SEARCH for Diabetes in Youth

Phase 3 Protocol

December 2010

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SEARCH Phase 3 Protocol - Section 1
Executive Summary

Background

Diabetes mellitus (DM) is one of the most common chronic diseases in children and adolescents. Although in some racial/ethnic groups (e.g., American Indians) the majority of cases in children may be type 2 diabetes (T2D), in most populations, type 1 diabetes (T1D) is the predominant form of the disease. T1D results primarily from the autoimmune destruction of the insulin producing β-cells of the pancreas. T2D, once rarely observed in youth, is becoming more common, especially among youth of racial/ethnic minority groups in the US. Although the pathophysiology of T2D in the pediatric population has not been well-studied, emerging evidence [1-3] suggests that it is similar to that seen in adults, in whom insulin resistance and progressive beta cell failure results in T2D [4].

Recent estimates of the prevalence and incidence of diabetes by type in the US population aged <20 years have been provided by the population-based, multi-center SEARCH for Diabetes in Youth study. SEARCH estimated that in 2002-2003 among children <10 years of age, the incidence of T1D was 23/100,000/year non-Hispanic whites. 13/100,000/year in African Americans, 12/100,000/year in Hispanics, 5.2/100,000/year in American Indians, and 6.9/100,000/year Asian/Pacific Islanders [5]. In older youth, there was a similar pattern: the incidence of T1D (per 100,000 person-years) among youth aged 10-14 and 15 to 19 years, was highest among non-Hispanic white children (32.9 and 15.1, respectively), followed by African American (19.2 and 11.1, respectively) and Hispanic youth (17.6 and 12.1, respectively), and lowest among American Indian (7.1 and 4.8, respectively) and Asian/Pacific Islander youth (8.3 and 6.8, respectively). In all racial/ethnic groups in the age group 0-9 years, T1D represented the majority of cases. However, in the 10-19 year old group, the proportion of cases due to T1D ranged from 85% in non-Hispanic whites to 14% in American Indians [5].

Worldwide, an annual increase of 2.8% in T1D incidence has been reported [6], especially among young children aged below 5 years (4.0% per year). In Europe, recent findings from the EURODIAB study, a population-based T1D registry of children diagnosed before age 15 years, showed an annual increase of 3.9% during 1989-2003, and that the increase was highest in the age group 0-4 years (5.4%) [7]. The underlying factors of this increase have not yet been identified. An internationally collaborative observational study aimed at identifying potential environmental factors of T1D is now underway.

In parallel to the increase in T1D, T2D is becoming more common in adolescents. This has been linked to the increase in obesity among youth observed in the last two decades in the U.S. [8] and around the world. Very limited data are available on the temporal trends in the incidence of T2D. Data from SEARCH estimates that T2D represented 86% of diabetes cases in American

Indians, 70% in Asian/Pacific Islanders, 58% in African Americans and 46% of cases in Hispanic youth.

In order to study trends in both T1D and T2D incidence, it will require long-term continuous monitoring of these two major forms of diabetes in diverse populations of youth less than 20 years of age. In addition to providing the population burden of the disease over time, surveillance is also pivotal for identifying potential risk factors, evaluating diabetes prevention strategies, and prioritizing the allocation of limited health care resources.

In children and adolescents with diabetes, acute complications are more common than chronic complications and, at this age, they carry a greater risk of morbidity and mortality [9, 10]. The most common acute DM complications observed in youth are diabetic ketoacidosis (DKA) and hypoglycemia. DKA is a serious, costly, and potentially preventable complication caused by insulin deficiency. If left untreated, it can lead to coma and death. DKA may be the clinical presentation of both T1D and T2D [11] or can occur in individuals with an established diabetes diagnosis. Recent findings from the SEARCH study demonstrated that this complication is present at diabetes onset in 1 out of 4 youth and 93% of these are hospitalized [11].

Data on the occurrence of diabetes acute complications are crucial to evaluate the effectiveness of diabetes awareness campaigns and education programs, disease management and to identify sub-groups of the youth population at increased risk for these serious complications.

Large clinical trials have indicated that glycemic, blood pressure, and lipid control can prevent or delay the onset of diabetes-related complications. Very little is known about the natural history of youth-onset T2D. Data from the Pima Indian longitudinal study indicated that among individuals with early-onset T2D (before age 20), by age 30, 45% developed retinopathy and 57% nephropathy, and they had a higher risk of developing end-stage renal disease and of dying by middle age [12, 13]. Furthermore, the life expectancy of individuals diagnosed with diabetes at age 10 years is reduced, on average, by 19 years [14]. These findings warrants further research to identify the factors that confer the elevated risk of these complications associated with early-onset T2D.

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 Phases 1 and 2

SEARCH Phases 1 and 2 involved six centers, coordinated in Cincinnati, Ohio; Denver, Colorado; Seattle, Washington; Columbia, South Carolina (and Chapel Hill, North Carolina); Honolulu, Hawaii; and Pasadena, California, that have identified prevalent and incident cases of diabetes (excluding gestational diabetes) in youth less than 20 years of age in defined populations for specific calendar years. Four centers (Ohio, Colorado, Washington, South Carolina) were geographically based - newly diagnosed diabetes cases were identified from a geographically defined population. Two centers (Hawaii and California) were membership-based - diabetes cases were identified among members of participating health plans.

The study identified diabetes cases that were prevalent in 2001 and 2009 and cases incident from January 1, 2002 through September 29, 2010. At all six SEARCH centers, the primary approach to identification of incident cases was a rapid reporting network of clinics and health care providers, including in some instances diabetes educators and school nurses.

In SEARCH Phase 1 and 2, approximately 6,400 prevalent 2001 cases were identified under the SEARCH Phase 1 protocol and 6600 prevalent 2009 cases were identified under the SEARCH Phase 2 protocol. For 2002 - 2010, approximately 11,000 incident cases were identified. Data collection in SEARCH Phases 1 and 2 included, at baseline, both for prevalent 2001 and incident 2002 - 2010 cases, questionnaire surveys and an invitation to an in-person visit (excluding incident 2007 and 2009 cases). For 2006 and 2008 cases, the in-person visit was an abbreviated "Typology" visit. For incident cases and a subset of prevalent 2001 cases, data collection also included medical record review. Incident 2002 - 2005 cases were asked to return for a follow-up visit at 12, 24 and 60 months after their baseline visit.

Table 1-1. Participation in SEARCH Phases 1 and 2 By Cohort

	2001 Prevalent	2002 - 2005 Incident	2006 - 2009 Incident	2009 Prevalent	2010 Incident
Case Registration	x	x	x	x	x
Initial Participant Survey (IPS)	x	x	x	x (for cases not incident in other years)	x
In-Person Visit (IPS)	x	x			x (through September 2010)
Typology Visit			x (2006 and 2008 only)		

Extended Typology	x	x			
12, 24, 60 Month Follow-Up		x			
Annual follow-up for contact information	x	x	x	x	x

SEARCH Phase 3 Objectives

Five of the original six SEARCH 1 and 2 centers were funded to participate in SEARCH3: (Carolinas, Ohio, Colorado, California, and Washington). The objectives of SEARCH Phase 3 include a registry component and a cohort component. Each component will be performed at all five clinical centers. In SEARCH Phase 3, many of the measurements which were collected during SEARCH Phases 1 and 2 will continue to be collected; additionally, there will be unique measurements collected for each component of SEARCH Phase 3.

Registry Study

The SEARCH for Diabetes in Youth Registry Study will continue to ascertain newly diagnosed incident diabetes cases in youth age < 20 years across five geographically dispersed Study Centers in order to accomplish the Specific Aims shown below. The study will continue to identify incident cases from September 30, 2010 through September 29, 2015, and will periodically re-ascertain cases from earlier years.

Aim 1: To continue to ascertain newly diagnosed (2010 - 2014) incident diabetes cases in youth age < 20 years in order to assess temporal trends in diabetes incidence and temporal trends in presentation of diabetes for the period 2002-2014, by age, sex, race/ethnicity, and diabetes type.

Specific characteristics to be examined are: age at onset of diabetes, markers of disease severity (diabetic ketoacidosis, residual insulin secretion, HbA_{1c}), immunogenetic markers (diabetes autoantibodies, HLA risk genotypes), markers of insulin sensitivity (insulin sensitivity score, waist circumference, body mass index), cardiovascular risk factors (lipid profile, blood pressure, microalbuminuria).

Aim 2: To provide consultation and support to inform the development of low-cost sustainable public health surveillance systems of childhood diabetes in the U.S., with a focus on challenges in ascertainment of cases with T2D and cases among older youth (ages 15 years or older) with any form of non-gestational diabetes.

Aim 3: Assess total and cause-specific mortality among 2002-2008 incident cases for the period from the date of diabetes diagnosis through December 31, 2010.

