on Type 1 diabetes use clinical definitions to establish diabetes type. Studies assume that clinical Type 1 is autoimmune-mediated but fail to measure diabetes autoantibody (DA) titers.

The incidence of Type 1 diabetes varies by race/ethnicity, age, sex, and time period. The risk of type 1 has been considered much greater among Europeans (mainly Northern-European origin), less in Africans and Hispanics, extremely low in Asians and Pacific Islanders, and virtually absent among American Indians (1). Across all racial-ethnic groups, incidence peaks at ages 4-6 and 10-14 (1). Although sex bias is characteristic of autoimmune diseases, girls and boys have similar incidences of Type 1 diabetes (2).

Most (3-11) but not all (12-16) population-based registries show increasing incidence of Type 1 diabetes over time. The discordance in incidence rates may be due to differences in ascertainment or sample size. A systematic review of incidence data from international, longitudinal studies ranging from 8-32 years in duration (1960-1996) showed a significant rise in incidence in 24 of 37 studies, with a similar trend in 12 more (17). The average annual increase was 3.0% (95% CI 2.6-3.3) with the EURODIAB study (1989-1998) showing 3.2% (95% CI 2.7-3.7). Due to the genetic stability of the population, environmental factors appear to be influential (18).

In contrast, most US studies have reported stable incidence of Type 1 diabetes over the last two decades (19). Exceptions include a rapid rise in Allegheny County, Pennsylvania (1985-1989), with an overall increase of 83% between 1966-1989. The most recent data from Allegheny County (1990-1994) reported an overall incidence of Type 1 diabetes among 0-19 year old White and non-White residents comparable to that reported for 1985-1989 (20). However, the annual incidence in non-Whites age 15-19 years from 1990-1994 (30.4/100,000) was more than twice that in 1985-1989 (13.8/100,000) and more than three times higher than in 1980-1984 (7.6/100,000). Additional suggestions of increasing incidence of Type 1 diabetes come from registries not only in Philadelphia (21) and Chicago (22), which have reported mainly an increase among African-Americans, but also Hawaii, which reported a four-fold overall increase (1980 to 1989) (23).

By continuing to ascertain prospectively newly diagnosed diabetes cases, SEARCH will estimate trends in the incidence of Type 1 autoimmune diabetes among US youth by age group and race/ethnicity, and determine diabetes type using a standardized protocol that employs biochemical data including DA titers and fasting C-peptide (FCP) concentrations.

2.2. TRENDS IN THE INCIDENCE OF TYPE 2 DIABETES

An increasing proportion of youth with apparent Type 2 diabetes has been reported in the last decade, especially in non-White populations (American Indians, Hispanics, Japanese), traditionally considered at low risk for Type 1 diabetes. Since the classification of diabetes based on etiopathogenesis is new (24,25) and requires information not typically included in past registry data collection efforts, there is potential for misclassification of different types of diabetes in youth in earlier efforts.

A limited number of population-based studies of childhood Type 2 diabetes exist. Most have been conducted in American Indians. A majority of these studies estimated prevalence based on a single oral glucose tolerance test (OGTT) or self-reported Type 2 diabetes. Thirty years of data collected among the Pima Indians of Arizona have shown increasing rates of antibody negative (26) diabetes among children (27). Two other population-based screening studies of the Cree and Ojibway First Nation children (28,29) showed high prevalence of Type 2 diabetes. In Japan, the incidence of Type 2 diabetes (per 100,000 per year) among junior high school students increased from 3.2 between 1974-81 (30) to 13.9 ten to fifteen years later (1991-95) (31).

In a clinic-based study in Ohio, the proportion of newly diagnosed cases under 19 with provider-assigned Type 2 rose from less than 5% (1991) to 17% (1994) with a majority African-American (32). The incidence of Type 2 diabetes (per 100,000) in 10-19 year olds was 0.7 (1982), 1.2 (1992), and 7.2 (1994) (32). In Arkansas, new-onset non-Type 1 diabetes has increased five-fold in ages 8-21 years (1990 to 1995) (33,34).

SEARCH, a population-based study, will estimate trends in incidence of Type 2 diabetes in a multi-ethnic group of US youth using biochemical definitions of diabetes types, limiting misclassification.

2.3. DETERMINANTS OF CLINICAL AND BIOCHEMICAL EVOLUTION OF DIABETES IN YOUTH

Despite rapid beta cell failure due to autoimmune attack, patients with Type1a diabetes have positive GAD65Ab and IA-2Ab titers for up to 12 years after diagnosis (35). The explanation is unclear. To investigate this observation, SEARCH will explore, using a longitudinal design, whether age at onset of diabetes, gender, race/ethnicity, and initial FCP concentrations are related to the rate of decline in DA positivity over time. The SEARCH approach will also expand the limited data available on conversion from negative to positive DA post-diagnosis and the association between DA positivity and clinical course. Örtqvist demonstrated that age, gender, and ICA-positivity correlate with duration of partial remission independent of each other (36).

Autoimmune diabetes can masquerade as Type 2 diabetes in adults (37) with approximately 5-25% (depending on age, race/ethnicity) with a clinical Type 2 phenotype having positive DA (38). DA-positive patients progress more quickly to insulin dependence than DA negative counterparts. Low GAD65A titers in adults have been associated with slowly progressive beta cell failure and labeled as Type 1.5 diabetes, latent autoimmune diabetes of adults (LADA), or slowly progressive insulin-dependent diabetes. Many features of insulin release and metabolic phenotypes in LADA patients distinguish them from both Type 1 and Type 2 patients. However, HLA DQ8, DQ2 or both alleles predominate in both LADA and Type 1 (37). Whether SEARCH biochemical subgroups are analogous to LADA in terms of HLA association or clinical course has not yet been established.

Most studies in youth with Type 2 rely on clinical features only (32, 34, 39). However, in a study of youth with clinical features of Type 1, Type 2 or an admixture of both, the frequency of DA positivity and T-cell reactivity in those with clinical features of either Type 2 diabetes or an admixture were 71% and 40%, respectively (40). Also, Hathout reported that 30.3% of the 48 subjects with a clinical diagnosis of Type 2 diabetes had positive GAD65Ab and 34.8% had positive IAA 9 (41). In a US study of DA in children with clinical diagnosis of Type 2 diabetes, all children who were ICA positive were on insulin therapy one year after diagnosis (41). However, of 125 Pima Indian youth with diabetes, only seven (5.6%) had weakly positive GAD65 indices. All were of full Indian heritage, had a relative with Type 2 diabetes, and only one was treated with insulin subsequently (42). These findings emphasize the need for standard and consistent definitions of diabetes types in youth and argue for large, ethnically diverse, longitudinal and prospective studies such as SEARCH to understand the clinical and biochemical evolution of diabetes.

SEARCH found that a sizeable fraction of patients with a clinical phenotype of Type 2 diabetes have biochemical criteria of Type 1a or hybrid diabetes. As the clinical profile of diabetes becomes more heterogeneous, due in part to increases in overweight and obesity (42), it is essential to understand the association between biochemical phenotype (number and titer of positive DA, rate of decline of FCP) and clinical phenotype and whether the rate of FCP decline is associated with one DA, a combination of DAs, or DA and HLA genotype. SEARCH will address these questions by careful prospective data collection. These data will be important in deciding the optimal therapeutic strategy and/or in designing future intervention studies.

2.4. RISK FACTORS FOR MACROVASCULAR COMPLICATIONS OF DIABETES IN YOUTH

The metabolic syndrome (MetS) is characterized by a clustering of cardiovascular (CVD) risk factors, including glucose intolerance, abdominal obesity, hypertriglyceridemia, low HDL-cholesterol and high blood pressure (44) associated with an increased risk of cardiovascular disease (45-47). Dabelea et al (48) reported associations among markers of

insulin resistance and coronary artery calcification in young adults with Type 1 diabetes. Recently, Krantz et al (49) reported that mean carotid IMT was greater in young persons with Type 1 diabetes than among non-diabetics. In contrast, a pilot study found that IMT did not differ between adolescents with Type 2 diabetes and either obese or normal-weight non-diabetic controls (50). Aortic pulse wave velocity, a measure of arterial stiffness, was highest in the Type 2 diabetes subjects (n=20), compared to obese or normal-weight controls ($p<0.001$). These findings emphasize the need for systematic collection of data on the prevalence, incidence, and evolution of MetS, the individual components of MetS, the clustering of components of MetS, other CVD risk factors, and the end-organ effects of each in youth with each type of diabetes. The SEARCH CVD study will provide a very strong foundation for prospective assessment of the natural history of CVD risk factors and their effect on end organs in the SEARCH cohort.

2.5. RISK FACTORS FOR MICROVASCULAR COMPLICATIONS OF DIABETES IN YOUTH

Among patients with diabetes under the age of 26 years in New Zealand, the prevalence of nephropathy was 19% (51). The Diabetes Incidence Study in Sweden (DISS) (52) reported that, among 469 patients diagnosed at age 15-34 years, 6.6% had incipient or overt nephropathy at a mean duration of nine years. Serum cystatin C, a recently recognized marker of glomerular filtration rate, is particularly useful in identification of mild diabetic nephropathy (53-55). In a population of elderly, cystatin C was predictive of CVD risk and death (56).

Many studies report increased risk for diabetic nephropathy with poor glycemic control (57-61) especially in the first five years after diagnosis (62). Diabetes duration has been associated with increased risk for nephropathy in some (57,59,64) but not all studies (56,65). High blood pressure has been associated with increased risk for nephropathy (59,65,66). Data in adults suggest an association of dyslipidemia (elevated triglycerides and LDL cholesterol) with microalbuminuria (67). Higher BMI may also be a risk factor for nephropathy (59,66) although data are inconsistent (58). Occurrence of puberty may accelerate the appearance of microalbuminuria (60-61,68). Inconsistencies in findings regarding risk factors for nephropathy may be due to inadequate sample sizes (commonly less than 500 total patients). These data highlight the need for systematic study of risk factors and the evolution of risk factors in a large cohort such as SEARCH.

2.6. QUALITY OF CARE AND QUALITY OF LIFE OF YOUTH WITH DIABETES

2.6.1. Overview and Conceptual Model

Of definitions of quality in health care (69-71), the Institute of Medicine (IOM) definition-“the degree to which health services for individuals or populations increase the

likelihood of desired health outcomes and are consistent with current professional knowledge" is cited most commonly. This definition provides the conceptual framework for advances in quality assessment in the last decade. The definition encompasses two important multidimensional health care outcomes--quality of life and satisfaction with care. SEARCH work on quality of care already undertaken and new work are based on the conceptual model that arises from this definition.

Donabedian's widely used model (69,72,73) for measuring the quality of care distinguishes the elements of quality as "structure", "process", and "outcome." Structure reflects characteristics of resources in the health system such as practitioner (e.g., specialty) or institutional characteristics (e.g., size, location). Process measures embody what is done to and for the patient such as ordering of a test for glycemic control. Outcomes are the end results of care or the effect of the care process on the health and well-being of patients and populations. Early attempts to measure quality centered on structure. The emphasis has moved to measures of process and outcome; both provide valid information about the quality of health care (74-75).

In health quality measurement, a distinction is drawn between "intermediate" and "ultimate" outcomes. Intermediate outcomes typically reflect clinical signs that patients may not directly experience but are causally linked to specific health outcomes. An ultimate outcome is one that a patient can directly experience (death, disease, discomfort). An HbA1c value of 9% is an intermediate outcome that the patient would not "feel" but could lead to complications--the directly experienced outcome. The SEARCH roadmap for assessing quality incorporates measures of structure, process, and outcome, including intermediate outcomes.

2.6.2. Special Issues in Quality of Care Measurement in Children/Youth

There are several published studies of the quality of care for children with diabetes that derive from large population-based samples in Europe and Australia (76-80) and small areas of the UK (81,82). Diabetes was one of several chronic conditions included in a quality of care assessment in children in Alexandria, Egypt (83).

In the US, despite the recognition that youth are particularly vulnerable to disparities in health and are often under- or uninsured (84), the assessment of quality and outcomes of care for children has lagged behind that of adults (84,85). Among the many contributors to the lag is the limited availability of measurement tools designed specifically to assess quality of care for children (84, 86).

A set of methodological issues pose particular challenges to assessment of quality of care for children and youth with diabetes. Age diversity within the population of children and youth with diabetes is reflected in differing age-related treatment goals and approaches, expectations for self-care, and quality of life issues. The family and the medical care provider have different roles in facilitating care (including self-care) depending on age

and developmental stage. The etiological and physiological differences between Type 1 and Type 2 diabetes are substantial, and measures of quality may not be the same for both. Although diabetes is the third most common chronic illness in children, the number of cases in any given geographic entity or care setting is fairly small, making large collaborative efforts necessary to assess care with validity and precision.

The limited published data available suggests the quality of care for children and youth with diabetes is sub-optimal. A study of children with diabetes covered by Medicaid reported low measurement rates for HbA1c and ophthalmology assessments, and a 20% rate of diabetic ketoacidosis in a one-year time period (87). Rewers et al. (88) found high rates of DKA and hypoglycemia in some subgroups of children/youth with diabetes in Denver, Colorado. SEARCH has also found evidence of suboptimal care (see Progress report; unpublished): attainment of optimal glycemic control in children/youth, especially adolescents is low; a high proportion of children/youth with diabetes have dyslipidemia, few are tested, and treatment with pharmacologic agents is infrequent even when lipid levels are high.

Although many publications address glycemic control in US youth with diabetes, they are based on small and select populations. Most report on the results of psychosocial interventions (89-94) or interventions based on new methods for monitoring glucose or administering insulin (95-97). Comprehensive assessment of the factors that influence glycemic control, including age, income, parental education, insurance, race/ethnicity, and psychosocial factors has not been done with large samples that encompass the diversity of youth with diabetes in terms of socioeconomic status and race/ethnicity.

Studies of quality of life as an important outcome for children and youth with diabetes are few. In comparison to a community sample, children and adolescents with chronic conditions, one of which was diabetes, have a lower self-reported health-related quality of life (98, 99). Age, gender, family dynamics and coping skills have been associated with the quality of life experienced by children and youth with diabetes (100-104). Importantly, the association between glycemic control and quality of life is not well established. A number of studies have reported a positive association (105,106). Others have found no association (100, 107, 108). SEARCH is in a unique position to further understand quality of life and its correlates.

2.6.3. Explicit Measures of Quality of Care Based on ADA Guideline Adherence

The ADA has published guidelines on the clinical care of children and adolescents with Type 1 diabetes (109). Adherence to guidelines falls within the IOM definition of quality as being “consistent with current professional knowledge.” SEARCH has begun analyses of data already collected that would measure the degree of adherence to ADA recommendations in SEARCH patients with Type 1 diabetes. The ADA guidelines also provide the foundation for the expanded work on quality process of care described later.

2.6.4. Research on Links between Process and Outcome in Diabetes

Research on the links between health care processes and outcomes, including intermediate outcomes, is an important component of health services research. For diabetes, the demonstration of a strong relationship between glycemic control and "ultimate" outcomes (e.g. microvascular disease) makes exploration of the factors that explain glycemic control a critical area for research. Glycemic control has been studied in relation to patient level, provider level and organizational factors (110-113). Research on factors that affect hospitalization for DKA, hypoglycemia, and ED use is also prominent in the health services literature on diabetes in childhood and adolescence (114-118). SEARCH investigators have begun a number of analyses exploring links between glycemic control, DKA, and quality of life with various structural features of care and health care. Prompt completion of these analyses is a priority.

2.7. PUBLIC HEALTH SURVEILLANCE OF DIABETES IN YOUTH

"Surveillance is the on-going systematic collection, analysis, and interpretation of health data essential to the planning, implementation, and evaluation of public health practice, closely integrated with the timely dissemination of these data to those who need to know. The final link in the surveillance chain is the application of these data to prevention and control." (119). Surveillance is not epidemiological research. It is better described as a problem-finding process with an immediate relationship to public health action (120). Surveillance systems also differ from health-information systems - primarily because health information systems may not be on-going, may not be integrated with timely dissemination, or may not be specifically applied to prevention and control efforts.

This definition of surveillance emphasizes the larger systematic or programmatic use of disease-specific epidemiologic data (e.g. incidence, prevalence, risk factors) such as that collected by SEARCH or registries. However, it also frames the context in which "...simple and low-cost case definitions and classifications of diabetes in youth that can be used for public health surveillance" must be developed. There are seven essential attributes of such a case definition: 1) simplicity; 2) sensitivity; 3) flexibility; 4) acceptability; 5) timeliness; 6) representativeness; and 7) high predictive value positive (121). Each of these attributes will be considered as SEARCH develops and validates competing definitions of diabetes types. SEARCH will provide consistent, sustainable, and simplified criteria for case classification for surveillance purposes across centers, across racial/ethnic groups, and over time.