Cohort Study

An in-person research visit with SEARCH participants incident in 2002 or later, with a duration of diabetes > 5 years, and with data from a baseline study visit (expected n=3,699). SEARCH has a well-established and ongoing infrastructure and is uniquely positioned to successfully address the following Aims:

Aim 1: Assess the prevalence and incidence of, and risk factors for chronic microvascular (retinopathy, nephropathy, and autonomic neuropathy) and selected markers of macrovascular complications (hypertension, arterial stiffness) of diabetes.

Aim 2: Assess the incidence of, and risk factors for, serious acute complications of diabetes including severe hypoglycemia and diabetic ketoacidosis (DKA).

Aim 3: Determine the degree to which barriers to care, quality of care, and the process of transition from pediatric to adult care impact disease factors, including dimensions of diabetes type (e.g., diabetes autoimmunity, insulin sensitivity), and diabetes-related outcomes (acute and chronic complications, quality of life, diabetes-related mortality).

Aim 4: Maintain and supplement the SEARCH repository for biological specimens, and promote access to SEARCH for conduct of scientifically and logistically appropriate ancillary studies.

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SEARCH Phase 3 Protocol - Section 2
Center Descriptions
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2. Description of Study Centers and Populations

SEARCH Phase 3 has five centers, located in Ohio, Colorado, Washington, South Carolina, 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. One SEARCH center (California) is membership-based - that is, diabetes cases will be identified among members of the participating health plans.

Each of the five centers will be participating in both the Registry component and the Cohort component of SEARCH Phase 3. The Registry component will include incident cases in defined populations areas from 2010 - 2014. The Cohort component will include follow-up visits with incident cases with at least five years duration of diabetes from SEARCH Phases 1 and 2 belonging to the incident 2002-2006 and 2008 cohorts.

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 5.

2.1. OHIO - 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

2.2. COLORADO - UNIVERSITY OF COLORADO DENVER CENTER

The population under surveillance at the Colorado SEARCH center consists of all youth age <20 years a) residing in the state of Colorado (64 counties) in 2010-2014, or b) members of the Navajo Indian tribe in Arizona, Utah and New Mexico residing on the Navajo Nation reservation. The estimated total population under surveillance at the Colorado SEARCH center is ~1.4 million youth age < 20 years.

The study is conducted by the University of Colorado Denver, Colorado School of Public Health Department of Epidemiology, through close collaboration with two major pediatric endocrinology units serving both metropolitan and remote areas: the Barbara Davis Center for Childhood Diabetes 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 10 years of the study, this center has established close and trusting partnerships with the Navajo Indian tribe. The study is conducted in the Navajo Nation through a partnership with the Navajo Area Indian Health Promotion and the Special Diabetes Prevention Program, under a Memorandum of Understanding with the Navajo Nation.

2.3. WASHINGTON - SEATTLE CHILDREN'S RESEARCH INSTITUTE

The Seattle center will conduct study activities with participants from the 5 Puget Sound counties (King, Kitsap, Pierce, Thurston, and Snohomish) surrounding Seattle and Tacoma. This area encompasses two-thirds of the Washington population and is the most ethnically diverse region of the state. Based on previous case ascertainment patterns, it is projected that an average of 244 incident cases per year will be identified out of a total 0-19 year old population of approximately 1 million. The Seattle center will use the U.S. census as the source of denominator estimates.

Seattle Children's Hospital is a teaching institution associated with the University of Washington, with direct access to a large population of youth with diabetes and their families. Investigators will work with families and providers to coordinate visits in conjunction with regular clinical appointments, at locations throughout the region, in order to ensure excellent experiences for families and high response rates.

The Seattle SEARCH investigators have established a rapid reporting network of over a dozen local health centers, institutions, and providers that identify eligible cases and provide data to characterize diabetes type and clinical characteristics. This includes all of the major pediatric endocrinology groups (Seattle Children's Pediatric Endocrinology, Woodinville

Pediatrics, Group Health Cooperative, Mary Bridge Health Center, and Madigan Army Medical Center), hospitals (Seattle Children's, Mary Bridge, Virginia Mason Medical Center, Providence St. Peter's, Swedish Medical Center, Group Health Cooperative, Harborview Medical Center, Valley Medical Center), adult endocrinologists and diabetes programs (University of Washington Diabetes Care Center and Joslin Diabetes Center), Certified Diabetes Educators, community health clinics (Community Health Centers of King County, SeaMar Community Health Centers, and Puget Sound Neighborhood Health Centers), hospital-based primary care networks and primary care clinics (University of Washington Physicians and Virginia Mason), college health centers, diabetes support groups, community events, family practitioners in rural areas, and practices serving ethnically diverse populations. Collaborations have also been established with the Washington State Department of Health Diabetes Prevention and Control Program, which works in partnership with major local, state and national organizations towards improving the health of people with diabetes and those at risk for developing diabetes.

2.4. CAROLINAS CENTER

The Carolinas center covers the state of South Carolina with administration and oversight provided through the University of North Carolina at Chapel Hill. To assist in statewide case ascertainment and recruitment, the Medical University of South Carolina (MUSC) in Charleston, SC, the Greenville Hospital System (GHS) in Greenville, SC, and the University of South Carolina (USC) in Columbia, 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). Thirty-seven percent (37%) 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).

2.5. CALIFORNIA - KAISER PERMANENTE SOUTHERN CALIFORNIA

Kaiser Permanente is a group model managed health care organization that delivered comprehensive medical care on a prepaid basis to approximately 3.3 million residents of southern California in 2009. It is a working partnership of two organizations: the not-for-profit Kaiser Foundation Health Plan and Hospitals and the Permanente Medical Groups. Members receive their insurance coverage through employers, MediCal and other low-income programs, and private payment. The Department of Research and Evaluation, part of the Southern California Permanente Medical Group (SCPMG), is the research arm of Kaiser Permanente Southern California (KPSC). This Department, located in Pasadena California, 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 San Diego County, will be identified and invited to participate in SEARCH. Youth will be identified based on monthly case reports from the Pediatric Endocrinologists (primary source) and through linking computer-stored clinical information on prescriptions, laboratory tests, inpatient, and outpatient encounters (secondary source) and validating these potential cases to confirm that they have a physicians' diagnosis of diabetes. Further, eligibility will be determined for all valid cases based on their health plan membership and geographic location within the region. This two-pronged approach allows for the identification of youth who are not seen or not reported by Pediatric Endocrinologists.

The California center will use its administrative membership database as the source of denominator information. Counts of the number of members by sex and one-year age category will determine the number persons in the denominator each year. All membership files are geocoded annually to account for new members, disenrollment in the health plan, and address changes for continuously enrolled members. Using these geocoded files, estimates of the number of children in each racial/ethnic group will be made based on census block-level geocoding of address information to the 2000 or 2010 decennial U.S. census which are updated annually based on changes in geographic boundaries as well as demographic changes within each census block.

In 2009, approximately 798,499 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, 48% of were Hispanic, 31% non-Hispanic White, 10% of Asian/Pacific Islander, 8% African American, and 3% other race or multiple race. In addition to the diversity in race/ethnicity, there is also significant diversity in the income and education of members of the KPSC health plan, which is also representative of the region.

SEARCH Phase 3 Protocol - Section 3
Study Organization
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3. Study Organization

3.1. PARTICIPANT ORGANIZATION

3.1.1. *Study Centers*

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

a) Collaborating in design and monitoring of the study, including regular attendance at Steering Committee meetings and participation in study-wide committees;

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; and,

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

3.1.2. *Coordinating Center*

The Coordinating Center (CoC) 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 data collection forms and procedures, and assuming responsibility for the translation, reproduction and distribution of forms, hardware, and software associated with data entry;

d) Training data coordinators and other clinical center research support 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) Providing support for committee meetings and conference calls; and,

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

3.1.3. *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 centers as needed;

d) Preparing monthly quality control reports for clinical centers;

e) Transmitting laboratory data to the CoC; and,

f) Participating as a scientific collaborator with SEARCH investigators.

3.1.4. *Federal Sponsors*

SEARCH is sponsored by the CDC Division of Diabetes Translation (DDT) and supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health. The SEARCH study centers are funded by a cooperative agreement, and the Coordinating Center is funded through a contract. The CDC Project Office is responsible for the funding, cooperative agreement administration, monitoring, and overall scientific integrity of the study. 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 communicating results relating to SEARCH.

The CDC reserves the right to prematurely terminate or curtail the study (or an individual award) in the event of human subject ethical issues that cannot be resolved.

3.1.5. *External Scientific Evaluation Committee (ESEC)*

The External Scientific Evaluation Committee (ESEC) includes 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 are completely independent of the SEARCH study centers and affiliated investigators. The ESEC reviews progress and conduct of the research. ESEC will advise the sponsors of any concerns and/or make recommendations regarding continuation, termination, or modification of studies. ESEC meets annually and hold additional meetings or conference calls as required for adequate monitoring.