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Site Descriptions
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3. Description of Study Centers and Populations

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

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

Table 3-1 outlines the base populations and case finding approaches at each SEARCH center. The following is a description of each study center, its case finding approaches, approach to denominator estimation, and study population characteristics. Further details on denominator estimation and case finding approaches are in Section 4.

3.1. CINCINNATI - CINCINNATI CHILDREN'S HOSPITAL MEDICAL CENTER

The Cincinnati center is located in Cincinnati, Ohio at Children's Hospital Medical Center. Children with diabetes who reside in Cincinnati and the eight metropolitan 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, provides 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. The database is updated daily with prospectively collected information on newly diagnosed patients with childhood diabetes. For SEARCH, the Cincinnati center will use the information in this computer database to identify cases.

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 of physicians, health care workers and educators 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 a non-white racial/ethnic background.

3.2. COLORADO - UNIVERSITY OF COLORADO CENTER

The population under surveillance at the Colorado SEARCH site consists of all youth age <20 years a) residing in the state of Colorado (64 counties) in 2006-2009, or b) members of American Indian populations in Arizona and New Mexico. These include: the Navajo Nation and the Gila River Pima Reservation. The estimated total population under surveillance at the Colorado SEARCH site is ~1.4 million youth age < 20 years.

The study is conducted by the University of Colorado Health Sciences Center, Department of Preventive Medicine and Biometrics, through close collaboration with two major pediatric endocrinology units serving both metropolitan and remote areas: the Barbara Davis Center and the Pediatric Endocrine Associates. In addition, the availability of computerized databases at large community health centers and the collaboration of major hospital systems provide a nearly complete and very efficient ascertainment network. In the first five years of the study this site has established close and trusting partnerships with American Indian Tribes in Arizona and New Mexico. The study is conducted through partnerships with the Navajo Area Indian Health Promotion and the Special Diabetes Prevention Program, under a Memorandum of Understanding with the Navajo Nation, and a data sharing agreement with the NIH Pima Indian Study.

3.3. HAWAII - PACIFIC HEALTH RESEARCH INSTITUTE

The Hawaii center is located in Honolulu, Hawaii at the Pacific Health Research Institute (PHRI). Partners in this project with 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. Case ascertainment of incident cases includes members of these three health plans on all of the six major islands of Hawaii (Oahu, Hawaii, Maui, Kauai, Molokai and Lanai). The combined membership of these three plans includes approximately 80% of the state's non-military residential population under age 20 as determined by the US Census.

PHRI is a non-profit research institute created in 1960. Since 1996, HMSA, Kaiser Permanente-Hawaii, and Med-QUEST have been contributing data to the Hawaii Diabetes Data Network (HDDN). For the incidence component of the study, case ascertainment includes members of the three major health plans in Hawaii (the Hawaii Medical Service Association (HMSA), Kaiser Permanente-Hawaii, and the State of Hawaii, Department of Human Services, Med-QUEST Division) who reside on any of the six major islands of Hawaii (Oahu, Hawaii, Maui, Kauai, Molokai and Lanai).

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 area from which cases are drawn.

In 2000, approximately 325,000 children and adolescents less than 20 years of age resided in 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 - CHILDREN'S HOSPITAL & REGIONAL MEDICAL CENTER

The Seattle center is located at Children's Hospital & Regional Medical Center (CHRMC). Children and adolescents 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.

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.

A combination of clinical and administrative data sources will be used to identify cases. Most of the eligible participants receive diabetes care at the major pediatric endocrinology groups in the region [Children's Hospital Pediatric Endocrinology, Woodinville Pediatrics, Group Health Cooperative (Bellevue), Pediatrics Northwest, and Madigan Army Medical Center (children of civilian status)], all of which will refer cases and share core information. Two major pediatric hospitals serve the 5-county Puget Sound area and will participate in the study: Children's Hospital and Regional Medical Center and Mary Bridge Children's Hospital. Cases will be ascertained through additional sources, including other area hospitals, adult endocrinologists, diabetes programs, family practitioners, community health clinics, hospital-based primary care networks and primary care clinics, college health centers, and diabetes support groups. This site also plans to collaborate with the Washington State Department of Health through the Washington State Diabetes Plan, building on their new initiative that emphasizes diabetes surveillance and research.

3.5. SOUTH CAROLINA

The South Carolina center is located in Columbia, SC at the University of South Carolina (USC). To assist in statewide case ascertainment and recruitment, the Medical University of South Carolina (MUSC) in Charleston, SC and the Greenville Hospital System (GHS) in Greenville, SC will serve as sub-centers. Incident cases will be ascertained in all 46 counties in South Carolina. Ascertainment of cases will continue through the active surveillance network comprised of a variety of health care providers. Specifically, the pediatric endocrinologists in South Carolina and in large bordering cities will report newly diagnosed

cases of diabetes in SC. Other health care providers, including adult endocrinologists, federally qualified health care centers, and hospitals will also participate in case ascertainment.

The South Carolina center will base race/ethnic-, gender-, and age- specific denominators on projections based on the 2000 US Census.

South Carolina has roughly 1.1 million children and youth under the age of 20 among a total population of more than 4 million (28% youth). Thirty percent (30%) of the population is African American, compared to 12.3% nationwide (Census 2000). Forty-two percent (42%) of all SC youth are enrolled in Medicaid or the State Children's Health Insurance Program (SC Office of Research Statistics), the proportion being even higher in rural parts of the state. SC has a high proportion of families of very low income: 18.8% of all SC youth live in families with incomes below the poverty level, including 10% of Whites, and 33% of non-White youth. Children in SC are more likely to grow up in households with lower educational attainment compared to the national average. In SC, 23.7 of adults over age 25 have no high school diploma, compared to 19.6% nationwide (Census 2000). In addition, 40% of SC lives in rural areas of the state (compared to 21% nationwide) (Census, 2000).

3.6. KAISER PERMANENTE SOUTHERN CALIFORNIA

Kaiser Permanente is a group model HMO that delivered comprehensive medical care on a prepaid basis to 3.1 million residents of southern California in 2005. The Department of Research and Evaluation, the research arm of Kaiser Permanente Southern California (KDPS), is located in Pasadena California, and is committed to conducting high-quality epidemiologic, behavioral, clinical, and health services research.

Children with diabetes who are members of KPSC, other than members who reside in the San Diego (SD) service area, will be identified and invited to participate in SEARCH. These youth will be identified using a rapid reporting system of clinics and physicians (Pediatric Endocrinologists) supplemented with computer-stored data on prescriptions and laboratory testing from the KPSC diabetes case identification database (DCID).

The Kaiser Permanente Southern California center will use its administrative membership database as the source of denominator information. Membership files are geocoded annually to account for new members, disenrollment in the health plan, and address changes for continuously enrolled members. Estimates of the number of children in each racial/ethnic group will be made based on block-level geocoding of address information to the 2000 decennial U.S. census which are updated annually based on changes in geographic boundaries as well as demographic changes within each census block.

In 2002, approximately 775,000 children and youth less than 20 years of age were members of the Kaiser Permanente Southern California other than in San Diego. Based on race/ethnicity data aggregated at the census block-level, 43% of were Hispanic, 10% African American, and 9% of Asian/Pacific Islander.

Table 3-1: Description of Base Population and Summary of Source of Estimated Cases for Incidence Component

	Base Population	Source of Cases	2002 Estimated, Denominator / (Approximate)
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	550,000
Colorado (University of Colorado Center)	All counties in Colorado; Native American reservations in Arizona and New Mexico	Referral to study by reporting network of clinics, pediatric endocrinologists, and diabetes educators; other practitioners, hospitals	1.5 Million
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	250,000
Seattle (Children's Hospital)	King, Pierce, Snohomish, Kitsap, Thurston counties	Referral to study by reporting network of clinics, pediatric and adult endocrinologists, and hospitals supplemented with record linkage	1.0 Million
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	1.1 Million
Southern California (Kaiser Permanente Southern California)	Members of the Kaiser Permanente Medical Care Program Health Plan in Southern California except those residing in the San Diego service area	Referral to study by KPSC reporting network of pediatric endocrinologists every month; Periodically updated record linkage database periodically to identify additional cases.	750,000

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 of age residing in the SEARCH incidence area in 2005 - 2009. Prevalent 2001 and Incident 2002 - 2004 cases have previously been ascertained and validated. SEARCH will estimate trends in the incidence of childhood diabetes by age, sex, race/ethnicity, and type for the period 2002 - 2008. Incidence estimates for 2009 will be incomplete in the last year of this five-year funding period. This section provides an overview of the general methods that will be used by study centers to accomplish case ascertainment.

To identify eligible cases, it is necessary to review protected health information (PHI). Access to such information is subject to federal regulations, state laws, and institutional policies. Issues relating to the confidentiality of PHI are addressed in Section 11.

4.2. DENOMINATOR ESTIMATION

Overview

To estimate incidence accurately, all of the cases of diabetes that are counted in the numerator must be from the population that is defined as the denominator. Every effort will be made to ensure that the numerator and denominator are aligned by applying the same criteria for inclusion in the denominator to the numerator, and by including case-finding data sources that would identify eligible cases from the eligible population.

The four geographically based SEARCH centers (Cincinnati, Colorado, Seattle, and South Carolina) will use population estimates based on the 2000 US Census non-institutionalized resident population with estimates of population changes from 2001 through 2008. The methods for making these estimates may vary by location, but will be standardized as much as possible across geographic-based centers using acceptable demographic methods.

A resident is defined by the US Census as a person with a permanent address within the defined geographic area at any time in the index year that is not noted to be living elsewhere or only temporarily residing at the eligible address.

The two membership-based SEARCH centers (Hawaii and California) will use administrative data on membership less than 20 years of age in the participating health plans in the given incident year as the total denominator for estimation of incidence.

American Indian populations participating in SEARCH as sub-sites of the Colorado Center will use Indian Health Service three-year moving average counts of the facility users for youth aged 0-19 years as the denominator. These users will be restricted to

members of participating tribes seen at defined IHS facilities as an approximation of the resident populations. Thus, the denominator for a given year (e.g., 2007) will be the annual user population from 2005, 2006, and 2007 divided by 3 and stratified by age, and sex.

Special populations

College students are counted in the US Census in their residence location as of April 1, which will usually be the city where they attend college. Geographically-based centers will identify diabetes cases in age-eligible college students in eligible geographic areas. Youth who are attending college while still members of the participating health plan cannot be identified as attending college (whether in or out of the area) using administrative data. Therefore, both geographically-based and membership-based centers will include college students in both the numerator and denominator.

Active duty military personnel are counted in the US Census at the base or community where they are assigned. However, no attempt will be made to identify diabetes cases in active-duty military personnel. Therefore, active-duty military will be excluded from the numerator and denominator.

Military dependents are counted in the US Census at their usual residence, whether on or off base, where their enlisted parents/guardians are assigned, and will be considered eligible for the study. Medical care for dependents will differ between base locations; access to health care systems (military or civilian) will determine the centers' abilities to identify these cases. Every attempt will be made to identify such cases in a consistent way across centers. Center specific methods (MOP) define how each center will identify cases in the military dependent population.

Institutionalized persons living in prisons, chronic care hospitals, and other institutions are not included in the US census counts of the civilian, non-institutionalized population (denominator). Therefore, they will not be eligible as cases (numerator).

Age, Sex, and Race/Ethnicity

The geographically-based centers (Ohio, Colorado, Washington, and South Carolina) will use estimates from the US Census to estimate the age, sex, and racial/ethnic composition of their populations.

The membership-based centers (California and Hawaii) will obtain membership counts by age and gender annually from participating health plans. The California center will geocode membership address information to the block-level and then will use block level data derived from the US Census to estimate race/ethnicity for each age and gender group in one-year increments (122). The Hawaii center will use US census estimates of race/ethnicity applied to the updated membership based denominators.

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 (123).

4.2.1. Eligibility Criteria

The beginning year for identification of incident cases was 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
- Age less than 20 years on December 31 of the onset year. Participants who turn 20 in the onset year are not eligible
- Reside in the eligible area during the onset year (for geographically-based centers) or member of the participating health plan during the onset year (for membership-based centers)
- Not active duty military
- Not living in an institution (as defined by the US Census)
- Not gestational diabetes mellitus.

4.2.2. Case Finding Approaches

At all six SEARCH centers, the primary approach to case-finding for incident cases of diabetes is a rapid reporting network of clinics and health care providers. This approach is viable because, at all centers, a relatively small number of referral practices (e.g. pediatric endocrinologists, adult endocrinologists, and adolescent medicine specialists) care for a high proportion of youth with new-onset diabetes. Centers will also query relevant and available databases for eligible cases that might have been missed through these active surveillance networks.

4.2.3. Case Validation

Cases of diabetes will be considered valid if the case has either:

1) a physician or health care provider diagnosis of diabetes; or

2) the parent/guardian or the youth self-reports a physician or other health care professional's diagnosis of diabetes at the time of an interview or survey such as the Initial Patient Survey.

A physician or health care provider diagnosis is made if any of the following conditions are met:

a. review of the medical records reveals a physician health other health care professional's diagnosis of diabetes
b. the diagnosis of diabetes is directly verified, or the diabetes case is "referred" to the study by a physician or other health care professional
c. the case is included in a clinical database that has a requirement for verification of diagnosis by a physician health other health care professional
d. Diabetes is listed as the underlying or contributing cause of death on a death certificate.

4.2.4. Estimated Number of Incident Cases

A table showing the estimated number of cases by age, race/ethnicity, gender and provider type is provided in Section 8 - Statistical Considerations.

4.2.5. Identification and Elimination of Possible Duplicate Cases

Incident case reports will be compared to registered cases to determine whether the case is a unique, unduplicated case. At all sites, duplicate cases will be identified and tracked for estimation of completeness of ascertainment.

The membership-based centers will use identifying information such as membership number, name, and date of birth to identify and remove duplicates.

The Cincinnati center has a registration system for cases that identifies duplicates based on name, date of birth, and other identifying information about the child and parents/guardians at the time of data entry. The other three geographically-based centers (Colorado, Seattle, South Carolina) will make use of full or partial identifying information to identify duplicates. At these centers, the following items may serve as variables to identify duplicate cases.

Potential Variables for Matching to Eliminate Duplicates

a. Name
b. Sex
c. Date of Birth
d. Date of diagnosis
e. Race/Ethnicity
f. Medical Record Number
g. Parent's last name
h. Mother's maiden name
i. Admission date of hospitalization(s)
j. Address, zip code, or county of residence
k. Telephone number
l. Social Security Number (in accordance with the policy of each center)

The specific approaches to duplicate removal are described in the center-specific case ascertainment section.

Some personal identifiers, such as name, medical record number, telephone number, social security number, parent's last name, mother's maiden name, and address are required to assess duplicates. This information will not be sent to the Coordinating Center.

4.2.6. Gestational Diabetes Mellitus

This study will not attempt to ascertain women who have been diagnosed with gestational diabetes mellitus (GDM) defined as any degree of glucose intolerance with onset or first recognition during pregnancy. If identified, these women will be ineligible. However, if glucose intolerance was first recognized during pregnancy but glucose intolerance persists after the end of pregnancy, these women will be eligible. The onset date will be the date of first clinical diagnosis of diabetes mellitus 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 estimates depends on complete ascertainment of cases through the case-finding approaches described above. The optimal 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.

4.3.1. Capture-Recapture

Capture-recapture (124 - 127) is a statistical method that produces estimates of the completeness of ascertainment from samples. This method requires a minimum of two data sources in which a case can be identified. The data required are the multiple locations where each unique eligible case was identified, which are then grouped hierarchically into source types (e.g. hospital, provider, pharmacy). The statistical method will incorporate multiple ascertainment sources, with adjustment for non-independence of data sources as required. Capture-recapture methods were used in the geographically-based SEARCH centers with multiple sources of cases (Cincinnati, Colorado, Seattle, South Carolina) in the first phase of SEARCH and will be used for the current phase.

SEARCH Protocol - Section 5
Data Collection
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5. Data Collection

5.1. GOALS

Accomplishing the research objectives for the SEARCH study requires utilization of data collected in SEARCH Phase 1, as well as collection and utilization of additional data under the SEARCH Phase 2 protocol. Thus, the SEARCH Phase 2 protocol will review data collection approaches for all SEARCH registered cases, including those enrolled under the SEARCH Phase 1 protocol.