3.1.6. *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 center will be the responsible custodian of the data. All personally identifiable data will reside at the respective clinical centers and will not be transmitted to the Coordinating Center. Data collected by the University of Colorado Denver on Navajo Nation participants belong to the Navajo Nation, as stipulated in the Memorandum of Understanding. 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. Additionally at the conclusion of the SEARCH study, a de-identified data set is required to be provided to the CDC and archived in a repository.

3.2. COMMITTEE STRUCTURE

3.2.1. *Study-wide Committees*

The following study-wide committees are established for SEARCH:

3.2.1.1. Study Group

The Study Group consists of everyone actively participating in the SEARCH study. 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 monthly 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.

3.2.1.2. Steering Committee

The Steering Committee will accomplish the scientific work of SEARCH. The Steering Committee will consist of the PI and one other member from each clinical center, the chairs of main study-wide committees (see below), two members from the CDC, one member from the NIDDK, the Co-PIs 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 centers 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 study center will have one vote, including Clinical Centers, Coordinating Center, Central Laboratory, CDC and NIDDK.

The Steering Committee makes final decisions on protocol changes, gives final approval prior to submission for all manuscripts, and directs the work of standing committees and Task Groups.

3.2.1.3. Executive Committee

The Executive Committee will consist of the study co-chairs, the CDC and NIDDK Project Officer, the CoC Co-PIs, and one of the P&P co-chairs. The chairs of the Ancillary Studies, Registry Oversight and Outcomes Committees will be asked to meet with the Executive Committee as needed. 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 administrative problems as needed.

3.2.1.4. Protocol Oversight Committee

The Protocol Oversight Committee (POC) will consist of representatives across the clinical centers, the CoC and the CDC. The POC will have co-chairs and voting members. Because of the nature of the committee's charge, the chair of POC will be the Director of the CoC. The committee will be responsible for reviewing aspects of the study protocol, including data quality control, adverse events, and recruitment and retention. The POC will also make recommendations to the Steering Committee on modifications to the study MOP and Protocol. The committee will report to the Study Group on a regular basis.

3.2.1.5. Publications and Presentations Committee

The Publications and Presentations (P & P) 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. The P & P committee will not necessarily include representatives from all centers. The P & P committee will consist of SEARCH investigators with expertise in surveillance, epidemiologic methods, biostatistics, complications, risk factors for complications, health services research. This P & P committee will have co-chairs and voting members; and one of the co-chairs will be a member of the Executive Committee. The committee will be responsible for reviewing and approving: abstracts; manuscripts; posters and oral presentations from SEARCH and its ancillary studies. The P & P committee is responsible for monitoring progress on manuscripts and presentations based on data from the main SEARCH study.

3.2.1.6. Ancillary Studies Committee

The 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 co-chairs and voting members. The Ancillary Studies Committee will have the responsibility of approving ancillary study proposals from SEARCH and non-SEARCH investigators.

3.2.1.7. Registry Oversight Committee

The Registry Oversight Committee (ROC) will consist of up to 10 members, not necessarily from each clinical center, with expertise and interest in epidemiologic and surveillance methods, study logistics, and biostatistics. This committee will have co-chairs, and voting members. Nominations will be made to the study co-chairs and the executive committee will determine the final membership. The ROC will provide oversight of issues concerning denominator estimation, including by race/ethnicity, completeness of case ascertainment, periodic case re-ascertainment, trends in incidence rates and prevalence, mortality surveillance and other areas as assigned by the executive committee.

3.2.1.8. Outcomes Committee

The Outcomes 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. The Outcomes Committee will focus on reviewing results of outcome measurements (retinopathy, neuropathy, arterial stiffness, nephropathy), developing and monitoring protocols, organizing feedback to participants. The committee will have co-chairs and voting members, with particular emphasis on clinicians, project managers and investigators and staff with relevant expertise.

3.2.1.9. Recruitment and Retention Committee

The Recruitment and Retention (R & R) Committee will consist of representatives from clinical centers and the CoC. The R & R committee will have a chair who will serve one year terms. The Recruitment and Retention Committee will be responsible for developing strategies for enhancing the recruitment and retention of SEARCH participants. The committee will meet monthly via conference call, and will provide feedback to the Study Group on a regular basis.

3.2.1.10. 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 voting members.

The 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. The committee will report to the Study Group on a regular basis.

3.2.2. *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.

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, usually in conjunction with Steering Committee meetings. Meetings independent of the Steering Committee meeting will require prior approval by the Steering Committee.

3.3. SEARCH COLLABORATORS

3.3.1. *Clinical Centers*

SEARCH Phase 3 has five centers, located in Ohio, Colorado, Washington, South Carolina, and California.

Four SEARCH centers (Ohio, Colorado, Washington, South Carolina) are geographically based - that is, diabetes cases will be identified from a geographically defined population of children. One SEARCH center (California) is membership-based - that is, diabetes cases will be identified among members of the health plan.

Location	***Center***
Colorado *Navajo Nation*	University of Colorado Denver Denver, CO
Ohio	Children's Hospital Medical Center Cincinnati, OH
Washington	Children's Hospital and Medical Center Seattle, WA
South Carolina	University of North Carolina at Chapel Hill, Chapel Hill, NC; and University of South Carolina, Columbia, SC
California	Kaiser Permanente Southern California Pasadena, CA

3.3.2. *Coordinating Center*

Wake Forest University School of Medicine
Winston-Salem, NC

3.3.3. *Federal Sponsors*

Centers for Disease Control and Prevention, Division of Diabetes Translation,
Atlanta, GA
National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases,
Bethesda, MD

3.3.4. *Central Laboratory*

Northwest Lipid Metabolism and Diabetes Research Laboratories
University of Washington
Seattle, WA

SEARCH Phase 3 Protocol - Section 4A
Registry Study
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4. Study Objectives & Background and Significance

4.1. SEARCH REGISTRY STUDY OBJECTIVES

4.1.1. *Goals*

SEARCH for Diabetes in Youth originally began in 2000 as a multi-center, epidemiological study, conducted in six geographically dispersed Study Centers that encompassed the racial and ethnic diversity of the U.S. The study was designed to estimate the prevalence and incidence of diabetes among youth age < 20 years, according to diabetes type, age, sex, and race/ethnicity, and to characterize selected acute and chronic complications of diabetes and their risk factors, as well as the quality of life and quality of health care. Major strengths of SEARCH include 1) race/ethnic diversity within the large cohort of youth with type 1 diabetes (T1D); and 2) size and diversity of the cohort of youth with type 2 diabetes (T2D). In addition, SEARCH has substantially contributed to the understanding of the etiologic and clinical dimensions of childhood diabetes that relate to classification of diabetes. Critical questions remain regarding ongoing trends in incidence of childhood diabetes, as well as the rationale and sustainability of public health surveillance systems for diabetes in youth. SEARCH is exceptionally strongly positioned to address these questions through its well-established infrastructure and surveillance system, and its highly experienced, collaborative and multi-disciplinary investigative team.

The SEARCH for Diabetes in Youth Registry Study in SEARCH Phase 3 will continue to ascertain newly diagnosed incident diabetes cases in youth age < 20 years across five geographically dispersed Study Centers (Ohio, Colorado, Washington, South Carolina, and California) in order to accomplish the Specific Aims shown below.

Aim 1: To continue to ascertain newly diagnosed (2010 - 2014) incident diabetes cases in youth age < 20 years in order to assess temporal trends in diabetes incidence and temporal trends in presentation of diabetes for the period 2002-2014, by age, sex, race/ethnicity, and diabetes type.

Research Question 1.1: What is the temporal trend of Type 1 Diabetes (T1D) incidence in US youth and how does this differ by race/ethnicity, age, and gender?

Research Question 1.2: What is the temporal trend of Type 2 Diabetes (T2D) incidence in US youth and how does this differ by race/ethnicity, age, and gender?

Research Question 1.3: Are there temporal changes in the clinical characteristics at onset of diabetes in youth and how do these differ by a) clinical diabetes type (T1D versus T2D); b) race/ethnicity (non-Hispanic white versus minority); and c) sex (males versus females)?

Specific characteristics to be examined are: age at onset of diabetes, markers of disease severity (diabetic ketoacidosis, residual insulin secretion, HbA_{1c}), immunogenetic markers (diabetes autoantibodies, HLA risk genotypes), markers of insulin sensitivity (insulin sensitivity score, waist circumference, body mass index), cardio-vascular risk factors (lipid profile, blood pressure, microalbuminuria).

Aim 2: To provide consultation and support to inform the development of low-cost sustainable public health surveillance systems of childhood diabetes in the U.S., with a focus on challenges in ascertainment of cases with T2D and cases among older youth (ages 15 years or older) with any form of non-gestational diabetes.

Research Question 2.1: Within the SEARCH surveillance system, what factors contribute to time from diagnosis to case ascertainment? Can an extended period of time to case ascertainment be accounted for by the time to receipt of specialty care or hospitalization? Are there temporal changes in time to case ascertainment?