Data collection requirements differ for prevalent cases, incident cases diagnosed in 2002-2005, and incident cases diagnosed in 2006-2009. A general summary of the data to be collected is outlined below. Table 5-1 lists a more detailed description of the data elements to be collected for each of the three cohorts. As shown in the table, some data elements apply to subgroups within these cohorts. These subgroups are determined by the age of the participant, the participant's level of previous participation, and results of previous laboratory tests. Whenever possible, data collection methods for SEARCH Phase 2 remain the same as SEARCH Phase 1 to allow comparability of data over time. This section of the study protocol outlines all elements of data collection.

The following is a summary of the data to be collected for each of the three cohorts.

- Prevalent cases, 2001 (date of diabetes onset before 1/1/02)
    - Quality of Care and Quality of Life surveys
        - mail in Year 3 of SEARCH Phase 2 (10/07-9/08) to all participants who completed the In-Person Visit (IPV) during SEARCH Phase 1
    - Annual mailings to maintain contact with participants and to update contact information - sent to prevalent cases who completed IPV during SEARCH Phase 1.
- Incident cases, 2002 - 2005 - continue data collection in SEARCH Phase 1 format
    - Ascertain, validate, and register new cases (only for year 2005)
    - Medical record review and core data elements
    - Initial Patient Survey (IPS)
    - Baseline in-person visit (IPV)
    - Follow-up visits conducted at 12, 24, and 60 months after baseline visit - same as SEARCH Phase 1 visit protocol, with addition of cystatin-C blood sample and QOC Survey

- Mailings to maintain contact with participants and to update contact information - sent at 36 and 48 months after baseline visit to those who completed IPV.

- Incident cases, 2006 - 2009 - new elements for SEARCH Phase 2 protocol
  - Ascertain, validate and register new cases
  - Core data elements - expanded core data form
  - Initial Patient Survey (IPS) - IPS Part 1 and part 2
  - Baseline Typology Visit - (exam, blood and urine samples, and Medication Inventory only)
    - All 2006 and 2008 participants will be seen for a Typology visit. Participants in the 2007 and 2009 incident cohorts will not be invited to the Typology visit due to the time-based sampling approach. To allow for study of monogenic diabetes children diagnosed with diabetes at less than 2 years of age may be asked to participate in the limited Typology visit regardless of their cohort. Alternative approaches to collect DNA samples include: blood sample, buccal swabs or from saliva (using the Orogene kit). (03/07)
  - Annual mailings to maintain contact with participants and to update contact information - sent to all participants who completed any part of IPS.

Table 5-1. Summary of Data Collection for Each of the Three Cohorts

Prevalent Cases, 2001			
Type of Data 2006, 2008*	Data Collected	Frequency	Details
Survey *(eligibility: 10% sample NHW youth and all minority youth who completed an IPV)*	Quality of Care/Quality of Life Survey	Once only - in Year 3 (10/07-9/08)	Quality of Care/ Quality of Life survey (see section 7)
Mailings *(eligibility: cases with a baseline IPV)*	Contact information	Annually except Year 3	Update contact information, send newsletters & information on other SEARCH ancillary studies
Incident Cases, 2002-2005			
Type of Data	Data Collected	Frequency	Details
Case Registration *(2005 cases only; 2002-2004 cases completed previously)*	Core data	Once	ID, age, date of birth, sex, race/ethnicity, county of residence, zip code, diabetes validated, method of validation, date of diagnosis, type of diabetes indicated by provider

Medical Record Review	Medical record	Once	Characteristics related to typology, clinical presentation, complications, co-morbidities, medications, health care utilization, diabetes education, Tanner staging,
Initial Patient Survey (IPS)	Questionnaire	Once	Residence eligibility, health plan eligibility, military eligibility, institutional eligibility, data for validation of diabetes type, acute complications, processes of care, contact information
Baseline In-Person Visit (IPV) (*eligibility: non-secondary cases*) *(2004-2005 cases only)*	Physical Exam	Once	Height, weight, waist, blood pressure, acanthosis
	Blood and Urine Samples		Diabetes auto-antibodies (DAA), Fasting C-peptide (FCP), lipids, glucose, HgbA1c, urine albumin and creatinine, serum and plasma storage, and DNA storage
	Stimulated C-peptide Test (SCPT) (only if ≥ 8 yrs of age)		Glucose and c-peptide at 0, 30, 60 minutes
	Health questionnaire		Symptoms at presentation, medications, medical care utilization, perceptions of care, SES/insurance
	Family history		family history
	PedsQL (child version if >5 yrs; parent version if >2 & <19		quality of life (generic and diabetes specific)
	Supplemental (≥ 10 yrs. of age)		health behaviors
	CES-D (≥ 10 yrs. of age)		depression
	Food Frequency (≥ 10 yrs. of age)		usual diet
	Tanner Stage (≥ 8 yrs. of age)		stage of pubertal development (self-assessment)
Follow-up Visit (12, 24, 60 months after baseline visit) (*eligibility: cases with a baseline IPV*)	Physical Exam	12, 24, 60 months	Height, weight, waist, blood pressure, acanthosis
	Blood and Urine Samples (added cystatin-C and DNA storage if <50 ug/dL available; otherwise same as SEARCH Phase 1)	12, 24, 60 months	DAA, FCP, cystatin-C, urine albumin and creatinine, lipids, glucose, HgbA1c, serum and plasma storage

	SCPT (only if SCPT performed at baseline and only if previous FCP ≥ 0.6 ng/ml)	12, 24, 60 months	Glucose and c-peptide at 0, 30, 60 minutes
	Health questionnaire (annual version)	12, 24, 60 months	Medications, medical care utilization, perceptions of care
	PedsQL (child version if ≥5 yrs; parent version if ≥2 & <19	12, 24, 60 months	quality of life (generic and diabetes specific)
	Supplemental, CES-D (≥ 10 yrs. of age)	12, 24, 60 months	health behaviors, depression
	Tanner Stage (≥ 8 yrs. of age)	12, 24, 60 months	stage of pubertal development (self assessment)
	Family history (update baseline information)	12, 24, 60 months	family history
	Food Frequency (≥ 10 yrs. of age)	12, 60 months	Diet - if completed at baseline
	Quality of Care Survey	24, 60 months	Quality of Care Survey
Mailings *(eligibility: cases with a baseline IPV)*	Contact information	36, 48 months	Update contact information, send newsletters & information on other SEARCH ancillary studies
Incident Cases, 2006-2009			
Type of Data	Data Collected	Frequency	Details
Case Registration	Core Data	Once	ID, age, date of birth, sex, race/ethnicity, county of residence, zip code, diabetes validated, method of validation (medical record review/direct verification by a physician/clinically verified database/death certificate/self-report), date of diagnosis, type of diabetes indicated by provider
Expanded Core	Core data (expanded for SEARCH Phase 2)	Once	Sex, race/ethnicity, zip code, county/state of residence, date of diagnosis, provider type of diabetes, weight and height at diagnosis, presence of Acanthosis nigricans, insulin use, diabetes autoantibody levels, c-peptide test results
IPS part 1	Questionnaires	Once	Sex, race/ethnicity, weight at birth, date of diagnosis, residence eligibility, health plan eligibility, military eligibility, institutional eligibility, provider type of diabetes, current insulin use, current weight/height, DKA, Acanthosis nigricans, PCOS

IPS part 2			Family history of diabetes, health insurance, diabetes and personal health care providers, diabetes education, education and family income, contact information
In person Visit (*eligibility: non-secondary case, 2006 and 2008 cohorts*)	Physical Exam Blood and Urine Samples Medication Inventory	Once	Height, weight, waist, blood pressure, acanthosis DAA, FCP, lipids, glucose, HgbA1c, serum and plasma storage, and DNA and urine storage List of current medications
Mailings *(eligibility: participants who completed In person visit or any part of IPS)*	Contact information	Annually	Update contact information, send newsletters & information on other SEARCH ancillary studies
Children under the age of 2 years old may be asked to participate regardless of cohort. Alternative approaches to collect DNA samples include: blood sample, buccal swabs or from saliva (using the Orogene kit). (03/07)			

5.2. LANGUAGE

English and Spanish forms will be provided by the study. Bilingual personnel will be used in sites with a large proportion of Spanish-speaking participants.

Some participants will speak languages other than English and Spanish. Local centers 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 from the study based on language.

5.3. CASE REGISTRATION

Cases that are valid, eligible and unique will be registered with the Coordinating Center (CoC). Minimal information about the participant (age, sex, race/ethnicity, type of diabetes reported by clinician, and center) will be uploaded to the CoC website in order to protect confidentiality. Names and contact information are not provided to the CoC.

5.4. EXPANDED CORE INFORMATION

A minimum amount of demographic and clinical information is needed for all registered cases in order for the study to be able to provide population-based rates of diabetes mellitus by age, sex, diabetes type and race/ethnicity. This information is called “core” information. Data sources for the core date elements differ according to the level of each person’s participation and the data sources available for participants who do not complete the SEARCH survey and/or in-person visit. These sources may vary from one site to another

based on local record availability, the relationship of the center study staff with patients and their families, and local IRB rules and HIPAA interpretations. For each element of core data, centers have defined acceptable data sources and a hierarchy of application of data from each source to be used in the final data analyses. Age, gender, race/ethnicity, county, zip code, clinically diagnosed type, and date of diabetes onset were core items in SEARCH Phase 1. Elements added to this list in SEARCH Phase 2 are weight, height, presence of acanthosis nigricans, history of insulin use and diabetic ketoacidosis (DKA), and test results for diabetes autoantibodies and c-peptide levels (see Table 5-1).

5.5. MEDICAL RECORD REVIEW

For 2004-2005 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 diabetes diagnosis. Information regarding insulin use and occurrences of DKA (up to 6 months after diagnosis) may be required to establish typology for a small number of incident cases.

5.6. INITIAL PATIENT SURVEY

The initial patient survey (IPS) will facilitate confirmation of case validation, residence and age eligibility, and uniqueness of the case. In addition, the IPS contains key data, including core information, needed to estimate incidence, facilitate diabetes typing, assess acute complication and processes of care. The IPS also requests contact information, for local use only. The IPS is designed to be administered either by mail (self-administered) or by an interviewer, via telephone or in person, according to local operational or participant needs. This flexibility is required to maximize response rates and overall data completeness.

5.6.1. Introductory Letter

An Introductory Letter may be used to describe the purpose of the study to potential participants and/or their parents. Each site will develop an introductory letter according to local operations and IRB requirements. Study brochures may be mailed with introductory letters.

5.6.2. Initial Patient Survey-part 1

Estimated time for completion: 5 minutes

The IPS-part 1 is essentially the same as the IPS used in SEARCH Phase 1. It collects information that confirm validity, eligibility and uniqueness of cases as well as

information that allows determination of diabetes type. It allows administration by the respondent or by an interviewer.

5.6.3. Initial Patient Survey-part 2

The IPS-part 2 includes selected additional questions critical to addressing major study aims, especially related to processes of care and quality of life of participants.

Estimated time for completion: 15 minutes

The IPS part 1 and part 2 may be administered either at the same time or at separate times to accommodate local and individual participant needs.

5.7. IN-PERSON VISIT

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

The In-Person Visit (IPV) differs for patients who are incident cases in 2002 - 2005 compared to those who are incident cases in 2006 - 2009 (see Table 5-1).

For 2002 - 2005 incident cases, the In-Person Visit consists of three components as originally administered in SEARCH Phase 1: physical examination, blood and urine specimens, and interviews/questionnaires.

For 2006 and 2008 incident cases, the Typology Visit is an abbreviated version of the IPV. All 2006 and 2008 participants will be invited for a Typology visit. Participants in 2007 and 2009 will not be invited to the Typology visit due to the time-based sampling approach. To allow for study of monogenic diabetes children diagnosed with diabetes at less than 2 years of age may be asked to participate in the Typology visit regardless of their year of diagnosis. (03/07) This abbreviated visit will consist of a physical examination and the collection of fasting blood and urine for laboratory measurements and storage. Measurements made to inform classification of diabetes type are fasting c-peptide (FCP), diabetes autoantibody titers (GAD65 and IA-2), and lipids. Hemoglobin A1c will be measured to inform analyses related to the quality of care. Plasma glucose is measured in order to be able to interpret FCP levels. In addition, samples (DNA/plasma/serum) will be stored in the study-wide repository for future work to be funded via ancillary studies. The minimum amount of blood/plasma necessary to conduct these tests will be collected and the total amount collected will not exceed standard, weight-specific guidelines.

Alert values have been established to ensure timely referrals as needed, with appropriate informed consent by participants or their parent/guardian for release of information to the appropriate health care professionals.

5.7.1. Physical Examination

Physical examinations will be performed on study participants ≥ 3 years of age at the time of the visit; and will consist of height, weight, systolic and diastolic blood pressure, waist circumference and a standardized examination to determine the presence or absence of acanthosis nigricans. This examination will be conducted for the IPV, the Typology Visit, and all Follow-up Visits.

5.7.2. 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 may be collected at any time after initial diagnosis.

Stimulated C-peptide (mixed meal challenge): Participants ≥ 8 years of age at the time of the baseline In-Person Visit will be invited to have a stimulated c-peptide (SCP) test. Following a mixed meal (Boost) challenge, c-peptide samples will be drawn at designated intervals consistent with current science. The stimulated c-peptide tests will be offered at the time of the 12, 24, and 60 month follow-up visits if: 1) a SCP test was conducted at the baseline visit AND 2) if the fasting c-peptide level from a previous visit was ≥ 0.6 ng/ml.

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.

5.7.3. Interviews/Questionnaires

The questionnaires will be administered in site-determined venues (e.g., a research clinic, health care provider office, van, home). The questionnaires administered during the IPV and Follow-up Visits vary and are listed in Table 5-1.

Some of the questionnaires are administered via interview, while others are designed to be self-administered (e.g., quality of life). If necessary, some of the questionnaires may be conducted over the telephone or via mail. The primary respondent for young children will be a parent or legal guardian. For older children, the child will typically be the respondent. The mode of administration (e.g., interview vs. self-administered; in-person vs. phone) and the respondent (e.g., participant, parent) will be documented. See Table 5-1 for a summary of the content of the questionnaires.

For supplemental questionnaires regarding health behaviors administered to youth ≥ 10 years of age, parents will be asked to waive their right to review their child's answers. Parents will be assured that appropriate referrals for care will be made according to established alert values. Parents have the option to refuse to consent for their child to complete these supplemental surveys.

Tanner stage self-assessment questionnaires will be provided for children ≥ 8 years of age.

The expanded data collection for SEARCH Phase 2 to address quality of life and quality of care includes a comprehensive survey of quality of care; including questions on receipt of ADA recommended screening tests. Surveys will be administered in year 3 to the selected prevalent 2001 cases who participated in a Typology visit and will be administered to Incident 2002 - 2005 cases during their follow-up visits at 24 and 60 months (see Table 5-1). (03/07)

5.8. FOLLOW-UP VISITS

All 2002-2005 incident cases who participated in a baseline in-person visit will be invited to a follow-up visit at 12, 24, and 60 months after the baseline visit. Table 5.1 shows the data elements to be collected at these follow-up visits.

5.9. MAILED FOLLOW-UP SURVEYS

Contact by mail will occur for the following situations (see Table 5.1): (1) Quality of Care surveys in for eligible prevalent cases in Year 3 (10/07 - 9/08) of SEARCH Phase 2 (section 5.7); (2) contact information for prevalent cases in all years and in 36 and 48 months for 2002 - 2005 incident cases; (3) annually for 2006 - 2009 incident cases.

5.10. VITAL STATUS

Vital status will be documented throughout the SEARCH study based on vital status at the time of data collection or when reported by family member or health care provider.

SEARCH Protocol - Section 6
Typology
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6. Typology

6.1. GOALS

a) To develop efficient and practical approaches to the classification of diabetes type for prevalent and incident cases

b) To describe and compare the clinical presentation and course of type 1, type 2, and other types (or hybrids) of diabetes.

These goals will be achieved by employing a classification system that uses a hierarchical approach beginning with definitions of diabetes type that are very specific and moving towards definitions that are more sensitive and less specific. The hierarchical scheme developed in SEARCH Phase 1 will allow flexibility in setting boundaries for rates and describing populations.

6.2. METHOD OF TYPOLOGY

6.2.1. Background

The report of the American Diabetes Association (ADA) Expert Committee on the Diagnosis and Classification of Diabetes Mellitus published in *Diabetes Care* serves as the basis for the definitions of the types of diabetes used in this study (128,129).

The Expert Committee defined diabetes mellitus as a spectrum of metabolic diseases caused by defects in insulin secretion, insulin action, or both. The committee concluded that a vast majority of the cases of diabetes fall into two broad etiopathogenetic categories. The first category, Type 1 diabetes, is caused by an absolute deficiency of insulin secretion. The major cause of this type of diabetes is autoimmune destruction of the beta cells (Type1A diabetes). Less frequently, genetic defects (MODY) in the insulin gene or in the beta cell's glucose sensing mechanism or idiopathic destruction of the beta cells result in insulin deficiency. The second category, Type 2 diabetes, is caused by a combination of insulin resistance, inadequate insulin secretion, and progressive beta cell failure. Despite emphasizing the presence of two major etiopathogenetic causes of diabetes, the committee acknowledged that the spectrum of diabetes includes individuals who develop diabetes as result of both autoimmune beta cell destruction and insulin resistance.

The spectrum of the etiopathogenesis of diabetes presents a significant challenge for developing a classification to assign diabetes type. In addition, any biochemical or clinical marker used to define diabetes type will in most cases be influenced by duration of diabetes since diagnosis. As a result, biochemical and clinical markers reflect current metabolic status that may or may not be consistent with the participant's pathophysiologic state at diagnosis. Any classification scheme must have the flexibility

to deal with both the range of pathophysiology and the ability of current metabolic status to describe diabetes type.

To address these issues, SEARCH chose to apply a hierarchical classification system to assign diabetes type. Hierarchical classification is a frequently used approach in epidemiologic studies where flexibility in defining the characteristics of a disease is required (130). The approach uses case definitions of disease defined by "Definite or Possible" categories. The advantage of this approach is that these definitions classify people into groups based on "certainty" and amount of information collected on the participants. The definitions begin with very specific, less sensitive definitions and then progress to more sensitive, less specific definitions. This approach allows for flexibility and accuracy in not only setting boundaries for rates of a type of a disease but also for describing the characteristics of segments of a population with a disease. Thus, the spectrum of the pathophysiology of diabetes and the issue of current metabolic status can be addressed within a hierarchical classification system.

6.3. DEFINITIONS OF TERMS USED FOR TYPOLOGY

6.3.1. General Definitions

6.3.1.1. Diabetes

Diabetes is defined as a diagnosis of diabetes by a health care provider.

6.3.1.2. Autoimmune Diabetes

Autoimmune diabetes is defined as the presence of one or more positive diabetes autoantibody (DAA) titers to a) glutamic acid decarboxylase (GAD), b) insulinoma-associated antibody (IA-2). To define the cut-off point for antibody positivity, GAD65 and IA2 analyses have been performed in 200 adults of both genders with no known history of diabetes. A GAD65 Index of 0.085 and an IA2 Index of 0.017, corresponding to the 99^{th} percentile of the non-diabetic control population, were used to define antibody positivity.

6.3.1.3. Low Fasting C-peptide

Low fasting c-peptide is defined as a fasting plasma C-peptide (FCP) < 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) Diabetes Complications and Control Trial investigators used a fasting C-peptide less than 0.6 ng/ml as a pre-defined entry criterion for the DCCT study and b) the 5th percentile for FCP in non-diabetic, healthy adolescents in the Bogalusa Heart Study was 0.8 ng/ml.

6.3.1.4. Elevated Fasting C-peptide

Elevated fasting C-peptide is defined as a FCP concentration $\geq$ 2.9 ng/ml based on findings in the 1999-2002 National Health and Nutrition Examination Survey (NHANES) healthy adolescents (133). The 83rd percentile for FCP in the adolescents in NHANES was 2.83 ng/ml. However, 17 percent of the adolescent population in NHANES were obese. The 50th percentile for FCP in the obese adolescent population in NHANES was 2.95 ng/ml. To account for the contribution of obesity to elevation in FCP, SEARCH investigators used the aforementioned data and chose $\geq$ 2.9 ng/ml as the cut-point for elevated fasting C-peptide.

6.3.1.5. Intermediate Fasting C-peptide

Intermediate fasting C-peptide is defined as FCP concentration $\geq$ 0.8 ng/ml but < 2.9 ng/ml.

6.3.2. Definitions of the Types of Diabetes

6.3.2.1. Type 1 Diabetes

Type 1 diabetes is defined as the progressive destruction of beta cells leading to an absolute deficiency of insulin which results in diabetes. A category of possible Type 1 diabetes will be established if all diabetes autoantibody titers are negative (see autoimmune diabetes 7.3.1.2) and FCP is low (< 0.8 ng/ml).

6.3.2.2. Type 1A Diabetes

Type 1A diabetes is the progressive, autoimmune destruction of the beta cells leading in time to an absolute deficiency of insulin resulting in diabetes. However, for a variable period of time following diagnosis insulin secretion can still be maintained. Type 1A diabetes will be established if one or more diabetes autoantibody titer is positive (see autoimmune diabetes 7.3.1.2) and FCP is intermediate or low (< 2.9 ng/ml).

- A category of definite Type 1A diabetes will be established if one or more diabetes autoantibodies are positive AND FCP is low (<0.8 ng/ml).
- A category of possible Type 1A diabetes will be established if one or more diabetes autoantibodies are positive AND FCP is intermediate (0.8-2.9 ng/ml).

6.3.2.3. Type 2 Diabetes

Type 2 Diabetes is the presence of insulin resistance and inadequate insulin secretion for the level of insulin action, with no evidence of autoimmunity. In SEARCH Type 2 diabetes will be established if all DAA titers are negative (see autoimmune diabetes 7.3.1.2) and the FCP is intermediate or elevated ($\geq$ 0.8 ng/ml).

- A category of definite Type 2 diabetes will be established if all DAA are negative AND FCP is high (≥ 2.9 ng/ml).
- A category of possible Type 2 diabetes will be established if all DAA are negative AND FCP is intermediate (0.8-2.9 ng/ml).

6.3.2.4. Hybrid Type Diabetes

Hybrid type diabetes is the presence of biochemical evidence of more than one type of diabetes. In SEARCH Hybrid type diabetes will be established if one or more of the DAA titers are positive (see autoimmune diabetes 7.3.1.2) and the FCP is elevated (≥ 2.9 ng/ml).

6.3.2.5. Other Specific Types of Diabetes

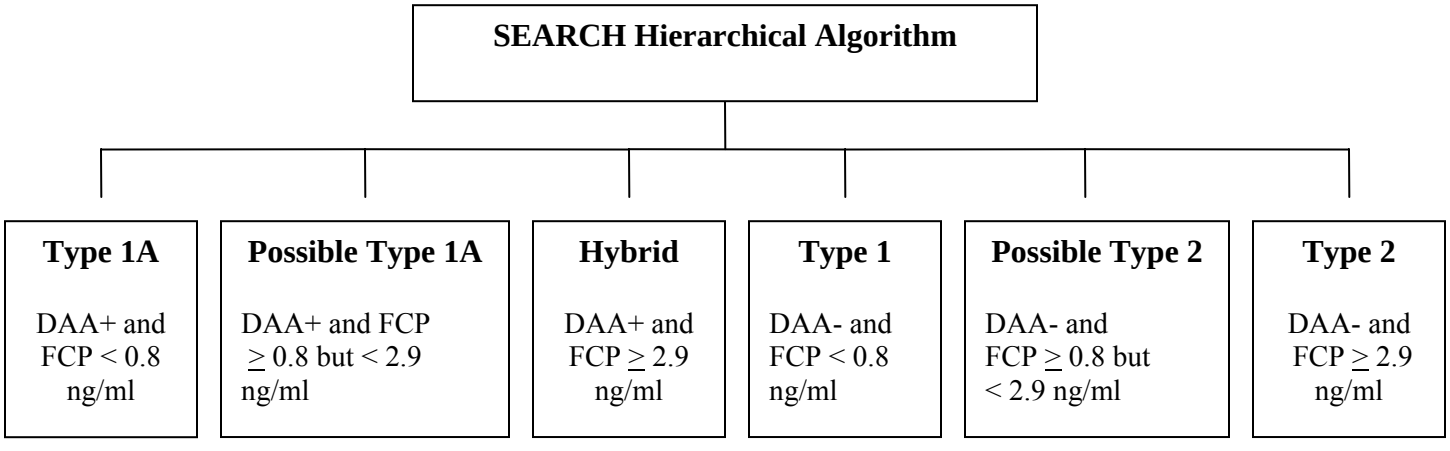
This definition includes monogenic forms of diabetes such as MODY and cases of diabetes that result from the presence of a disease or the administration of a drug causing beta-cell destruction or dysfunction or insulin resistance (secondary diabetes)(134). Individuals with MODY will participate in the SEARCH protocol.

6.3.2.6. Gestational Diabetes

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy. A woman with a history of GDM will be eligible for SEARCH *only if* a physician or other health care professional verifies that she has diabetes mellitus post-partum, demonstrating that her glucose intolerance persists after her pregnancy has ended.

6.3.2.7. Clinical Diabetes Type

Clinical Diabetes Type is the diabetes type assigned by the health care provider.



6.4. SEARCH HIERARCHIAL ALGORITHM

6.4.1. General Approach

Individuals diagnosed as having diabetes by their health care provider are eligible for participation in SEARCH. After validating the case, participants will be invited to participate in an in-person visit (see Section 5). DAA and FCP in addition to other biochemical and clinical data will be obtained at the in-person visit. DAA and FCP will be used to establish diabetes type using the SEARCH hierarchical algorithm (see figure 1). Typing of participants who have missing DAA or FCP or who did not participate in the in-person visit will be performed as described below (see section 6.4.2). These methods of typing include either estimating diabetes type using statistical modeling, or using clinical diabetes type as assigned by the provider (clinical diabetes type). Clinical diabetes type can be used for all SEARCH registered cases, not only for those who do not participate in the research visit. The method of typing chosen for a specific analysis and manuscript will be based on the scientific question that needs to be addressed.

6.4.2. Specific Approaches to Establishing Diabetes Type for Individual Cases

A. Typing of participants who had a SEARCH in-person visit with measurement of DAA and FCP, regardless of duration from diagnosis to the research visit. Employ SEARCH hierarchical algorithm.

B. Typing of participants who had a SEARCH in-person visit but either the DAA or FCP is missing. Employ any of the following methods:

   1. Missing FCP: Antibody status will be used per the SEARCH hierarchical algorithm, then model with probability. The highest probability match to the SEARCH hierarchical algorithm type will be used to assign the participant a SEARCH diabetes type.

   2. Missing DAA: Using the SEARCH hierarchical algorithm but ignoring DAA, the FCP will be used to identify the potential SEARCH types, then model with probability. The highest probability match to the SEARCH hierarchical algorithm type will be used to assign the participant a SEARCH diabetes type.

   3. Clinical diabetes type

C. Typing of participants who had a SEARCH in-person visit but are missing both DAA and FCP or participants who did not participate in a SEARCH in-person visit but data are available through other SEARCH data collection methods (initial patient survey, medical record data, core data). Employ any of the following methods:

1. Model with probability: The highest probability match to the SEARCH hierarchical algorithm type will be used to assign the participant a SEARCH diabetes type
2. Clinical diabetes type

6.4.3. Specific Approaches to Establishing Incidence and Prevalence Rates

Employ any of the following methods:

1. Incident cases (2002-2005)
    a. Employ the SEARCH hierarchical algorithm. For participants with missing data or no data, employ statistical modeling
    b. Clinical diabetes type
2. Prevalent cases (2001)
    a. Clinical diabetes type

6.5. USE OF NEW INFORMATION

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.

Additionally, if new information becomes available that suggests different cut-points to be considered for DAA or FCP, the algorithm will be modified accordingly.

6.6. COMPARE CLINICAL PRESENTATION AND COURSE OF DIABETES TYPES

To compare clinical presentation and course of the various types of diabetes, all participants in incident years 2003, 2004, 2005 who are > 8 years of age at their first SEARCH visit will be invited to undergo a mixed meal challenge test (see Section 5) with measurement of plasma C-peptide. The mixed meal challenge will be performed at each subsequent visit until the FCP is < 0.6 ng/ml.

SEARCH Protocol - Section 7
Processes of Care
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7. Quality of Care and Quality of Life of Youth with Diabetes

7.1. GOALS

A primary objective of the SEARCH Study is to assess the impact of quality of diabetes care in youth on short- and long-term outcomes including quality of life. To achieve this objective, the SEARCH Phase 2 Study has incorporated the following two goals:

a. To complete analytic work initiated in SEARCH as described in the Quality of Care Roadmap.

b. To expand the scope of quality of care assessment initiated in SEARCH in order to explore the interrelationships of patient characteristics, important domains of health care with outcomes, including glycemic control, satisfaction with care, receipt of recommended services, complications, and quality of life.

7.2. METHODS

7.2.1. Background

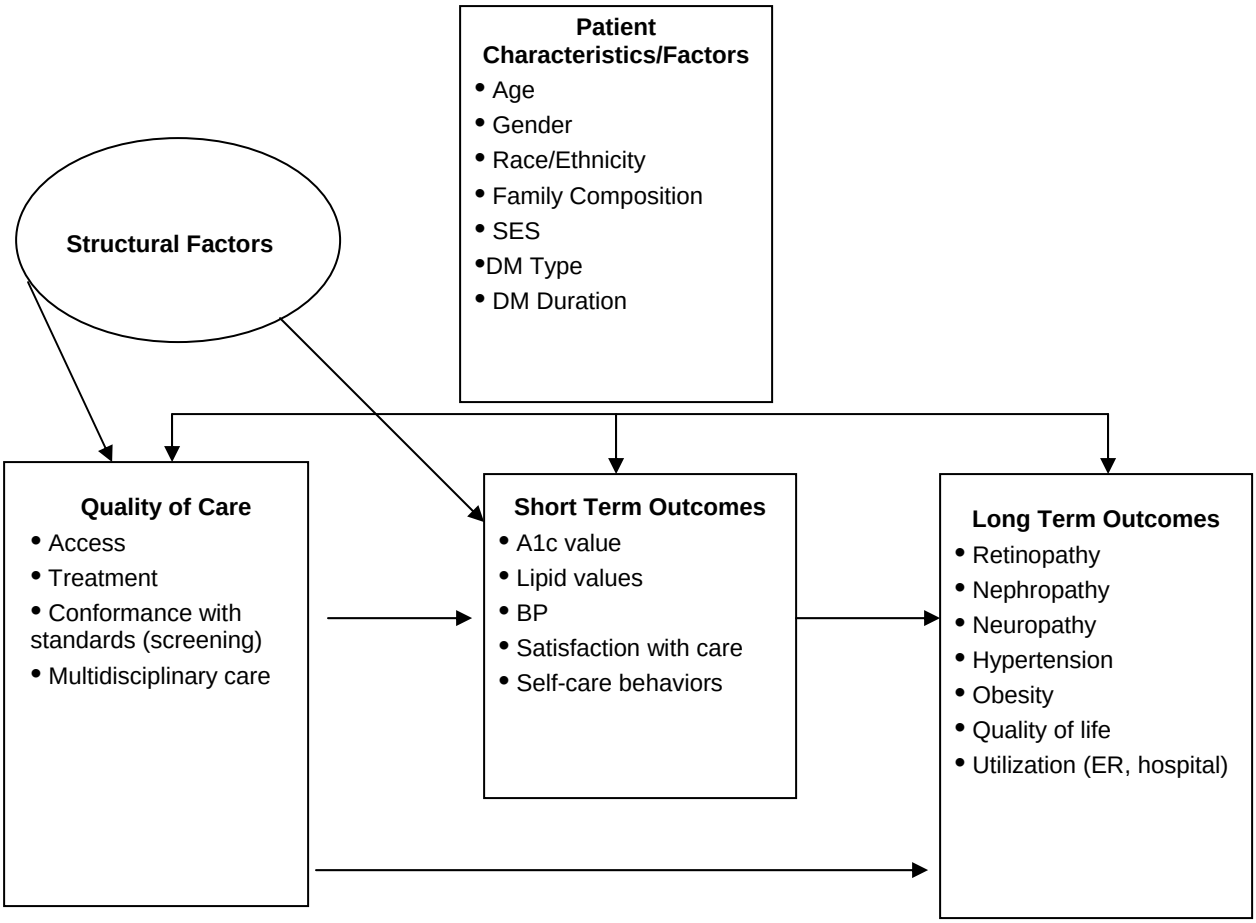
A secondary aim of the SEARCH Phase 1 Study was to evaluate health care utilization, processes of care and quality of life in children and youth with diabetes. A team of SEARCH investigators formed a Quality of Care workgroup to develop a conceptual framework to guide the study of quality of care and quality of life among children and youth with diabetes, as well as a specific analytic strategy, or "roadmap" to evaluate quality of care and quality of life among SEARCH participants. The conceptual model incorporates both the Institute of Medicine's (IOM) definition of quality, "the degree to which health services for individuals or populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge" and Donabedian's model for the measurement of health care quality, emphasizing organizational structure, processes and outcomes of care (see Figure 7.1 SEARCH Quality of Care Conceptual Model).