Research Question 2.2: Within and across health care systems, using the same case ascertainment algorithm, are patterns of care different for youth with T2D or older youth with any type of diabetes, around the time of clinical diagnosis, and thereafter? Are there temporal changes in observed differences, both within and across systems?

Aim 3: Assess total and cause-specific mortality among 2002-2008 incident cases for the period from the date of diabetes diagnosis through December 31, 2010.

Research Question 3.1: Are the frequency and causes of mortality in youth with diabetes different than non-diabetic, age comparable youth? Among youth with diabetes, does the frequency of mortality differ by type of diabetes, race/ethnicity or other socio-cultural factors?

4.2. BACKGROUND AND SIGNIFICANCE

Diabetes mellitus is one of the most common severe chronic diseases of childhood. Much of our knowledge of the epidemiology of diabetes in young people has been generated by large collaborative efforts based on standardized registry data, such as the DIAMOND Project worldwide [1, 2] and the EURODIAB Study in Europe [3, 4]. These registries showed that, while at the start of the 20th century childhood diabetes was rare and rapidly fatal, by the end of the century a steady increase in incidence had been reported in many parts of the world [2]. However, epidemiological data for temporal trends in childhood diabetes are still lacking or are minimal for most of the global population of children, including in the U.S. In addition, the epidemiology of diabetes in youth is changing. As youth are becoming increasingly overweight, we are seeing more obese children with a clinical phenotype of T2D or "adult onset" diabetes. As demonstrated by SEARCH for Diabetes in Youth [5], T2D is becoming the major form of diabetes in young people in several non-white populations, such as American Indians, Asian and Pacific Islanders, and African-Americans.

4.2.1. *Importance of Diabetes Registries in Youth*

4.2.1.1. Overview, Strengths and Limitations

The need for, and utility of, long-term incidence-based registries of youth with diabetes has been recognized since the late 1970's [6, 7]. Registries facilitate tracking of long-term trends in incidence in defined geographic regions [8, 9], providing potential clues to etiology, as well as allowing the determination of differences in presentation, patterns of treatment, access to care, acute and chronic complications , quality of life, quality of care and survival differences [10]. Such registries have proven utility in monitoring cancer [11, 12], and other chronic conditions. Registries can also include the assessment of genetic predisposition, environmental and behavioral risk factors, treatment patterns, and quality of care from prevention through chronic complications that helps form the basis for new hypotheses about etiology and prognosis [11]. Linkage of registry information to census-based neighborhood and socio-demographic information through geographic information system methods also allows potential clusters and spatial locations to be identified [13]. Registries located at academic institutions with access to a cadre of well trained epidemiologists, clinicians, and biostatisticians also allows for the efficient use of registry data to form the basis for additional nested studies and in-depth research on hypotheses developed from the main incidence data [14 - 19].

There are limitations to such diabetes registries, which include difficulties in complete ascertainment of cases, due to multiple providers caring for youth with diabetes which results in complex care patterns with few common ascertainment locations. There is no requirement for hospitalization at onset, increasing the potential for cases to be missed in isolated primary care locations, and there is no

centralized source for validation of case status (such as pathology laboratory reports for cancer). In the U.S., increasing concerns about privacy and confidentiality have led individual hospitals or providers to refuse to participate in registries. It is critical in the estimation of incidence rates and temporal tends in rates that case ascertainment be virtually complete, and if incomplete, that the degree of ascertainment be consistent over time. The relatively low frequency of diabetes occurrence requires longer time periods and larger populations for stable rate and trend estimates. There is also reluctance on the part of older youth and young adults to participate in registration activities. Many of the limitations in developing registries of diabetes in youth in the U.S. are inherent in the underlying health care system (lack of common health identification system, multiple and fragmented care sites, privacy concerns, data systems designed to address only billing) and are not due to the registries themselves. As demonstrated by the SEARCH for Diabetes in Youth registry, the majority of such limitations can be successfully addressed, resulting in unbiased estimates of rates and disease-risk factor associations.

4.2.2. *Burden of Diabetes, Disparities, Clinical Presentation, Patterns of Care, Quality of Care*

4.2.2.1. Burden of Diabetes in Youth

In the year 2001, approximately 3.5 million children less than 20 years of age were under surveillance at six SEARCH research centers. We estimated that 1.8 per 1,000 youth or at least 154,000 children/youth in the U.S. had diabetes in 2001 [(20)]. Since 2002, approximately 5.5 million children less than 20 years of age (about 6% of the under 20 years U.S. population), have been under surveillance each year by SEARCH research centers to estimate diabetes incidence by type, age, sex, and race-ethnicity. The overall incidence of diabetes in 2002 and 2003 was estimated to be 24.3 per 100,000 per year. Case ascertainment completeness was 93% across all 4 geographically based sites. SEARCH estimated that annually 15,000 youth are diagnosed with T1D, and 3,700 youth are diagnosed with T2D [(5)]. Additionally, SEARCH data indicate that diabetes prevalence and incidence vary across major racial/ethnic groups. The CDC used these data to estimate the number of existing and new cases of diabetes in youth that would occur in the US each year (http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2007.pdf).

4.2.2.2. Health Disparities

In March 2009, a Supplement to Diabetes Care was published, entitled, “The Many Faces of Diabetes in American Youth: Type 1 and Type 2 Diabetes in Five Race and Ethnic Populations”. This series of SEARCH publications presented a comprehensive description of the prevalence and incidence of T1D and T2D, as well

as the clinical, behavioral, and socio-demographic characteristics, for each of the five race and ethnic groups included in SEARCH [21 - 26].

4.2.2.3. Clinical Presentation and Patterns of Care

Over 50% of youth are hospitalized at onset with diabetes. One in four children newly diagnosed with diabetes suffer from diabetic ketoacidosis (DKA). Young and poor children are more likely to be affected [19].

A high percentage of U.S. youth with diabetes do not achieve the recommended target levels of glycemic control. 17% of T1D patients (n=3947) and 27% with T2D (n=552) had HbA_{1c} levels that reflected poor glycemic control ($HbA_{1c} \geq 9.5\%$). African American, American Indian, Hispanic, and Asian/Pacific Islander youth with either T1D or T2D were significantly more likely to have higher HbA_{1c} levels compared with non-Hispanic white patients [27].

The prevalence of multiple cardiovascular disease (CVD) risk factors was high in children and adolescents with diabetes, especially in adolescents with T2D [28].

About half of the SEARCH participants had a low-density lipoprotein-C (LDL-C) concentration above the optimal level of 100 mg/dL. In older youth (≥ 10 yrs of age), the prevalence of abnormal lipids was higher in type 2 (33%) than in type 1 (19%). Only 1% of youth were on pharmacologic therapy for dyslipidemia [29]. Moreover, poorer glycemic control was associated with a worse lipid profile, regardless of diabetes type [30, 31].

Youth with T2D had a high prevalence (22.2%) of elevated albuminuria in youth with T2D, well over twice the percentage for youth with T1D (9.2%). This suggests the possibility of a relatively more rapid progression to diabetes-related vascular complications in this population [18].

Nutritional intake in adolescents with diabetes was poor and did not follow current recommendations. Recommendations for total dietary fat intake were met by only 10 percent of youth with diabetes and recommendations for saturated fat intake by only 7 percent [32]. In youth with T1D, a higher adherence to DASH diet was inversely related to hypertension, independent of demographic, clinical, and behavioral characteristics [33].

4.2.2.4. Quality of Life (QOL)

Age, gender, family dynamics and coping skills have been associated with the QOL among children and youth with diabetes, while the association between QOL and health outcomes such as glycemic control is not well established.

About 9% of adolescents with diabetes had moderate or severely depressed mood, with more girls than boys being affected. Depressed mood was associated with poorer glycemic control and a higher number of emergency room visits [34].

Youth with T1D receiving Medicaid or another government funded insurance programs had lower health related quality of life (HRQL) than those with private insurance. HRQL was also higher in youth using an insulin pump as compared to those injecting insulin, in those with a $HbA_{1c} < 9\%$, and in those with no co- morbid conditions, fewer emergency department visits or hospitalizations [35].

4.2.3. *Temporal Trends in the Incidence of Childhood Diabetes*

4.2.3.1. Type 1 Diabetes

The majority of epidemiological data on T1D are based on a clinical definition including physician diagnosis of diabetes and daily insulin injections [36]. In addition, most studies have limited the age range of populations to < 14 years, to avoid misclassification of diabetes type. It has been assumed, but not confirmed via measured diabetes autoantibodies (DA), that "type 1" diabetes is autoimmune mediated diabetes. SEARCH for Diabetes in Youth is unique in that it extends the surveillance effort to youth age < 20 years, and it collects data on DA close to the time of diagnosis, to validate the clinical assessment of diabetes type.

The majority of epidemiological data on T1D are based on data on populations of European origin. SEARCH demonstrated that in 2002-2003 the incidence of T1D was highest in non-Hispanic whites (NHW), followed by African Americans (AA) and Hispanics, and it was lowest in Asian/Pacific Islanders (API) and American Indians (AI) [5]. SEARCH for Diabetes in Youth is the only registry effort to include a comprehensive assessment of T1D burden and risk across all major racial/ethnic groups.