The roadmap developed by the Quality of Care workgroup defines specific areas of analyses relevant to this conceptual framework, including the prevention of acute and chronic complications, adherence to screening guidelines for the early detection of complications, maximization of quality of life and satisfaction with care and prevention of hospitalization and ER use associated with acute complications. Additionally, the roadmap defines specific variables relevant to these analyses and links them to available data collected during SEARCH Phase 1.

The infrastructure established during SEARCH Phase 1, coupled with the work accomplished by the Quality of Care workgroup, has provided the necessary foundation to enable the study of quality and outcomes of care among children and youth with

diabetes as a primary objective of the SEARCH Phase 2 study. Plans for SEARCH Phase 2 also include obtaining the consulting services of an established investigator in the field of quality of care for children, to enhance the success of the study in meeting this objective.

Figure 7.1 SEARCH Quality of Care Conceptual Model



7.2.2. Completing Analytic Work Initiated in SEARCH as Described in the Quality of Care Roadmap

The roadmap defined specific analyses/planned papers using SEARCH Phase 1 data to address explicit hypotheses about quality of care, process/outcome links, general and diabetes specific quality of life and correlates of these relationships. For each of these analyses, a writing-group chair was designated and a literature review conducted. A major goal of the first year of SEARCH Phase 2 is the completion of these nine planned analyses.

In addition to the completion of the analyses planned during SEARCH Phase 1, additional proposals will be developed to further explore quality of care and quality of life issues outlined in the roadmap that can be addressed using the data collected during SEARCH Phase 1, as well as relevant questions that can best be answered by using a combination of SEARCH Phase 1 and SEARCH Phase 2 data.

7.2.3. Expanding the Scope of Quality of Care Assessment Initiated in SEARCH

Quality of Care assessment will be expanded in scope in the second phase of SEARCH in order to explore the interrelationships of patient characteristics, important domains of health care with outcomes, including glycemic control, satisfaction with care, receipt of recommended services, complications, and quality of life.

Diversity in age, diabetes type and duration of diabetes has historically imposed significant limitations on studies of quality of care and quality of life for children and youth with diabetes. The SEARCH Phase 2 Study, as a large scale, population-based study, designed to capture diversity in age, type and race/ethnicity, offers a unique opportunity to explore the complex relationships of patient characteristics, quality and outcomes of care. The broad questions we seek to address in this phase of the study are:

- To what extent does the care received by SEARCH participants conform to ADA recommendations for testing?
- How does access to care affect glycemic control, satisfaction with care, and quality of life?
- What medical care factors are associated with the development of complications of diabetes including acute complications (DKA, hypoglycemia, and ED use) and chronic complications (self-reported hypertension, retinopathy, and nephropathy)?

7.2.3.1. Patient Sample

The research plan to analyze these interrelationships focuses on three distinct patient groups participating in the SEARCH Study: 1) newly diagnosed cases in 2006-2008; 2) 2002-2005 incident cases who have had a SEARCH in-person visit; and 3) 10% of Non-Hispanic White youth and all minority youth prevalent cases in 2001 who have had a SEARCH in-person visit. (03/07) Patients who have been identified as having diabetes secondary to another condition, or treatment for another condition, in each of these three groups will be excluded from this aspect of the study. Specific issues related to quality and outcomes of care that are likely to vary by age, diabetes type and duration will be addressed through analyses of data for each of these three patient groups individually, in combination and on a stratified basis.

7.2.3.2. Measures

A series of domains of quality of care and quality of life, as well as intermediate and long term outcomes of interest, have been identified by SEARCH study investigators for further exploration during SEARCH Phase 2. Specific measures for the identified domains of interest have been selected from validated, age-appropriate instruments whenever possible, including the Consumer Assessment of Health Plan Survey (CAHPS), and the PedsQL. Additional considerations in the selection of measures included respondent burden, versatility in modes of administration, the availability of Spanish versions and comparability to measures previously used in the study.

With the assistance of a consultant with expertise in the area of pediatric quality of care and health services research, SEARCH investigators have finalized a series of measures and instruments based on the following criteria:

1. Direct relevance to SEARCH Study aims and conceptual model of quality of care.
2. Published literature documenting the importance of particular patient characteristics, aspects of quality of care, self-care and outcomes relevant to children and youth with diabetes.
3. The availability of age appropriate, reliable and validated measures/instruments.
4. The availability English and Spanish versions of measures/instruments.
5. Flexibility of administration for face-to-face interviews, telephone and self-administered modes of data collection.
6. Limitations of the burden of data collection upon respondents.
7. Comparability to previously collected SEARCH Phase 1 data where relevant.

Some measures, particularly those that relate to conformity of care to American Diabetes Association (ADA) guidelines, were created for the purposes of this study. Final survey instruments were pilot tested, and new measures validated to the extent possible, to ensure that they are easily administered and clearly understood by potential respondents.

7.2.3.3. Data Collection

The SEARCH Phase 2 Study will entail new data collection for selected measures of quality of care, quality of life, intermediate and long term outcomes. For the 2006 - 2008 incident cases, data will be collected via the Initial Patient Survey (IPS)-part 2, which has been expanded for SEARCH Phase 2. For the 2002-2005 incident cases who have had a previous in-person visit (IPV), data will be collected

at the 24-month and 60-month follow-up IPV. If this is not feasible, efforts will be made to collect information via telephone interview and/or mailed survey. For 2001 prevalent cases who have had a previous IPV, data will be collected via telephone or mailed survey to be conducted during year 3 of SEARCH Phase 2. Data collected on selected measures of quality of care, quality of life and outcomes will differ across the three patient groups based on their relevance to the specific aims of the study, the unique characteristics of the patient group and the opportunities for data collection from each of the three groups. Based on the preliminary domains selected by investigators, it is anticipated that data will be collected for each of the three patient groups as shown in Table 7.1.

Table 7.1

POC/QOC/Outcome Domain	2006-2008 Incident Cases	2002-2005 Incident Cases	2001 Prevalent Cases
Eligibility Criteria	All cases	Baseline IPV completed	10% sample NHW youth and all minority youth who completed Baseline Typology visit..
When collected	IPS-part 2	24 and 60 months after baseline visit	in Year 3 of SEARCH Phase 2
Socioeconomic Status Indicators	√	√	√
Access to Care			
Insurance Coverage	√	√	√
Financial Barriers	√	√	√
Non-Financial Barriers		√	√
Relationship with Provider	√	√	√
Satisfaction with Care	√	√	√
Quality of Care Experienced		√	√
Processes of Care			
Multidisciplinary Care	√	√	√
Receipt of Screening tests in accordance with ADA recommendations		√	√

POC/QOC/Outcome Domain	2006-2008 Incident Cases	2002-2005 Incident Cases	2001 Prevalent Cases
Self-Care Behaviors		√	√
Intermediate Outcomes			
Glycemic Control	√	√	√
Hypertension		√	√
Dyslipidemia		√	√
Quality of Life		√	√

SEARCH Protocol - Section 8
Statistical Considerations
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8. Statistical Considerations

The primary aim for statistical analyses is to address the 4 objectives of SEARCH Phase 2 that require statistical methods. For all analyses, the underlying assumptions for the techniques that we propose will be examined. These usually involve testing for linearity, normality and homoscedasticity of variances in linear models. When violations are found, appropriate methods such as transformations or non-parametric techniques will be employed. The methods to be used to determine appropriate denominators and denominators for incidence rate estimation will be clearly outlined , including power and sample size considerations, for describing the trends in the incidence of diabetes in youth, by age-group, gender, race/ethnicity and diabetes type for the period 2002 - 2008.

8.1. STATISTICAL CONSIDERATIONS FOR SEARCH STUDY AIM 1

Aim 1: Prospectively ascertain newly diagnosed (2006 - 2009) incident cases aged < 20 years and collect data that permit estimation of temporal trends in the incidence of diabetes in youth, by age-group, gender, race/ethnicity and diabetes type for the period 2002-2008. In order to achieve the goals of this Aim input must come from both the clinical sites and the CoC. Details concerning Case Ascertainment, Case registration and data collected during the initial patient survey and typology visit will be of primary importance.

8.1.1. Denominator and Numerator Estimation for Incidence Rates

Due to the fact that there will exist some amount of missing data concerning race/ethnic-specific designations for all participants and that not all participants identified during a specific year as an incident case will attend the typology visit at a clinical site, the following approach will be used in SEARCH Phase 2 to estimate the denominators and numerators needed for incidence rate estimation.

8.1.1.1. Denominators for Incidence Rate Estimation

For denominator estimation in SEARCH Phase 2 for years 2004 - 2009, geographically based sites will continue to use US census population projections and membership sites will use administrative data on membership on December 31 of the index year. Additionally, in SEARCH Phase 2, we will disaggregate the denominator data for the category Asian/Pacific Islander into Asian, Pacific Islander and mixed Asian/Pacific Islander and to disaggregate the Asian group for all cases over the entire data collection period 2002 - 2008 to estimate incidence rates specific for Asians and Asian subgroups and for Pacific Islanders.

8.1.1.2. Numerators for Incidence Rate Estimation

In order to determine the numerators needed for incidence rate estimation for diabetes types for individuals with incomplete SEARCH data, the CoC will fit a sequence of multinomial logistic regressions on participants with 'complete' data, then will use these models to impute probabilities of DM types using a regression-based imputation strategy described by Little and Rubin (135). This method allows the imputation of probabilities of DM type that are conditional on the variables measured on participants with missing biochemical data. These probabilities will be used together with information on type of diabetes in SEARCH participants with complete data to calculate consistent and unbiased estimates of incidence and prevalence rates for different diabetes types.

8.1.1.3. Analytical Considerations

To determine whether there is a significant change in incidence rates over time overall and within specific subgroups, SEARCH Phase 2 will test the hypothesis that there is no change in incidence rates over time versus an alternative hypothesis that the rates are changing over time. This will be a two-sided hypothesis test since overall and within certain subgroups we are not certain whether changes will indicate an increase or decrease in incidence of diabetes. The specific tests (overall and by subgroup) will be to examine whether the slope of the line describing incidence rates over time is different from zero (i.e., slope of zero would indicate incidence rates remained the same over time).

8.1.2. Power/Sample Size Considerations

The value in collecting incidence data for many years in succession is the gain in statistical power to detect whether there is a change in the incidence rate over time. In order to determine the detectable differences in incidence rates we need to have the following data inputs: baseline incidence rate, baseline number of cases, baseline total population, α level, Power level, and number of years of follow-up.

Table 8.1. Detectable Differences in Incidence for 3-Year, 7-Year and 8-Year Follow-up

		3 Years Follow-up Detectable Difference		7 Years Follow-up Detectable Difference		8 Years Follow-up Detectable Difference	
Group	Baseline Incidence Rate	Absolute	Relative (%)	Absolute	Relative (%)	Absolute	Relative (%)
Total population	25.529	1.156	4.5	0.309	1.2	0.252	1.0
By Age Group							
Age 0-9	20.527	1.491	7.3	0.399	1.9	0.325	1.6
Age 10-19	30.214	1.751	5.8	0.468	1.5	0.382	1.3

By Sex							
Male	24.337	1.580	6.5	0.422	1.7	0.345	1.4
Female	26.773	1.693	6.3	0.453	1.7	0.369	1.4
By Race/Ethnicity							
NHW	27.495	1.561	5.7	0.417	1.5	0.341	1.2
AA	26.695	3.127	11.7	0.836	3.1	0.682	2.6
H	21.266	2.640	12.4	0.706	3.3	0.576	2.7
API	16.536	3.338	20.2	0.892	5.4	0.728	4.4
AI	24.551	6.727	27.4	1.798	7.3	1.468	6.0
By SEARCH Biochemical Type							
Type 1a	11.3	1.071	9.5	0.286	2.5	0.234	2.1
Possible Type 1a	7.2	0.855	11.9	0.228	3.2	0.187	2.6
All Type 1a	18.5	1.370	7.4	0.366	2.0	0.299	1.6
Possible Type 1a	1	0.319	31.9	0.085	8.5	0.070	7.0
Type 2	3.6	0.604	16.8	0.162	4.5	0.132	3.7
Possible Type 2	4.8	0.698	14.5	0.187	3.9	0.152	3.2
All Type 2	8.4	0.923	11.0	0.247	2.9	0.201	2.4
Hybrid	1.3	0.363	27.9	0.097	7.5	0.079	6.1

8.2. STATISTICAL CONSIDERATIONS FOR SEARCH STUDY AIM 2

Aim 2: Conduct longitudinal follow-up of SEARCH 2002 - 2005 incident cases SEARCH to:

a) Document the evolution of newly diagnosed DM according to clinical and biochemical factors

b) Characterize the evolution of key risk factors for DM complications, by DM type and race/ethnicity.

Longitudinal data collected on SEARCH 2002 - 2005 incident cases during the new grant period will be combined with previously collected SEARCH data (baseline and follow-up). Possible follow-up times and duration will depend on the baseline data collection date. Generally, a minimum of 2 years of annual follow-up will be possible on all cases; only a subset of cases will reach eligibility for five-year follow-up in SEARCH Phase 2.

The focus of the longitudinal data collection and analysis is to meet research Aims 2 and 3. This section outlines a general data analysis plan for Aim 2; a plan for Aim 3 is outlined in a subsequent section.

The natural history of DM in newly diagnosed youth will be defined according to features both clinical (e.g., insulin dependence) and biochemical (e.g., FCP). Much work has already been accomplished by the SEARCH team on developing a baseline typology algorithm (see section on Typology). This algorithm will be used as the basis for estimation of the natural history of DM by type. The clinical and biochemical course of participants within DM type, and comparisons between types, will be estimated and tested for continuous outcomes using mixed effects analysis of covariance models (136-137). These models allow for both time-varying changes in covariates, and departures from linearity in the relationship between the outcome and time. Time-varying covariates might include weight or BMI, and their relationships might depart from linearity as well. Mixed effects models are flexible enough to permit random rates of progression, consistent with a perspective that different participants progress through time at different rates. Use of random intercepts and/or slopes provides a source of autocorrelation between repeated measures. More flexible structures for the correlation between repeated measures will be investigated using combination mixed models that allow the specification of separate parameters representing variation between experimental units, and serial correlation within units (138). Our choice of methods for accounting for serial correlation depends on the plausibility of the model, and the number of outcomes relative to the number of participants. For example, with many participants and few repeat measurements, unstructured covariance matrices can provide the most efficient model parameter estimation.

For analysis of longitudinal discrete outcomes (e.g., insulin dependence), we will use the generalized estimating equation (GEE) approach to fit logistic or log-linear models that account for the dependency between repeated measures (139-142). GEE techniques provide a mechanism for estimating model parameters and their 87 standard errors from longitudinal data having continuous and categorical responses and potentially missing observations. An advantage of this technique is that the assumptions required are weaker than those of maximum likelihood techniques: one need not specify the distribution of the dependent variable, just the relationships between the marginal mean and variance/covariance.

8.2.1. Power Analysis

For the purposes of estimating the sample size needed to detect a significant difference with sufficient power, calculations were based on comparing 5-year FCP measurements after adjusting for baseline FCP (assessed during the baseline typology visit for incident cases from 2002 and 2003). These calculations need to account for the proportion of the variance in the outcome (5-year FCP) that is explained by the baseline FCP values. Although our full longitudinal models will incorporate all intermediate time points into the final analysis (Follow-up year 1 and follow-up year 2), our power calculation is based on examining the difference in FCP adjusting only for baseline FCP. Therefore, these are

conservative power calculations, since the additional information provided by the intermediate (yearly) assessments of outcome measures are not included. The following formula was used to describe the minimum detectable difference in terms of standard deviations between the participants with autoimmune DM (Type 1A and Hybrid - AD) and participants with non- autoimmune DM (non-AD):

$$\Delta = \frac{\sqrt{(1-r^2)(Z_{1-\alpha/2} + Z_{1-\beta})^2 (k\sigma^2 + \sigma^2)}}{\sqrt{n_1}}$$

In the above, r^2 is the percent of the variance of the follow-up outcome explained by the baseline measurements, $Z_{1-\alpha/2}$ is the value from the standard normal distribution corresponding to the alpha level chosen (1.96, which corresponds to alpha=0.05 [two sided]), $Z_{1-\beta}$ corresponds to the power chosen for the study (80%), σ^2 is the variance of the outcome of interest (FCP), n_1 is the number of participants in the AD group, k is the ratio of n_1/n_2 (sample size in AD and non-AD groups, respectively) and Δ corresponds to the detectable difference in the mean values of the two groups being compared. Using this formula, we examined the detectable differences for several possible r^2 values assuming 80% power and alpha=0.05. From SEARCH Phase 1, it was estimated that the standard deviation for FCP was approximately 1.6 ng/ml. Using these numbers the Table below describes the detectable differences if there were 500 participants in the AD group and 149 in the non-AD group. This assumes a 60% response rate from 2002 - 2003 incident cases after 5 years.

Table 8.2. Detectable Differences in the Correlation between baseline and Follow-up Fasting C-Peptide

Detectable differences with 80% Power	**Correlation Between Baseline and Follow-up FCP**			
Sample Size (n_1/n_2)	.75	.80	.85	.90
500/149 (Autoimmune versus non-autoimmune group)	.276 ng/ml	.251 ng/ml	.220 ng/ml	.182 ng/ml

As shown, if the correlation between the baseline and follow-up measurements is large (.85) then we have 80% power to detect a difference of 0.220 ng/ml for the AD versus non-AD group comparison. As stated above, these estimates should be conservative since when the additional yearly measurements are incorporated into the longitudinal analyses, there will be additional precision which should reduce variability and allow for smaller between group differences to be detected.

8.3. STATISTICAL CONSIDERATIONS FOR SEARCH STUDY AIM 3

Aim 3: Assess the impact of quality of diabetes care in youth on short- and long-term outcomes including quality of life by:

a) Completing analytic work initiated in SEARCH as described in the Quality of Care Roadmap

b) Expanding the scope of quality of care assessment initiated in SEARCH to explore the interrelationships of patient characteristics, important domains of health care with outcomes, including glycemic control, satisfaction with care, receipt of recommended services, complications, and quality of life.

The following are key questions to be answered by analysis of new data collected as part of this aim in conjunction with data already collected and data to be collected as part of the study for other reasons:

How does access to care affect glycemic control, satisfaction with care, and quality of life? Are these relationships modified by family socioeconomic status, parental education, race/ethnicity, access to care/insurance, and care by a specialist/specialist team?

What medical care factors are associated with the development of complications of diabetes including acute complications (DKA, hypoglycemia, and ED use) and chronic complications (self-reported hypertension, retinopathy, nephropathy)?

A modeling approach similar to that outlined for longitudinal data analysis in Aim 2 will be used in Aim 3. When possible, the instruments for Aim 3 have been standardized for administration by phone or in-person, are validated, and are available in English and Spanish. Every effort will be made to collect at least two measurements on each participant for each instrument. For participants lost to follow-up, we plan to use all available information until loss to follow-up. If loss to follow-up is related to the level of the outcome being analyzed, as often occurs, then our results will be somewhat biased. The magnitude of this problem will be investigated by using measurements taken at previous visits to predict loss to follow-up. Variables determined to predict loss to follow-up will be included in our predictive models in order to satisfy the conditions described by Little and Rubin for the data to be considered “Missing at Random” (MAR). (135) Estimation techniques such as maximum likelihood will be used to estimate parameters. If the MAR assumption is untenable, one must assume that “informative censoring” has occurred. For example, biased estimates can result if participants with adverse experiences are more likely to withdraw (or, conversely, tend to be relatively less likely to withdraw). One approach to this problem is to only include participants with complete data in the analyses; this could lead to substantial bias if the missing participants are not randomly distributed between various groups. Another approach is to

assign a pre-specified score to the missing data (143) or assign observed participant-specific values (e.g., baseline values) (144). These methods generate tests that are less powerful than the tests used assuming random censoring or do not account for imputation uncertainty. A growing body of literature describes two alternative approaches: explicit modeling of the censoring mechanisms (145-151) and pattern-mixture models (152). We have experience with these approaches for handling non-ignorable non-response and will analyze the data using several of these methods which incorporate varying assumptions about the missing observations (153). This will provide useful information about the limitations in the ability to interpret results in the presence of informative censoring.

8.4. STATISTICAL CONSIDERATIONS FOR SEARCH STUDY AIM 4

Aim 4: Develop and validate simple and low-cost case definitions and classifications of DM types in youth that can be used for public health surveillance

a) Determine the best practical typing algorithm for public health surveillance, using all available, already collected demographic, clinical and biochemical information. Validate the algorithm against the "gold standard" biochemical DM type.

Overview - The development and validation of case classification methods and definitions useful for clinical and public health work was begun in SEARCH 1 and is summarized in the progress report (see section C.7.i.i). This analytic aim will be achieved using existing biochemical, clinical, and survey data collected in SEARCH 1 from the 2001-2005 cohorts. In the following sections we describe an analysis approach for how these methods will be extended and how the SEARCH DM types will be further explored and extended for public health surveillance use. The general approach will be to develop and further refine the 'gold standard' definition of type using biochemical and clinical variables based on already collected data (incident cohorts from 2002-2005, with DM duration < 12 months). This definition will then be validated on the new cohorts from 2006-2008 depending on numbers of participants in race/ethnic and type subgroups. No new data collection in addition to that already collected is required to accomplish this aim.

8.4.1. Model Building

The first step in developing algorithms that can predict the biochemical 'gold standard' is to use the previously collected information related to DM type (demographic, clinical, biochemical) on participants with a biochemical DM type (SEARCH type). The complexity of our problem arises from the fact that there are more than two potential categories that each participant could be a member of (i.e., T1, T1a, T2, etc) which means that simple cut point rules may not easily be applied. There are many potential statistical methods that can be employed to examine the predictive ability of a set of measurements

in "predicting" a particular multi-level outcome (DM type). We will use two methods for classifying individuals into diabetes type. These methods are multinomial logistic regression and the CART approach. CART may suffer from weaknesses in over-fitting the models as well as possibly having poor predictive performance. The predictive performance of both methods will be compared to ensure that if one does perform worse than the other we can use the better performing approach. In addition, since we collect data annually for incident cases, we can use the model from a previous incident case year to predict diabetes type in a future year and compare the results to those found from the actual biochemical algorithm used on those participants. As the predictive models are developed, it is likely that there will be simple sets of risk factors that can be used in these models and eventually tables can be constructed for clinical use in predicting diabetes type in much the same way risk appraisal function tables are currently used in cardiovascular medicine to predict cardiovascular risk given a set of observed risk factors.

8.4.2. Multinomial Logistic Regression Approach

Using multinomial logistic regression, SEARCH type will be predicted using all available data [demographic (race/ethnicity, gender, etc), clinical history (age at onset, insulin use, diabetic ketoacidosis (DKA, etc.], examination (BMI, waist, acanthosis nigricans, blood pressure), and laboratory [stimulated C peptide (SCP), lipids, extended typology makers]. In this model the outcome will be the multi-level variable SEARCH type. Once the overall model is fit, simpler models will then be fit where we will remove variables in sets based on the difficulty of collection. For example, selected laboratory data will be removed first to see if models without these data can reasonably predict SEARCH type. Then examination data not routinely collected will be removed (e.g., acanthosis), and so forth. The goal will be identification of a set of variables of increasing simplicity that will have known misclassification probabilities. Such an approach has been used to predict diabetes and IGT using non-glucose measures (154). These models will then be validated against the newly collected incident cases identified from 2006 - 2008.

8.4.3. Classification and Regression Tree (CART) Approach

A second approach we will implement to address this Aim will use recursive partitioning Classification and Regression Tree (CART) analysis. This approach has been described recently as an approach to predict DM using multivariable models (155). This approach will differ from the multinomial logistic regression approach above primarily in that the goal of this approach is to explore which variables and their cut-points best discriminate between SEARCH types of DM (e.g., age, age at diagnosis, treatment, history of DKA, BMI, waist circumference, FCP, DA level, among others). The method will help identify a set of cut points for each measure and classify participants based on their observed measures relative to these cut points. The multinomial logistic regression modeling does not identify cut points for each measure but rather models the relationship of the measure

to the outcome (SEARCH type) on a continuous scale. We will examine different sets of variables to determine whether there are simpler combinations that are available to classify participants accurately.

8.4.4. Validation of Models

An exciting opportunity that will exist in SEARCH Phase 2 is that we will be able to validate the models we identify above using the new cohorts that are collected from 2006 - 2008. Thus, the set of models identified using the multinomial logistic regression, CART, and hierarchical approach will then be applied to new participants in SEARCH Phase 2 who have definitive DM type measured. We will examine the goodness of fit of each model and compare the models with each other. Despite the fact that the multinomial logistic regression approach and CART approach are different, we anticipate that the ultimate set of risk factors identified to be used in the models should be quite similar if not the same.

A potential concern about the validation approach is that there is a potential that the relationship between risk factors and DM type is changing over time. For instance, one may wonder whether the relationship between demographic characteristics, such as gender, and DM type remains constant from 2002 through 2008. An advantage of using the SEARCH 1 and 2 data is that we can explicitly study this question. That is we can fit predictive models where the time (year of measure) and time by risk factor interaction is included to see whether there is evidence that the relationship between risk factors and DM type is changing over time. We do not anticipate these interactions to be significant, however if they are it would assist us in identifying risk factors that may be becoming more (or less) important in predicting DM type.

8.4.5. Evaluation of the Utility of Definitions

Once definitions of type using various prediction models are formed they will be evaluated for their public health utility by convening a meeting of public health professionals from the CDC and select state/local health departments to discuss the feasibility and methods to obtain such information in ‘real-world’ settings. This step is of great importance since the utility of the statistical models described above can only be judged successful if they can be integrated into the real-world clinical setting.

SEARCH Protocol - Section 9
Data Management
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9. Data Management

The most popular method of developing a data management system is through the use of remote data entry through a web-based interface. This method was used for the first phase of SEARCH and will be used for SEARCH Phase 2. The WFUSM SEARCH Coordinating Center (CoC) data management system operates on a web browser (Netscape or Internet Explorer) user interface, which provides an easy to use, platform independent, data entry and retrieval environment. Data is stored centrally at the CoC in a Windows NT-based SQL Server data warehouse. Front-ends were built using HTML and Cold Fusion middleware was used to integrate the SQL Server data within the HTML interface. While the interface has been developed to be browser independent, browsers do not always display information consistently across versions. Therefore, sites are required to use either Netscape or Internet Explorer, versions 4.0 or later.

In this model, the clinic staff use a PC to access the study site and enter the data directly. Given their familiarity with the data, inconsistencies found during the data entry process are correctable during the original data entry session, thereby reducing error. Since data submitted is automatically entered into the central database, any reporting or further edit validation processes are based on the most current data. Email messages are generated at the time of data entry to alert study and clinic personnel of outstanding issues.

9.1. QUALITY CONTROL

The WFUSM SEARCH CoC is responsible for developing and implementing QC procedures. QC techniques will be incorporated into each phase of the study from case ascertainment, recruitment and registration of persons with diabetes to data acquisition, reading and/or interpretation of the results and their analyses and publication. The CoC has worked with and will continue to work with the Protocol Oversight Committee reporting to the Steering Committee and to the External Scientific Advisory Committee. The CoC created dynamic QC reports for the QC Committee, and will continue to utilize this highly effect method during the second phase of the study.

9.2. DATA ENTRY

For SEARCH, a web-based application for study data entry has been implemented that is complemented by a clinic-based application to manage participant contact. Through use of the local application, the clinics will be able to better track the number of participant contacts that they have encountered, while improving their data quality by being able to print barcode labels that will be attached to all forms, specimens, and any other participant data source. Each PC is equipped with a barcode scanner designed to read the barcode label. This reduces the amount of data error due to incorrect participant ID entry.

9.3. ELECTRONIC FORMS

Electronic forms are being used for SEARCH Phase 2. Online versions of the forms have been developed that closely resemble the paper version as possible. Electronic data is managed centrally at the CoC. After reviewing case report forms (CRF) for gross errors and errors of omission, clinic staff begin the web-based entry process.

After selecting a valid menu option and entering a valid patient ID, the staff member is given a list of forms that can be entered or edited. After the selection is made, the form will be displayed and any existing information will be pre-filled. Upon completion of entry or edits, the user can submit or cancel the form. If the save option is selected, the appropriate tables are updated and any audit information is saved. With the exception of registration data in the tracking database, no electronic data will be housed at the clinics. Data will reside on the database server at the CoC in a Windows NT-based SQL Server database.

9.3.1. Computerized Edit Checks

The CoC performs numerous computerized edit checks to ensure data quality. These include, but are not limited to: (a) initial screening of data, using logic and range checks that are built into data entry screens; (b) cross-form functional and consistency checks; (c) edits assessing the serial integrity of data, particularly in studies with longitudinal data collection; and (d) assessing means, ranges, and standard deviations of registry and laboratory data.

All questions are pre-assigned missing values for the purpose of data entry. The data entry screens require a set degree of completeness before a form can be considered finalized. Should a form be incomplete, the missing value would be entered into the database. Validation checks are applied during the data entry process. Checks will be programmed using JavaScript routines activated as clinic personnel enter data, from each CRF. Additional data validation is performed on the server at the time the form is submitted. Feedback regarding the status of the form and any missing or inappropriate data is available to the data entry person immediately after form submission as well as on cumulative reports available online for clinic review. If it is determined that certain data points are truly missing, a separate code is entered to designate this. This information, along with the rationale for this designation is noted in study logs.

A more sophisticated series of checks is made after data have been entered. Computer edits are performed across forms to detect and correct instances of entry and transcription errors that pass the cross-sectional (intra-form) logical and range checks of the data entry screens. Lists of these errors are sent to study coordinators at the clinics for verification based on hard-copy records of forms or clinic information. When errors are discovered in the data, special records are kept to certify when and by whom the error was

discovered, what steps were taken to ascertain the correct information, and when and by whom the database was corrected. The checks of means, ranges, and standard deviations allow for detection, retrospectively, of any relative bias in definitions or measurements. While it may not be possible to rectify these biases (post hoc), these edits will at least identify variables for which care must be taken in interpreting analyses.

9.3.2. On-site Monitoring

Site visits to the SEARCH study sites are conducted based on a timeline developed by the SEARCH Protocol Oversight Committee. Clinics may be selected for extra site visits based on concerns arising from CoC and Protocol Oversight Committee contacts or via problems noted on monitoring or QC reports. For example, if the quality of data from a particular study sites is poor, the Protocol Oversight Committee may recommend special site visits of the Center to identify and correct the problems. Site visits 1) provide a means for continual training, retraining and reinforcement of standard study procedures; 2) enhance communication between the study sites and the CoC; and 3) detect and document the extent of problems in implementing the protocol.

The data collection/entry performance of the clinical centers and laboratory are evaluated during periodic site visits. These site visits include auditing of data collection/entry results received by the CoC for randomly selected participants. The study sites and laboratories are sent a list of the randomly selected participants and requested to have the clinic records and patient files for these participants available on the day of the audit. The auditor brings from the CoC study data on participants from the central database. A direct comparison of these data with the patient records is performed. Auditors attempt to determine whether discrepancies are due to data entry errors, misinterpretation of study protocol, or other reasons. Data collection/data entry completeness is assessed. Detailed audit results and the preliminary report are discussed on the spot with key staff investigators and data managers. A final report is prepared and issued subsequent to each site visit. An audit visit summary is presented to the Protocol Oversight Committee. The review of ten participant records at each site visit should be adequate, unless the study site has been targeted for more extensive review due to previous problems.

9.3.3. Clinic Performance Monitoring

The SEARCH CoC will continue to provide input to clinic staff through the internal website with regard to clinic performance in ascertainment of IPS, patient participation in IPV, and performance of study measures (blood pressure, waist circumference, height). Cumulative data reports will be discussed with the Program Administrator and will be a regular agenda item of Steering and Protocol Oversight Committees.

9.3.4. Security

Normally, data are transmitted across the Internet as plain text. It is possible, though highly unlikely, for someone with access to the proper equipment to monitor this traffic and to reconstruct individual pieces into the original data. Because of this threat, the CoC employs a digital server certificate from Verisign, Inc. This certificate allows the communications between the web server and the client system to be encrypted. This encryption is as advanced as is now allowable by the United States Government. This mechanism is the same as is used by the banking industry and for electronic commerce.

Restricted areas of the web site are protected by user login. Prior to gaining access to the restricted area, the user is required to enter a username and password that is checked against a database. The organization of the SEARCH database is such that it allows the CoC to restrict functions of an individual user by their login. The CoC and restrict their ability to view entire sections of the web site, reports, data elements and more. For security purposes, once a user has successfully logged into the system, inactivity for a period of 30 minutes will automatically force the user to re-authenticate prior to using the system again. Users are recommended to log out of the system before leaving their work area for any extended period.

WFUSM is protected by a Cisco firewall that limits the source and type of traffic coming into the institution. This product remains under constant monitoring and control. In addition, the institution is currently implementing a suite of Net Ranger products that will assist in the detection and circumvention of certain well-known attacks. Using attack signatures, the products monitor incoming traffic, looking for data streams that match the signature of attacks. If found, information is collected about the attack and the transmission is terminated.