4.2.3.1.1. Incidence Trends

Most [10, 37 - 41] but not all [42 - 46] population-based registries showed an increasing incidence of T1D over time. An updated report from the DIAMOND project examined the trends in incidence of T1D from 1990-1999 in 114 populations from 57 countries. Based on 43,013 cases of T1D from a study population of 84 million children ≤14 years [2], the average annual increase in incidence over this time period was 2.8% (95% CI 2.4-3.2%). Similarly, the EURODIAB study, a large European survey including 20 population-based registries in 17 countries showed a 3.2% (95% CI 2.7-3.7) annual increase for the period 1989-1998 [4], and a more recent 3.9% (95% CI 3.6-4.2) increase from 1989-2003 [8]. Interestingly, the observed incidence rates confirmed, and in fact exceeded, the incidence predicted for 2010 by earlier projections [47]. In EURODIAB [8], estimates of the

rates of increase were highest in the youngest age-group [5.4% (4.8–6.1) for children age 0-4 years].

Recent data from the U.S., where registry efforts have been less coordinated, suggest similar trends. While the U.S. stood apart from other parts of the world in reporting a stable incidence of childhood T1D in the 1970's through the 1990s [48], SEARCH recently reported that the 2002-05 incidence of T1D in NHW youth aged ≤ 14 years was 27.5 per 100 000 per year [49] a rate that exceeds the incidence predicted for 2010 from older data from Allegheny County [47]. Using data from the Colorado IDDM registry and the SEARCH-Colorado site the incidence of T1D was shown to increase in youth age ≤ 17 years over the past 3 decades [9]. During a 26 year period, the incidence of T1D increased by 2.3% (95% CI 1.6-3.1) per year and was much higher than predicted from earlier Colorado data [47]. Of note, the increase was significant for both NHW (2.7%; 95% CI 1.9 - 3.6 per year, $P < 0.0001$) and Hispanic youth (1.6%; 0.2-3.1 per year, $P < 0.013$). Similar to the EURODIAB data, in Colorado, the increase in incidence was highest among the 0- to 4-year age-group (3.5%; 95% CI 2.1-4.9 per year). Additional suggestions of increasing incidence of T1D come from registries in Philadelphia [50, 51], Chicago [52] and Allegheny County [53], reporting mainly an increase among AA, but also Hawaii, reporting a four-fold overall increase (1980 to 1989) [54].

4.2.3.2. Trends in Genetic Susceptibility to T1D

Genetic susceptibility plays a large role in T1D with the human leukocyte antigen (HLA) genotypes (DR and DQ genes) explaining approximately 40-50% of T1D risk [55]. The genetic variation can explain the variation in incidence across racial/ethnic groups, but it is unlikely to explain the rapid increase in the incidence of T1D. Recent studies have suggested that the contribution of high risk HLA genotype DR3,4 has been relatively stable or has decreased over time [56 – 58]. Of note, one of these studies was conducted in Colorado, based on the prior Colorado IDDM and the current SEARCH data, and found a significant decrease in the proportion of cases of T1D with the high risk HLA genotype in the last two decades among both NHW and Hispanic participants [59]. These data suggest that the increase in T1D over the past half century is likely not due to increased incidence among those at the highest genetic risk in the HLA region, and must rather be explained by an increase in environmental factors, increased penetrance of low/moderate HLA genotypes or other genetic loci, or interactions between environmental risk factors and non-HLA genes.

4.2.3.3. Trends in Clinical Presentation

Younger Age at Onset of T1D: Several European studies [60 - 63] and one from Colorado [64] have suggested a trend toward an earlier age at diagnosis of T1D. Based on current model-based rates of increase the EURODIAB study predicted a doubling of new cases of T1D in European children younger than 5 years between 2005 and 2020 [8]. The reason for this rapid increase in the very young is unknown. It is possible that this younger group has a higher proportion of HLA susceptibility genes, but it is also possible that there is an increased disease penetrance in this age-group due to harmful changes in environmental risk factors. In addition to estimating trends in the incidence of T1D by age-group, SEARCH will also be able to explore temporal trends in onset age and the possible interaction with changes in distribution of HLA susceptibility genes, thus advancing the knowledge of T1D etiology.

Severity at Onset of T1D: The onset of T1D is heterogeneous, ranging from severe diabetic ketoacidosis (DKA) requiring hospitalization to a relatively gradual onset. Younger age at onset is usually associated with a more severe onset, more need for hospitalization, a greater chance of DKA, lower C peptide levels and higher HbA_{1c}. As onset age is decreasing, the presentation of diabetes in very young children is increasing, and can be particularly difficult for parents to recognize [65]. SEARCH found an increasing prevalence of DKA at onset of T1D with younger age: 15% of children 15-19; 27% of children 5-9; 25% of children 10-14; and 37% of children age 0-4 [19]. This study also revealed that the incidence of DKA at diagnosis of T1D has not changed significantly over the past two decades, despite efforts to improve awareness regarding diabetes symptoms to facilitate the earlier diagnosis and treatment of diabetes in children. By continuing to assess the presence of DKA at onset of T1D, SEARCH will be positioned to document potential temporal trends in the severity of T1D onset and to explore potential determinants of such trends.

Other characteristics which differ by age at onset include fasting C peptide (FCP) levels, and level and type of autoantibodies. A study examining FCP at diagnosis of T1D found that higher levels were associated with older age at onset, less hyperglycemia, and a reduced insulin requirement [60]. SEARCH also found that, among youth with T1D and positive DA, older onset age and lower HbA_{1c} levels were associated with preservation of FCP within the first year of diagnosis [17]. It is not known if the percent of youth with T1D and preserved beta cell function is changing over time. Such knowledge may have important implications for clinical care and clinical trials.

The presence of islet cell (ICA), insulin (IAA), 65-kDa isoform of glutamic acid decarboxylase (GAD65), insulinoma-associated protein 2 (IA-2) or islet zinc transporter (ZnT8) autoantibodies is highly predictive of T1D risk. It is believed that

seroconversion occurs early in life [66]; however, autoimmunity can occur at any age [67]. The Diabetes Prevention Trial - Type 1 recently confirmed that not only presence, but number of DA, type and titers are also predictive for T1D risk [67]. Differences in the levels of DA have also been reported by onset age. Zimmet et al reported a higher frequency of GAD65 positive antibodies among patients who were diagnosed with T1D at age 10+ compared to those diagnosed before age 10 [68]. Similarly, SEARCH reported a higher prevalence of GAD65 antibodies in T1D youth age 10+ compared with those < 10 years old at diagnosis (65.6% vs. 56.4%) [5]. Data on trends in autoimmunity at presentation with T1D are very limited. It is unknown if autoimmunity is shifting to younger ages over time as seen with T1D onset age. Such knowledge of a potential shift in DA seroconversion would narrow the exposure window and help in identifying potential environmental triggers.

Obesity at Onset of T1D: It has also been suggested that the typical presentation with T1D has changed over time, and that youth with T1D are more obese at diagnosis. Libman and colleagues [69] examined the prevalence of overweight or obesity among black and white children with newly diagnosed T1D in Pittsburgh over two periods: 1979-1989 and 1990-1998. The prevalence of overweight or obesity increased from 12.6% to 36.8%. Similarly, the prevalence of overweight among SEARCH youth with T1D was higher than among those without diabetes (22.1% vs. 16.1%, $P < 0.05$) [23].

The "accelerator hypothesis" postulates that obesity-associated insulin resistance accelerates the disease process of T1D. The marker is an earlier age at onset of T1D associated with increased BMI [70]. Prospective data from population-based studies in Europe [71] and the U.S. [72] have shown that children who develop T1D have faster growth trajectories before onset of autoimmunity [72] and diagnosis of diabetes [71, 72]. Several studies have demonstrated an inverse association between age at T1D diagnosis and childhood BMI [73, 74]. The SEARCH study reported that a higher BMI was associated with a younger age at diagnosis only in youth with substantially reduced β-cell function at diagnosis [16], suggesting that obesity may operate after initiation of autoimmunity by accelerating the β-cell decline, thus leading to an earlier T1D diagnosis. The Australian Baby Diab Study recently reported that weight gain early in life independently predicts development of islet autoimmunity [75]. These combined findings suggest that obesity may both trigger the autoimmune process as well as accelerate β-cell loss after autoimmunity development. By collecting data on height, weight and other markers of insulin resistance at onset of T1D, SEARCH will answer questions related to temporal trends in clinical presentation, providing important clues to etiological research.

4.2.4. *Type 2 Diabetes*

T2D has been traditionally viewed as an adult disease, with risk increasing with advancing age. An increasing proportion of youth with apparent T2D has been reported in the last two decades, especially in minority populations [76, 77]. The epidemiology of T2D in youth is yet unclear, due to its relative rarity, the unclear clinical and epidemiological definition, and the small number of appropriate, population-based studies. Therefore, the true magnitude of T2D in youth may be under- or overestimated, depending on the study setting (clinic versus population-based), characteristics of populations under study, and definitions used.