9.3.5. Disaster Recovery

Each night, all data, programs, code, documents, etc. associated with the SEARCH project are backed up to a DLT tape library. These tapes are kept indefinitely and are located in a fireproof cabinet that remains locked at all times. Periodically, copies of tapes are moved to an off-site location for storage. In the event that there is any loss of data, the information can be restored from tape in a matter of hours. The entire WFUSM Public Health Sciences computer facility is provided with conditioned power, UPS capability and environmental sensors with notification protocols.

9.3.6. Tracking and Monitoring of Laboratory Data

Study sites log each shipment of specimens sent to central laboratory by use of barcode labels that it will attach to all samples being shipped to the central lab. Once samples are received at the central lab, they are scanned into the central laboratory database. Central laboratory data is transferred electronically to reduce the possibility of error upon re-

entry. By using a web interface, data are transferred to a repository on the server. If needed, firewall accounts can be obtained from the institution to allow outside laboratories to deposit data into the repository. Specific import routines are developed to verify and merge these data with the main database.

9.3.7. Data Tracking and Reporting

The tracking of data collection through the study is implemented using a web-based interface. Checks are run to see that any expected data has arrived within the specific window of time allotted for that data. Automated reports list delinquent data items which are maintained online. Some missing data elements are emailed automatically to study sites. In addition, a variety of online reports are constructed for use by the study sites, the CoC, and possibly CDC and NIDDK in order to monitor study progress and protocol compliance. These reports differ in content depending on the requirements of the individual user, and access is restricted to persons with the appropriate security clearance. Automated reports are developed that circulate this information to the appropriate places (e.g., PI, IRBs, etc.). Security reports are available to monitor authorized and unauthorized attempts to access portions of the system.

9.3.8. Data Conversion and Extraction

SAS analysis files are extracted from the database using SAS/Access. Programmers develop routines to create other specialized analysis files from the SQL Server database or the SAS database. Prior to merging or extracting any data into or from the database, merge/extraction routines are developed and thoroughly tested. All testing is documented in study logs. Since data arrives from differing locations, verification includes consistency checks across all platforms as well as any other routine checks. All routines are properly documented and changes and updates to the code are noted.

9.3.9. Database Closure and Documentation

Upon study completion, after all clinic and laboratory data have been collected and filtered through various QC routines, the resulting SQL Server database will be converted to SAS and ASCII data sets and certified. The database will be taken offline and archived on magnetic tape and/or CDROM. The final data sets will be certified and issued version numbers to synchronize analytic efforts. They will then be distributed in accordance with SC and institutional policy. The choice of media and database copy distribution method to the investigators will depend upon the systems and media available**.**

Documentation will be prepared that contains a brief overview of the project, the goals, and the type of data collected. This will be followed by a data dictionary, including a list of variable names, their positions, and short descriptions of each variable contained on the media. Unique data transformations and clarifications will be provided. The CoC will also create a plan for developing a distributed data set with SEARCH investigators. The CoC has appropriate HIPAA relationships with each of the six SEARCH CCs.

9.3.10. Data Sharing

SEARCH investigators understand the need to publicly share study research data in a timely fashion. They also understand the need to maintain the confidentiality of the study participants. The procedures for data sharing ensure that: 1) confidential information is not disclosed; 2) data are released in a form that does not endanger national security or compromise law enforcement activities; and that 3) proprietary data (i.e., data owned by private organizations such as Managed Care Organizations, Preferred Provider Organizations, or technology firms) are not released inadvertently.

The final study analytical database will be processed in a timely fashion for public data sharing. During this process we will de-identify the patient data by using standard acceptable processes which include: removal of identifiers, translation of dates and ages to delta time values, assignment of random study identifiers and any other methods that are acceptable at that time. Out of this process will be a series of de-identified data files representing the final analytical data set. These data files will be provided in a standard format which is readable across a variety of applications and operating system platforms, such as Microsoft Excel for example. Documentation that will be provided along with the data sharing file will include but not be limited to: data dictionary, data code book, valid variable ranges (where provided), the protocol, procedure and operational manuals, and any electronic versions of any paper forms that were used in data collection. Documentation will be provided in a standard format (such as Adobe Acrobat and Rich Text Format) that is readable on a variety of platforms. Any requests for copies of the data sharing files and documentation will be provided by the Principal Investigator through an industry acceptable medium such as CD-ROM, DVD-ROM, web site download, or any other transfer medium that has wide support at that time.

9.3.11. Data Destruction

9.3.11.1. Data Destruction Guideline

Only those records retained for a period of time greater than the applicable retention schedule may be disposed of in accordance with these guidelines. PHI will be destroyed/disposed by using a method that ensures the PHI cannot be recovered or reconstructed. EPHI will be done in the same fashion.

9.3.11.2. Retention Period

The HEALTH INSURANCE PORTABILITY AND ACCOUNTABILITY ACT OF 1996 requires that data be kept for a minimum of 6 years beyond the close of the study, or in compliance with local IRBs. Therefore, all records must be maintained until that point. The schedule for destruction/disposal shall be suspended for records involved in any open investigation, audit or litigation.

9.3.11.3. Destruction of Paper Records

Paper records containing confidential information should be destroyed according to this guideline, not simply thrown out with other classes of records or with miscellaneous trash.

9.3.11.4. Destruction of Electronic Records

Deletion of the contents of digital files and emptying of the desktop "trash" or "waste basket" is the first step. It must be kept in mind however, that reconstruction and restoration of "deleted" files are quite possible in the hands of computer specialists. With regard to records stored on a "**hard drive**," it is recommended that commercially available software applications be utilized to remove all data from the storage device. When properly applied, these tools prevent the reconstruction of any data formerly stored on the hard drive. With regard to **floppy disks** and **back-up tapes**, it is recommended that these storage devices be physically destroyed.

9.3.11.5. Destruction Records

A destruction record is an inventory describing and documenting those records, in all formats, authorized for destruction, as well as the date, agent, and method of destruction. The destruction record itself shall not contain confidential information.

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Study Organization
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10. Study Organization

10.1. PARTICIPANT ORGANIZATION

10.1.1. Study Sites

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, Centers for Disease Control and Prevention (CDC), and National Institutes of Health (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 Study group;

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

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

10.1.3. Central Laboratory

The central laboratory has primary responsibility for training clinical center personnel on blood draw, processing and shipping procedures, monitoring quality of samples received, ensuring that samples are tested according to study protocol, and generating laboratory results for the study. Additional responsibilities of the Central Laboratory include:

a) Developing and distributing a laboratory manual of procedures

b) Participating in Protocol Oversight and Steering Committee meetings and conference calls

c) Providing supplies and support to clinical sites as needed

d) Preparing monthly quality control reports for clinical sites

e) Transmitting laboratory data to the CoC

f) Participating as a scientific collaborator with SEARCH investigators.

10.1.4. Federal Sponsors

SEARCH is sponsored by the CDC and supported by the National Institute of Diabetes and Digestive and Kidney Diseases (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 NIDDK of the 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.

10.1.4.1. External Scientific Advisory Committee

The External Scientific Advisory Committee (ESAC) will include experts in the fields of diabetes, pediatrics, epidemiology, biostatistics, and health services research, augmented with ad hoc members as necessary, with appointments being made by the CDC in consultation with other sponsors. Members will be completely independent of SEARCH. ESAC will review progress and conduct of the research. ESAC will advise the sponsors of any concerns and/or make recommendations regarding continuation, termination, or modification of studies. ESAC will meet annually and hold additional meetings or conference calls as required for adequate monitoring.

10.1.5. Data Ownership

The data collected as part of SEARCH will belong to 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

10.2.1. Study-wide Committees

The following study-wide committees are established for SEARCH:

10.2.1.1. Study Group

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

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

10.2.1.2. Steering Committee

The Steering Committee will consist of the PI and one other member from each site, the chair of the Project Managers Committee, two members from the CDC, one member from the NIH, the PI and one other member from the CoC, and the PI from the Central Laboratory. The Steering Committee will 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 Steering Committee. Only these individuals will participate in calls. Alternates can attend Steering Committee meetings when it is impossible for the designated members of this committee to attend.

All members of the Steering Committee are full participants in discussions and work of this committee. In matters that require a vote, each member of the committee will have one vote.

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

10.2.1.3. Coordination and Planning Committee

The Coordination and Planning Committee will consist 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.

10.2.1.4. Protocol Oversight Committee

The Protocol Oversight Committee will consist of at least one representative from each clinical center, the CoC, the CDC and the Central Laboratory. This committee will have a chair, vice chair, and voting members. The committee will be responsible for six major study areas: quality control, recruitment and retention, clinic operations, site visits, adverse events, and laboratory operations.

10.2.1.5. Publications, Presentations and Ancillary Studies Committee

The Publications, Presentations and Ancillary Studies Committee will consist of representatives from clinical centers, the CoC, the CDC and the Central Laboratory; representing a range of scientific expertise relevant to major aims of SEARCH. This committee will have a chair (non-voting member), vice-chair, and voting members. The committee will be responsible for reviewing and approving: abstracts; manuscripts; posters and oral presentation slides; and ancillary study proposals.

10.2.1.6. Project Managers Committee

The Project Managers Committee will consist of representatives across clinical centers and the CoC. The Project Managers will have a chair and vice chair and voting members. The chair and vice chair will serve one year terms. The committee will be responsible for providing input to the Protocol Oversight Committee regarding clinic operations, recruitment and retention, and various aspects of protocol oversight.

10.2.2. Face-to-Face Meetings

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

Members of the Study Group who are not members of the Steering 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 Steering Committee.

10.3. SEARCH COLLABORATORS

10.3.1. 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***
Colorado	University of Colorado Health Sciences Center Denver, CO
Hawaii	Pacific Health Research Institute Honolulu, HI
Ohio	Children's Hospital Medical Center Cincinnati, OH
Seattle/Puget Sound	Children's Hospital and Medical Center Seattle, WA
South Carolina	University of South Carolina Columbia, SC
Southern California	Kaiser Permanente Southern California Pasadena, CA

10.3.2. Coordinating Center

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

10.3.3. Federal Sponsors

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

10.3.4. Central Laboratory

Northwest Lipid Metabolism and Diabetes Research Laboratories
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

This study will involve ascertainment of newly diagnosed cases for the period 2006 - 2009 and follow-up of prevalent cases in 2001 and incident cases in 2002 - 2005 from SEARCH Phase 1. Specific detail about the data collected on SEARCH participants is provided in Section 5 - Data Collection. Detail on the sites recruiting participants for this study is provide in Section 3 - Site Descriptions.

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. 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 participant recruitment material will be prepared by the Protocol Oversight Committee, customized by sites and submitted for approval by the local IRB committees.

A certificate of confidentiality 301(d) for all sites has been obtained by the CDC for SEARCH Phase 1 and will be requested for SEARCH Phase 2, adding another level of protection for the data collected in this study.

11.3. SITE-SPECIFIC GUIDELINES

Each of the six sites and the Coordinating Center in SEARCH work with one or more local IRBs, and it is expected that each IRB will have separate requirements. Content of the materials is 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 participants 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. ESTIMATED NUMBER OF SEARCH CASES

Table 11.1 Estimated Number of SEARCH Cases

Ethnic Category	Sex/Gender		
	Females	**Males**	**Total**
Hispanic or Latino	299	351	650
Not Hispanic or Latino	2394	2348	4742
Ethnic Category: Total of all Subjects *	2693	2699	5392
Racial Categories			
American Indian/Alaska Native	79	61	140
Asian	25	48	73
Native Hawaiian or Other Pacific Islander	73	50	123
Black or African American	518	316	834
White	1988	2224	4212
Racial Categories: Total of All Subjects *	2693	2699	5392

11.6. 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.

11.7. RESEARCH MATERIALS

Elements of the research material collected for SEARCH are described in Section 5 - Data Collection. All data will be recorded both manually and electronically.

Upon confirmation of study eligibility, each research participant will be assigned a unique SEARCH identification number. Each of the six SEARCH centers will maintain names and contact information on a local basis, accessible only to the local research team. The Protected Health Information (PHI) that is transmitted to the SEARH CoC for registered cases is the minimum necessary to conduct this research. It consists of date of birth, county, zip code, date of diagnosis for diabetes, and dates of inpatient and outpatient visits. Data transmitted to the CoC qualifies as a HIPAA Limited Dataset. Each of the six centers will enter into a Limited Data Use Agreement with the

Coordinating Center in compliance with the Standards of Privacy of Individually Identifiable Health Information as outlined by HIPAA. Local access to participant identifiers will be governed by the requirements of the local IRB. Laboratory specimens will be associated with the SEARCH identification number and the date of specimen collection. Data transmitted to the laboratory qualifies is de-identified to the HIPAA standard. Laboratory personnel are not able to identify individuals based on the information sent to them.

The data elements included in the initial patient survey, the baseline in-person visit, the follow-up in-person visit, and the quality of care survey will be collected specifically for this research study.

11.8. CONSENT FORMS

The Processes of Care Committee 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 older will sign as the participant 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

11.9. ASSENT

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

11.10. PATIENT INCENTIVES

Patients will receive incentives commensurate with level of involvement and effort.

11.11. 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 Protocol Oversight Committee.

11.12. 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 participant, 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 Principal 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.

11.13. PARTICIPANT RISKS AND BENEFITS

For all centers, potentially-eligible participants will be identified by a network of reporting providers; and for California and Hawaii, additional participants will be identified via health plan databases. Procedures for participant identification will be

conducted in a manner that is HIPAA-compliant and according to the requirements of the local IRB.

For case identification and registration will be done based on procedures in ways that minimize the risk of loss of privacy and any consequence.

Potentially-eligible participants will be mailed an introductory letter that gives a brief description of the research study. For participants who are less than 18 years of age, the introductory letter will be mailed to the participant's parent or guardian. Letters sent to participants who are 18 years of age or older will be addressed to the participant. After mailing this introductory letter, a designated member of the local research team will call the parent/participant to complete the initial patient survey. Consent requirements for completion of this survey will be governed by the local IRB.

Participants who are eligible to participate in the in-person visit will be given an explanation of the study and will be asked if they would like to participate. If interested, the participant will be scheduled for an appointment and a team member will explain the pre-appointment instructions to the participant or parent. When the participant arrives for the in-person visit, a research team member will review the study requirements with the participant and/or parent and address any questions or concerns they might have. Since the in-person visit includes optional serum/plasma and DNA blood samples for storage, the consent form includes two special sections which explain the purpose of these extra samples for serum/plasma and DNA storage. Participants or their parent must indicate in writing whether or not they are giving their consent for these additional samples. They may choose to have both samples stored, only one sample, or no stored samples. If the participant is less than 18 years of age, the parent or guardian must give written informed consent prior to the initiation of any study procedures or data collection, according to the requirements of the local IRB. Written assent of participants who are less than 18 years of age is also governed by the requirements of the local IRB. If the participant is 18 years of age or older, the participant must give written informed consent. Copies of completed consent forms will be maintained in the participant's research record, according to local protocol.

11.13.1. Protection Against Risk

To minimize the possibility of risks associated with the blood draw, experienced medical staff will obtain the blood samples. A local numbing medicine may be placed on the skin before the blood is drawn to decrease any pain. Participants who have a history of fainting or who develop symptoms of light-headedness will be placed in the supine position.

Study personnel will be trained to identify the signs and symptoms of a blood glucose level that is low or high. They will also be trained to check the blood glucose level, using a glucometer. If a low blood glucose occurs (< 60 mg/dl.), study personnel will be

trained to administer 15 grams of an oral carbohydrate, and to repeat as needed every 10 minutes until the blood glucose level is $\geq$ 60 mg/dl. If the blood glucose level is above 300 mg./dl., study personnel will be trained to check urinary ketones. After the blood specimens have been obtained and the blood glucose level has been measured, participants will be instructed to take their usual dose of insulin or other diabetes medication as prescribed; and the participant will then be given breakfast. In cases of low or high glucose levels (with or without the presence of urinary ketones), additional medical interventions may sometimes be needed. Local policies dictate these procedures, which may include a one-time adjustment in the dose of insulin taken and/or the administration of glucose gel, glucagon, or intravenous glucose. If the participant is eligible for a stimulated C-peptide test, the blood glucose level will be checked by study personnel prior to the initiation of this test. If the blood glucose level is < 60 mg./dl. or > 300 mg./dl., the test will not be done and the participant will be asked to re-schedule this test for another day.

The CES-D questionnaire is administered to identify participant who may be at increased risk for clinical depression. If the participant has a high score ($\geq$ 22 for males or $\geq$ 24 for females), the participant or parent (if participant is < 18 years of age) will be informed of the test result. If the participant is not already receiving mental health treatment or counseling, study personnel may recommend follow-up by a mental health professional. Specific referral procedures are dictated by a written local protocol at each center.