SEARCH for Diabetes in youth is the first population-based study to provide comprehensive estimates of T2D incidence in youth according to race/ethnicity. Overall, T2D was relatively infrequent, except among 10-14 and 15-19 year old minority groups (17.0 to 49.4 per 100,000/year) [5]. Consistent with previous reports [78, 79], SEARCH demonstrated that T2D contributes considerably to the overall diabetes incidence among minority youth age ≥ 10 years of age.

Many studies rely on data collected from diabetes clinics. A strength of such studies is that assignment of diabetes type is likely to be more accurate (though not always uniform) than in population-based studies. However, a clinic population may not accurately represent the general population.

Several clinic-based studies reported an increased incidence of T2D. For example, T2D incidence rates reportedly rose by 9%/year from 1985-94, based on medical records of 735 AA and Latino children with insulin-treated diabetes in Chicago [80]. The incidence was higher in AA than Latinos (15.2 vs. 10.7/100,000/year), with a female predominance. Similarly, among 1027 consecutive patients attending a Cincinnati diabetes clinic [81], T2D incidence increased by 10-fold, from 0.7/100,000/year in 1982 to 7.2/100,000/year in 1994. Onset was typically around puberty, the majority were AA, and the female: male ratio was 1.7:1. Among 569 adolescents presenting to a Florida diabetes clinic between 1994 and 1998 (82), the proportion of new cases with T2D rose from 9.4% to 20%. In Arkansas, new-onset non-T1D increased fivefold in youth aged 8-21 between 1990 and 1995) [79].

Similarly, a study in Thailand [83] reported a rise in the proportion with T2D referred to a diabetes clinic from 5% to 17% during 1997 to 1999. Another study of 0- to 16-year-olds from U.K. identified 67 cases of T2D (defined as diabetes with elevated insulin or FCP levels and/or the absence of DA) during the period 2004-2005 [84]. The U.K. T2D incidence was 0.53/100,000/year and was higher in blacks and South Asians compared to whites. A study from the only pediatric diabetes clinic serving approximately 2 million Australians, documented a rise in the incidence of T2D among youth aged 0-17 years [85].

Between 1990 and 2002, average annual rises were 23% in the indigenous, and 31% in the non-indigenous population.

With the exception of SEARCH, only a limited number of population-based studies of childhood T2D exist. Most have been conducted in American Indians and Native Canadians [78, 86 - 87] and showed high prevalence of T2D. While there is evidence supporting an increasing incidence and prevalence of T2D among youth, it is possible that this rise is mainly a feature of high-risk ethnic groups. Well-designed studies of youth in Germany, Austria, France and the U.K [88 - 90] all indicate that T2D remains a rarity in these populations, accounting for only 1-2% of all diabetes cases. A survey of all children with diabetes from 177 U.K. pediatric diabetes centers found that <1% of all cases were due to T2D [91]. A single center in France [89] reported that only 2% of 382 children (aged 1-16) with diabetes had T2D. Using an Austrian national register, Rami et al [92] found that T2D represented only 1.5% of all newly diagnosed cases of diabetes under the age of 15 from 1999-2001. In contrast, while the SEARCH data [5] support the notion that T2D in youth is predominantly occurring in high risk ethnic groups, T2D accounts for 14.9% of all diabetes cases among NHW adolescents age 10 years and older. Although differences in obesity rates between U.S. and European youth are likely contributors, the full explanation for these discrepancies remains uncertain and deserves further study. By continuing to ascertain prospectively newly diagnosed diabetes cases, SEARCH will be in the unique position to estimate trends in the incidence of T2D among US youth by age-group, sex and race/ethnicity.

4.3. PUBLIC HEALTH SURVEILLANCE OF DIABETES IN YOUTH

4.3.1. *Rationale*

Diabetes surveillance holds promise to inform public health action by tracking rates over time and exploring population-level associations. The relative recency of more comprehensive diabetes registries suggests that such public health impacts will only occur with the continuation of existing registries and the opportunities for further surveillance. An efficient network of diabetes registries that cover major race/ethnic, geographic, and socioeconomic segments of the U.S. population with adequate resources can be utilized to provide national estimates (e.g. http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2007.pdf) of prevalence, incidence, presentation, temporal trends, and other outcomes, without the need for a national system [93]. In order to fully realize the potential of diabetes registries in youth, it is also necessary to develop simple and lower cost case definitions and classifications that can be used for diabetes surveillance in youth. SEARCH will evaluate consistent, sustainable and simplified criteria for case classification for surveillance purposes, across centers, across racial/ethnic groups, and over time and will explore existing data and linkages with systems of care to determine if more efficient mechanisms for surveillance exist.

4.3.2. *Limitations of Existing Systems and Role of SEARCH*

There are a number of limitations to public health surveillance that have been identified by SEARCH that require further development. These include difficulties in ascertaining youth with T2D and youth 15 years of age and older with either type of diabetes, groups that had not previously been included in the majority of ongoing studies of childhood diabetes. While a substantial majority of youth with T1D (and younger children with T2D) receive care or consultation from pediatric endocrinologists [27], patterns of care for youth with T2D are not as well described. In addition, the approach to determining the date of diabetes diagnosis, race/ethnicity, and the type of diabetes is often difficult using existing health care data, especially from administrative data sources which are developed for billing purposes and do not include and/or code this information consistently. The 'type' of diabetes as applied by the care provider has been explored by SEARCH and found to agree well (>95%) with a pathophysiological assessment based on markers of autoimmunity and insulin resistance, for cases that fit the typical picture of T1D (young onset, no overweight, insulin using) and T2D (adolescent onset, overweight, minority youth, perhaps with no insulin treatment), indicating that clinical diabetes type as assessed by the care provider may be used as an initial step for surveillance purposes. However, it is not known whether the use of provider type is adequate for tracking trends in incidence by type, since there may be changes in provider beliefs and practices over time that will not be obvious from collected data. SEARCH will explore additional collected data on main etiologic dimensions of diabetes type (autoantibodies, genetic predisposition to autoimmunity, insulin sensitivity, residual insulin secretion) to determine the sensitivity, specificity, and predictive values of constellations of variables that may improve on this and be useful for public health surveillance. SEARCH will explore existing data systems (Indian Health Service, HMO, integrated health care system with electronic medical records) as other ways to extend and validate public health surveillance approaches on a pilot basis.

4.4. MORTALITY IN YOUTH WITH DIABETES

Short term mortality risk in youth with DM is an indicator of quality of health care. It may also be associated with socio-demographic factors, including sex, race/ethnicity, socioeconomic status, and access to health care. Few studies have evaluated mortality risk among persons diagnosed with DM during childhood and the majority has been limited to persons with T1D. Population-based studies from countries including the United Kingdom [94], Italy [95], Scandinavia [96 - 98], Estonia and Lithuania [99], and the United States [100] all reported increased mortality for persons with youth-onset DM compared to the general population. The Chicago Childhood Diabetes Registry investigators reported standardized mortality ratios of 1.90 for African Americans and 3.37 for Latinos for youth diagnosed with DM at < 18 years compared to an age-matched population [100]. DKA was the most frequent cause of death, while deaths from CVD, infection, trauma, and other causes were also

observed. Among Pima Indians with early-onset (<20 years) T2D, the SMR for this group was 3.0 compared to the non-DM population;[102] 4 of the 11 deaths attributed to diabetic nephropathy. As part of the SEARCH Registry study, we will determine overall and cause-specific mortality rates and risk factors for mortality among over 9,000 racially/ethnically diverse youth diagnosed with T1D and T2D from a contemporary (2002-2008) cohort.

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SEARCH Phase 3 Protocol - Section 4B
Cohort Study
Study Objectives & Background and Significance
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4. Study Objectives & Background and Significance

4.1. SEARCH COHORT STUDY OBJECTIVES

4.1.1. *Goals*

SEARCH is an on-going, multi-center, epidemiological study consisting of the largest and most culturally diverse population of youth with diabetes ever assembled. Initiated in 2000, SEARCH encompasses the major racial/ethnic groups in the U.S: non-Hispanic white (NHW), African-American (AA), Hispanic (H), Asian-Pacific Islander (API) and American Indian (AI). SEARCH was designed to estimate the prevalence and incidence of diabetes among youth, and to characterize diabetes-related health outcomes and their risk factors including barriers to care and quality of health care. However, critical questions remain regarding the impact of diabetes on the health outcomes of affected youth. In the SEARCH Phase 3 Cohort Study, we will conduct an in-person research visit with SEARCH participants whose diabetes was incident in 2002 or later, with duration of diabetes > 5 years who completed a baseline study visit (expected n=3699). SEARCH has a well-established and ongoing infrastructure and is uniquely positioned to successfully address the following Aims:

Aim 1: Assess the prevalence and incidence of, and risk factors for chronic microvascular (retinopathy, nephropathy, and autonomic neuropathy) and selected markers of macrovascular complications (hypertension, arterial stiffness) of diabetes.