If any of the test results identify complications of diabetes or an increased risk for developing complications, the results may cause some anxiety. Study personnel may recommend follow-up by the participant's diabetes provider or a mental health professional. Specific referral procedures will be dictated by local protocol.

Study personnel will be trained to compare blood pressure measurements to a table of blood pressure measurements at the 95th percentile, based on the participant's gender, age, and height percentile. If the participant's blood pressure (systolic or diastolic) is higher than the 95th percentile, the participant or parent (if participant is < 18 years of age) will be informed that the blood pressure is higher than expected. If the participant is not already being monitored or treated for high blood pressure, study personnel will recommend that they follow-up with their healthcare provider. Participants who have a blood pressure > 180/110 will be referred to their health care provider or the Emergency room for immediate attention.

Whenever a participant has a triglyceride level of > 1000, the Central Laboratory will notify the appropriate center Principal Investigator or his/her designee within 24 hours. Local personnel are then responsible for referring the participant to their health care provider for appropriate follow-up.

Storage of Serum/Plasma/Urine: Since the study visit includes optional participation in the storage of serum/plasma, the consent form includes a special section which explains the purpose of the stored samples. Participants or their parent must indicate in writing whether or not they are giving their consent for the additional sample. They may choose to have serum/plasma stored or not stored. If the participant is less than 18 years of age, the parent or guardian must give informed consent prior to the initiation of any study procedures or data collection, according to the requirements of the local IRB. Assent of participants who are less than 18 years of age is also governed by the requirements of the local IRB. If the participant is 18 years of age or older, the participant must give informed consent. Copies of completed consent forms will be maintained in the participant's research record, according to local protocol. No tests will be performed on the serum/plasma obtained and stored in this study without first requesting and receiving approval of the IRB. If the IRB decides that consent of each individual is required prior to performing an additional test on the stored sample, the investigators will seek and obtain consent prior to performing the test. It is the responsibility of the Steering Committee to determine if clinically relevant results should be reported and determine the appropriateness of reporting the results. Clinically relevant results may be reported to the participant.

Storage of DNA: Since the study visit includes optional participation in the storage of DNA, the consent form includes a special section which explains the purpose of the storage of DNA. Participants or their parent must indicate in writing whether or not they are giving their consent for the additional sample. They may choose to have DNA stored or not stored. If the participant is less than 18 years of age, the parent or guardian must give informed consent prior to the initiation of any study procedures or data collection, according to the requirements of the local IRB. Assent of participants who are less than 18 years of age is also governed by the requirements of the local IRB. If the participant is 18 years of age or older, the participant must give informed consent. Copies of completed consent forms will be maintained in the participant's research record, according to local protocol. No tests will be performed on the DNA obtained and stored in this study without first requesting and receiving approval of the IRB. If the IRB decides that consent of each individual is required prior to performing an additional test on the stored sample, the investigators will seek and obtain consent prior to performing the test. Clinically relevant results may be reported to the participant.

Data will be recorded, both manually and electronically. The data management system for this study will utilize the combination of a local tracking application and a web browser-based interface. The local tracking application is a Microsoft Access database. It will be used by local study personnel to manage demographic data, contact information, consent, appointments, visits, and communications with the participant. This database will be password-protected and accessible to local study personnel only.

The web browser-based interface will be used for recording the majority of the data collected as part of this study. Usernames and passwords will be required to access the SEARCH web site. The Coordinating Center will control web access rights by assigning individual usernames and passwords to each staff member, according to the level of access required. The web-based data entry system will protect confidentiality and data security by utilizing 128-bit encryption and Secure Socket Layer (SSL).

All Protected Health Information (PHI) will be used or disclosed in compliance with the Health Insurance Portability and Accountability Act (HIPAA). A limited amount of Personal Health Information (PHI) will be shared with the SEARCH Coordinating Center. This data includes date of birth, county, zip code, date of diagnosis for diabetes, and dates of inpatient and outpatient visits. Each of the six centers will enter into agreements with the Coordinating Center in compliance with the Standards of Privacy as specified by HIPAA contingent on the interpretations and processes defined by the local IRBs/Privacy Boards. Local access to participant identifiers will be governed by the requirements of the local IRB.

As an added protection for the privacy of study participants, we have applied for a Certificate of Confidentiality for SEARCH Phase 2.

11.13.2. Potential Benefits of the Proposed Research to the Participant and Others

There are no direct benefits to study participants. In some cases, however, test results may help to more clearly define the type of diabetes an individual may have. Test results may also identify the presence or increased risk for some of the complications associated with diabetes. If the participant gives their consent, test results will be shared with their healthcare provider. In some cases, based on SEARCH test results, the healthcare provider may choose to make changes to the treatment plan.

Participation in this study may also result in potential benefits to society. This is a large, multi-center study that will be well-represented by young people from a variety of racial/ethnic backgrounds. The information obtained in this study will help clinicians to better understand the prevalence and incidence of childhood diabetes, the characteristics of various types of diabetes, the frequency of the occurrence of complications associated with diabetes, and the impact diabetes has on the lives of these young people. This information will also be important in the planning of the distribution of medical and financial resources for the care of young people with diabetes in the future.

11.13.3. Importance of the Knowledge To Be Gained

Diabetes is the third most common chronic disease of childhood and adolescence. In the past, childhood diabetes was thought to consist almost exclusively of Type 1 diabetes. Over the past two decades, however, an increasing number of cases of Type 2 diabetes

have been reported within this population. Overall, the total number of diabetes cases affecting people less than 20 years of age seems to be increasing over time.

This is a large, multi-center study that will be well-represented by young people from a variety of racial/ethnic backgrounds. The information obtained in this study will help clinicians to better understand the prevalence and incidence of childhood diabetes, the characteristics of various types of diabetes, the frequency of the occurrence of complications associated with diabetes, the impact diabetes has on the lives of these young people, and the factors that relate to high quality diabetes care for children/youth. This information will also be important in the planning of the distribution of medical and financial resources for the care of young people with diabetes in the future.

11.13.4. Data and Safety Monitoring Plan

Even though this study is not a clinical trial, an internal Processes of Care (POC) Committee will be established to: 1) oversee personnel training and certification procedures to assure consistency of measurements among all six SEARCH centers; 2) review the quality of the data collected, as well as the laboratory results; and 3) review any adverse events that might occur. In addition, an external monitor will be established to review the activities of the studies, based on reports from the POC Committee. The external monitor will provide interim and annual safety reports to the Director of the CoC and the POC Committee. The interim reports will be quarterly and will clarify issues of interest for the monitor. They will be interactive in nature. Issues raised by the monitor will be queried by the POC Committee to the relevant clinics; and clinic responses will clarify handling of issues, with copies of event reports signed by the Principal Investigator sent to the POC Committee, the CoC, and to the monitor.

The annual report will summarize the findings of the monitor over the year period, will be on academic letterhead, and will be dated and signed by the monitor. It will include comments about event rates, types of events and relatedness to the study, and other issues which the monitor thinks transmit the safety profile of the study to the Principal Investigators, and to local IRB's.

11.14. REPOSITORY

Testing related to diabetes is limited to basic testing as mentioned in both Section 5 (Data Collection) and Section 6 (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 participants 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.

11.14.1. 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.

11.14.2. Consent for Sample Storage

The consent process will allow study participants to consent or refuse to have samples stored in the repository laboratory. Consent will be structured in such a way that participants 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.

11.14.3. Sample Maintenance

11.14.3.1. 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.

11.14.3.2. Sample Destruction

Individual participants (or their parents if participants 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).

11.14.4. Use of Repository Samples

Samples will be made available (with Steering 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.

11.15. 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 Steering Committee. Involvement in the ancillary studies will vary by site. Each ancillary study will require separate IRB approval, and a separate source of funding.

11.16. 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.

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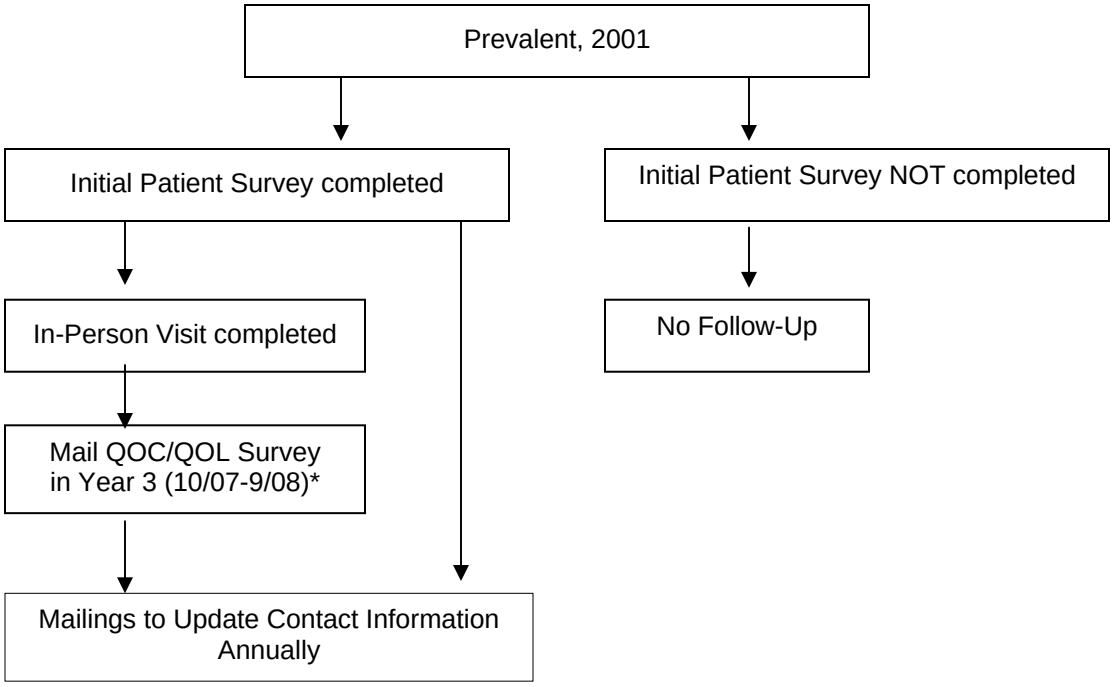
Appendix I - Data Collection for 3 Study Cohorts

Figure 1. Data Collection for Prevalent, 2001



* 10% of Non-Hispanic White youth and 100% of minority youth. (03/07)

Figure 2. Data Collection for Incident 2002-2005

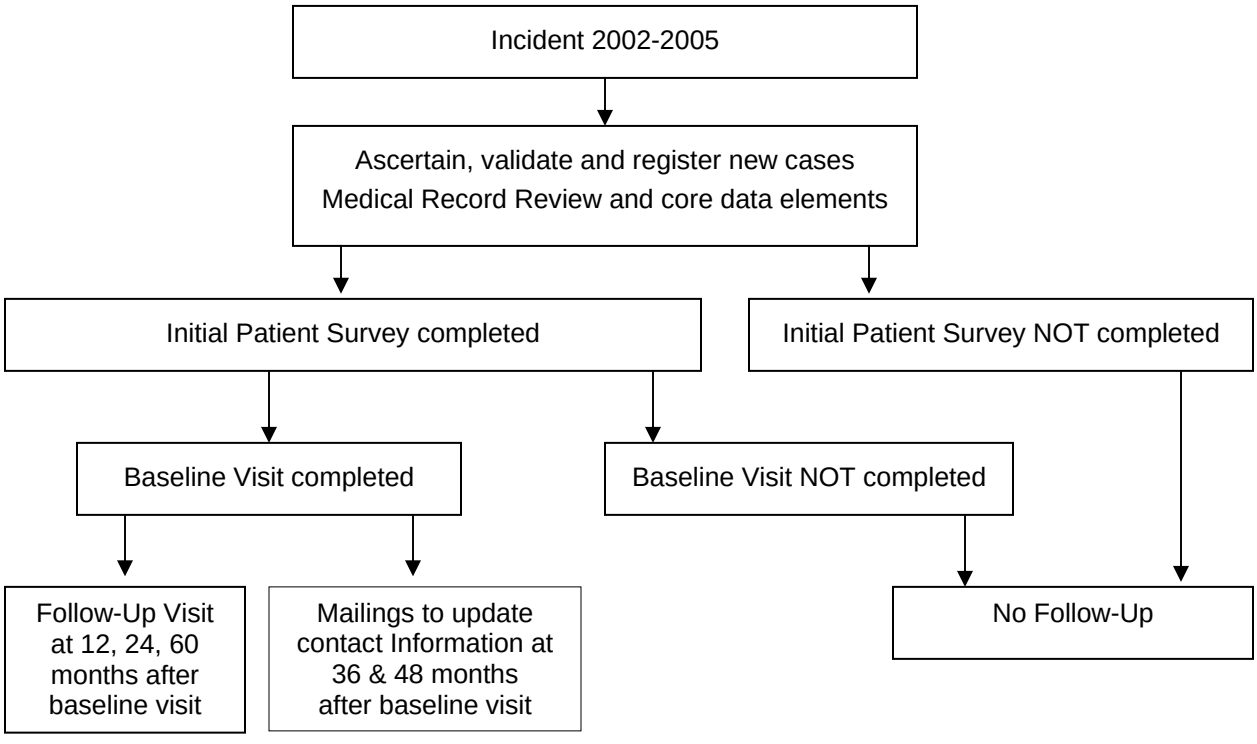
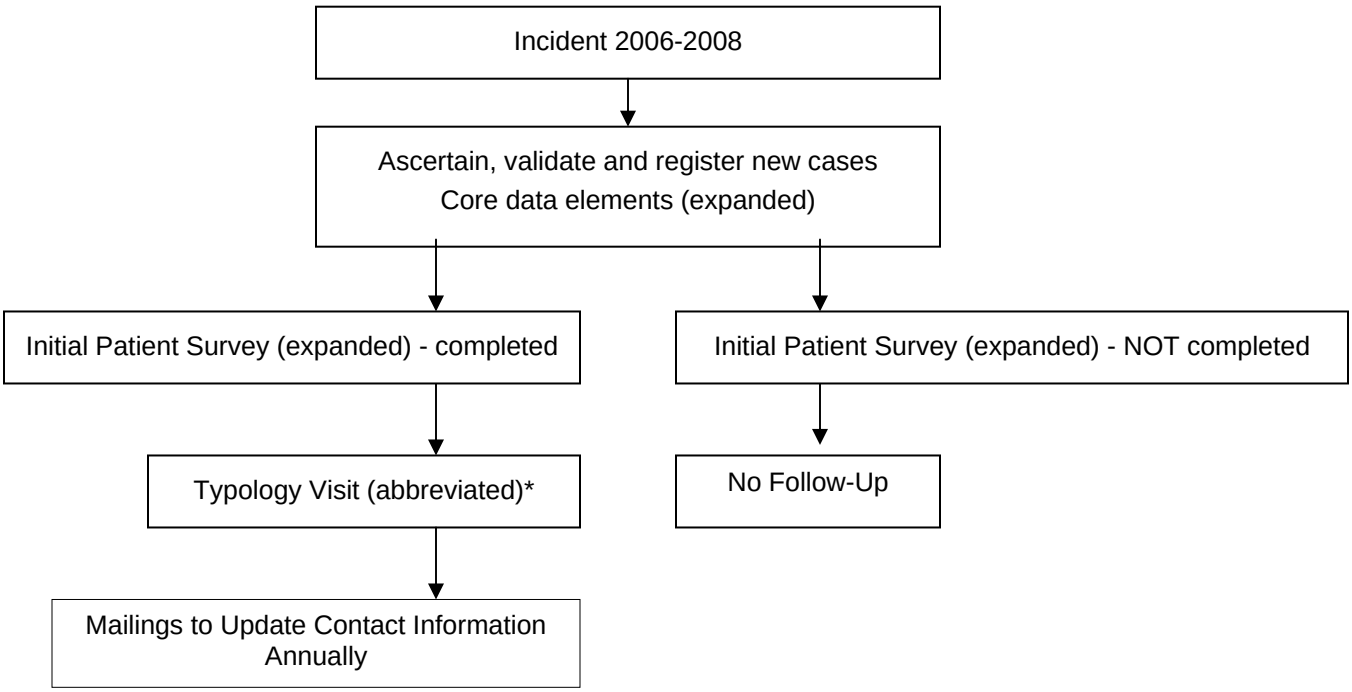


Figure 3. Data Collection for Incident 2006-2008



* Time based sampling. Incident cases in 2006 and 2008 will be invited to Typology visit; 2007 incident cases will not be invited. (03/07)

Figure 4. Data Collection for Incident 2009