Research Question 1.1: Is the presence and incidence of selected chronic complications and markers of complications different according to a) clinical diabetes type (Type 1 or Type 2 Diabetes); b) biochemical dimensions of diabetes type (autoimmunity, insulin sensitivity score, residual insulin secretion); or c) metabolic risk factors (hyperglycemia, hypertension, obesity, dyslipidemia, presence and severity of diabetic ketoacidosis at onset or thereafter)?

Research Question 1.2: Is the presence of risk factors for, and selected markers of, chronic complications associated with race/ethnicity or other socio-cultural factors (e.g., family structure, household income, or parental education)? Using data collected at previously study visit(s), what are associations of selected factors including physical inactivity, high fat diet, selected nutrient biomarkers (e.g., plasma vitamin D), cigarette smoking exposure, and depressive symptoms and these vascular markers?

Aim 2: Assess the incidence of, and risk factors for, serious acute complications of diabetes including severe hypoglycemia and diabetic ketoacidosis (DKA).

Research Question 2.1: Does the incidence of serious acute complications differ according to biochemical dimensions of diabetes type (autoimmunity, insulin sensitivity score, residual insulin secretion), glycemic control or diabetes treatment regimen?

Research Question 2.2: Does the incidence of serious acute complications differ according to race/ethnicity or other socio-cultural factors (e.g., family structure, household income, or parental education)?

Aim 3: Determine the degree to which barriers to care, quality of care, and the process of transition from pediatric to adult health care impact disease factors, including dimensions of diabetes type, and diabetes-related outcomes (acute and chronic complications, quality of life, diabetes-related mortality).

Research Question 3.1: Do specific barriers to care and quality of care assessed early in the course of their diabetes effect a) the evolution of key dimensions of diabetes type; b) metabolic status (e.g., A1c, lipid profile, weight status); c) markers of acute and chronic complications of diabetes; or d) quality of life?

Research Question 3.2: Do specific barriers to care and quality of care explain differences in health outcomes experienced by minority youth, compared to their non-Hispanic white counterparts with the same type of diabetes (T1D or T2D)? Health outcomes will include dimensions of diabetes type, metabolic status, markers of acute and chronic complications, quality of life, and mortality.

Research Question 3.3: What are the specific barriers to care that emerge as youth with diabetes move into early adulthood (e.g., loss of or change in insurance; change in health care provider)? Do these barriers affect metabolic status and co-morbidities? Are these barriers more common among persons of minority race/ethnicity compared to NHW individuals, independent of other socio-cultural factors (e.g., family structure, household income, or parental education)?

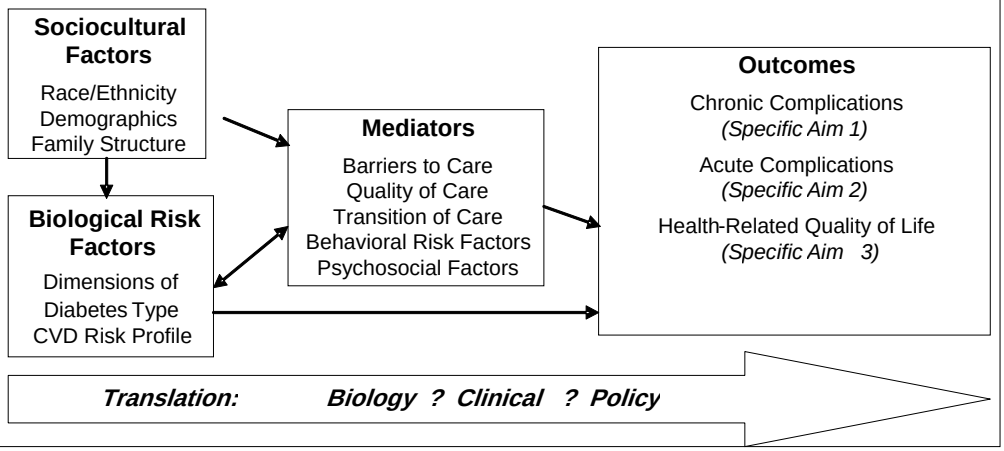
Aim 4: Maintain and supplement the SEARCH repository for biological specimens, and promote access to SEARCH for conduct of scientifically and logistically appropriate ancillary studies.

4.1.2. *Research Strategy*

The SEARCH Cohort Study is a highly interdisciplinary effort, inclusive of experts in diabetes-related physiology and epidemiology, clinical researchers, and health services researchers. Together, we have developed a conceptual framework to ensure realization of our overarching vision to improve the health and well-being of individuals diagnosed with diabetes in youth. Our framework is shown Figure 3, in which socio-cultural factors, biological risk factors and mediators including health care access and quality together drive diabetes-related health outcomes. The core content of the present

application was assembled collaboratively by the SEARCH team, and represents the scientific accomplishments and vision for the SEARCH Cohort Study, by consensus of all current SEARCH centers and central units.

Figure 3 SEARCH Cohort StudyConceptual model



4.2. BACKGROUND AND SIGNIFICANCE

4.2.1. *Goals*

The goal of the SEARCH Cohort Study is to advance substantially knowledge of the natural history and determinants of adverse health profiles among racially and ethnically diverse youth with T1 or T2 diabetes diagnosed in 2002 - 2008 who had a baseline study visit and who have had diabetes for at least 5 years duration. To accomplish this goal, the SEARCH Cohort Study will describe and characterize acute and chronic diabetes-related complications and their risk factors, diabetes-related quality of life, mortality, and the degree to which barriers to care, quality of care, and transition from pediatric to adult care affect diabetes related health outcomes.

Previous studies have contributed significantly to knowledge regarding the natural history of type 1 diabetes in youth. From 30 years of follow-up in the Pittsburgh Epidemiology of Complications (EDC) study of persons diagnosed with T1D in childhood from 1950-1980, rates of mortality, renal failure, and neuropathy declined significantly with diagnosis in more recent eras. Unfortunately, such favorable trends for complications, including coronary artery disease, overt nephropathy and proliferative retinopathy, were not observed [(1)]. Recent changes in the characteristics of youth with diabetes raise the question of whether the previously described patterns of health outcomes continue to apply. Specifically, clinical care for childhood diabetes has evolved, now encompassing a number of new types of insulin, delivery systems for insulin, and systems for documenting glycemic excursion. Concurrently, the epidemiology of diabetes has evolved. The incidence rate of T1D has increased around the world [(2)] and from SEARCH incidence data substantial proportions of adolescent minority youth have T1D (for AA adolescents, 42% of incident DM are T1D; 54% for H, 30% for API, and 14% for AI) [(3)]. Within the last two decades T2D has gone from an infrequent diagnosis, to 15% of all diagnoses of diabetes in youth [(4, 5)]. Finally, as the ethnic diversity of diabetes in youth has changed, so also have broader socio-cultural patterns. For example, approximately 50% of AA youth with T1D live in single-parent households and are on Medicaid insurance [(6)] and similar socio-cultural patterns are observed for other minority subgroups and for youth with T2D [(7 - 10)]. Because of the importance of these patterns in key aspects of diabetes management and control [(11)], it is critical to incorporate consideration of socio-cultural patterns into the study of the impact of diabetes on health outcomes.

The SEARCH Cohort Study provides a tremendous opportunity to assess prevalence, incidence, and correlates of diabetes-related health outcomes by utilizing the well-established SEARCH study populations and infrastructure. The SEARCH Cohort Study will build on previous work by SEARCH investigative team that has contributed substantially to our understanding of the health impacts of diabetes in youth. In the

sections below, we provide the key findings from SEARCH in the context of the present literature. Information is presented below regarding health status of youth with diabetes: acute complications, chronic complications, risk factors; mortality; and the effects of barriers, care quality, and transition to adult care.

4.2.1.1. Health Status of Youth with Diabetes: Complications and Risk Factors

4.2.1.1.1. Acute Complications

The major acute complications of diabetes in youth are diabetic ketoacidosis (DKA) and hypoglycemia. Two European studies reported a frequency of DKA of between 21-26% [12, 13]. In pediatric patients with established diabetes, the frequency of DKA ranged from 1-10 per 100 patient years [14, 15]. Older age, higher HbA_{1c}, higher insulin doses, mental health diagnoses, and underinsurance were associated with higher risk of DKA [15]. Youth with T2D may also present with DKA, with frequencies of 11-25% reported [16 – 18]. They may also present with hyperglycemic hyperosmolar non-ketotic coma (HHNK) [19]. SEARCH reported a similar frequency of DKA at diagnosis of 25.5% [20].

Severe hypoglycemia occurs in 10-25% of children with diabetes each year [21]. In addition, unrecognized hypoglycemia occurs commonly with up to 73% of hypoglycemic episodes occurring without detection by children or their parents [22]. Hypoglycemia unawareness, a condition more common in those with more intensive glycemic control, longer duration, and younger age of onset further increases the risk of severe hypoglycemia. Early evidence suggests that use of continuous subcutaneous insulin infusions (CSII) paired with continuous glucose monitoring (CGM) as a “closed loop artificial pancreas” was associated with a 57-80% decrease in nocturnal hypoglycemia [23]; however, the impact of new technologies on acute complications in diverse populations is not known. From SEARCH, we know that insulin treatment regimens impact the frequency of acute complications, with youth on CSII having fewer acute complications, including hospitalizations, than youth on other regimens [24]. SEARCH provides a large, multi-ethnic population of youth from diverse economic backgrounds with both T1 and T2D to address how acute complications are influenced by both the biochemical dimensions of diabetes type, race/ethnicity, other socio-cultural factors, and by health care and barriers to care. Findings will inform recommendations for diabetes management and health care delivery to reduce risk for acute complications.

4.2.1.1.2. Chronic Complications

Macrovascular Disease. Non-invasive techniques are now used to evaluate arterial structure and function well before diabetes-related vascular disease becomes irreversible [25 - 30]. Pulse wave velocity (PWV), a measure of arterial stiffness (AS), is associated with CVD risk factors [31] and predicts mortality in both T1 and T2 diabetic adults independently of traditional CV risk factors and glycemic control [32]. In adults with T1D [27, 33] or T2D [28] another measure of arterial stiffness, the augmentation index (Aix), was found to be increased compared with controls. From a limited number of small studies in youth, higher PWV in children with either T1D [34] or T2D [35] was found compared to controls, and increased AIx was observed in children with T1D [36].

From a sub-set of SEARCH patients with T1D (N=535) and T2D (N=60) age 10-23 years, from Colorado and Ohio sites (diabetes duration 65+/-49 months) [37, 38], youth with T2D had increased PWV and AIx than those with T1D ($p<0.01$ for each). These differences were largely mediated through increased central adiposity and higher blood pressure in youth with T2D. In addition, youth with T1D had significantly worse PWV and AIx than 241 historical controls from Ohio [38]. An ongoing SEARCH ancillary study in Colorado and Ohio (SEARCH CVD, R01DK078542, Dabelea PI) is collecting these and other measures in youth with T1D and healthy controls and will be able to provide a healthy control group to SEARCH. Our data, together with the limited available literature, suggest that premature CVD is already present in youth with both T1D and T2D, even at young ages and with relatively short disease duration. Study of the evolution of CV risk profile and subclinical atherosclerosis within a contemporary cohort of youth with T1 and T2D will provide insights into natural history of vascular disease in diabetes that will substantially inform new directions to what otherwise appears to be intractable excess risk.

Diabetic Retinopathy. Several studies published in the last five years have provided evidence that risk factors for diabetic retinopathy (DR) deserve further study. Estimates of the prevalence of DR among youth with T1D vary from 4.6% [39] to 20% (mean duration 6.8 yr) [40]. Interestingly, the prevalence of retinopathy among Australian youth with T1D declined significantly over three time periods (1990-1994, 1995-1998, 1999-2002) from 49% in the first time period to 24% in the second time period [41], despite matching these cross-sectional analyses on age and diabetes duration (median duration, 7.5 yr) with no difference over time in HbA_{1c}. The authors postulated that a much higher proportion of youth were on more intensive insulin regimens in later years, and this may have contributed to the decline in DR prevalence. Cheung et al [42] reported incidence of DR among 645 initially retinopathy-free T1D youth age 12-20 yrs of 14.8 per 100 person

years, over a median follow-up of 2.5 yr. Longer duration of T1D, lower BMI, and higher A1c were significantly associated with incidence of DR, as was larger retinal arteriolar caliber. Differences in mean arterial blood pressure, gender, and albumin excretion rate did not significantly predict DR.

The literature on youth with T2D is even more limited. From the Australian cohort, prevalence was 4%, however only 25 youth with T2D were evaluated for retinopathy (mean duration 1.3 yr). Among 15 youth with T2D (mean duration 2.1 yr), no retinopathy was detected; however several retinal abnormalities were detected that were absent among non-diabetic control youth [43]. Associations of a variety of measurements of retinal vascular caliber to the incidence and progression of DR are an active area of research [42-45].

There are no data available to enable evaluation of risk factors for early DR in a contemporary multi-ethnic cohort of adolescents with T1 and T2D in the US. In Year 5 of SEARCH 2, we initiated a pilot study of the feasibility of obtaining retinal photos as part of the SEARCH follow-up visit protocol. To date, 325 SEARCH DR pilot participants have had retinal photos completed and 20% of these have evidence of DR in at least one eye. SEARCH is uniquely positioned to obtain critical information on the prevalence of and risk factors for DR among youth by diabetes type and race/ethnicity as well as by risk factor data obtained from earlier study visits.

Diabetic Nephropathy. The incidence of diabetic end-stage kidney disease (ESKD) in 2007 was more than double that in 1990 [46], with even greater increases among AA and AI populations. Worsening glomerular filtration rate (GFR) carries up to a three-fold risk of cardiovascular event and six-fold risk of death [47]. Correlates of diabetic kidney disease include glycemic control [48, 49], diabetic retinopathy [50], blood pressure [51, 52] and possibly lipids [53, 54], inflammatory and fibrotic markers [55 - 57], vitamin D deficiency [58, 59] and diagnosis during puberty [60 - 65]; and in T2D, nephropathy has been associated with increased pulse wave velocity [66, 67]. From SEARCH, the prevalence of elevated urinary albumin-to-creatinine ratio (ACR) was 9.2% in youth with type 1 and 22.2% in type 2 diabetes ($p< 0.0001$). In multiple logistic regression analysis, female sex, higher A1C and triglyceride values, hypertension, and type of diabetes (T2 versus T1D) were significantly associated with elevated ACR. Adjustment for variables related to insulin resistance (obesity, hypertension, dyslipidemia, and inflammation) attenuated, but did not completely explain, the association of diabetes type with elevated ACR [68]. The SEARCH Cohort Study will provide much needed additional information in a longitudinal design. SEARCH is uniquely positioned to obtain critical information regarding the prevalence and risk factors of diabetic nephropathy across subgroups of diabetes

type and race/ethnicity. Especially important, since so little is known, SEARCH will provide much needed information on early nephropathy in T2D.

Neuropathy. The topic of diabetic neuropathies is complex both due to the diverse clinical manifestations and due to difficulties in measurement methods. Here we focus on chronic distal symmetric polyneuropathy (i.e., peripheral neuropathy) and cardiac autonomic neuropathy.

Peripheral neuropathy may occur in at least 20% of adults with diabetes, and risk increases with glycemia, dyslipidemia, hypertension, diabetes duration, height and possibly with cigarette smoking and alcohol consumption [61, 69 - 71]. There is limited information available on the prevalence and determinants of peripheral neuropathy among youth with diabetes, and studies are quite difficult to interpret due to substantial differences in measurement methods. Eppens et al [40] reported 1,433 T1DM youth with onset < 18 years of age, compared with 68 T2D subjects from Australia, with a median duration of 6.8 years (T1D) and 1.3 years (T2D). There was no difference between T2D and T1D in the prevalence of peripheral neuropathy (21% vs. 27%).

Cardiac Autonomic Neuropathy (CAN). Commonly assessed by heart rate variability (HRV) [72] is associated with hyperglycemia [73] and with recurrent hypoglycemia [74]. CAN was associated prospectively with increased arterial stiffness among individuals with T1D [75], and low HRV predicted a 2-3 fold increase in mortality among adults with diabetes, independent of other risk factors [76].

Among 130 newly diagnosed patients with T1D in Germany, the prevalence of CAN was 16.9% [77] and ranged from 6-34% with longer duration of T1D [77, 78]. Evidence of CAN was also observed in two additional studies of youth with T1D [79, 80] and HRV was correlated with long term glycemia (over 4 years) [79].

Pilot data on diabetic neuropathy have been collected on a small number of individuals from the 2002-2005 SEARCH cohort during SEARCH 2, Year 5 as part of the follow-up visit protocol. Measures include: 1) the Michigan Neuropathy Screening Instrument (MNSI); and 2) CAN assessment using electrocardiogram analyses. Evaluation of the associations of peripheral neuropathy and CAN with measures of subclinical macrovascular disease and its risk factors in the SEARCH Cohort study will yield important information.

4.2.1.2. Risk Factors

Glycemic Control. Studies among children and youth with diabetes generally report a constellation of related socio-demographic factors that are associated with poor glycemic control, including race/ethnicity, socioeconomic status, lower parental

educational attainment, parental involvement in diabetes management, and family dynamics [81 - 87]. Similar patterns were observed in SEARCH, both for T1 and T2D youth [11], and may be partly mediated by our observation of worse glycemic control among T1D youth on insulin regimens other than CSII [24]. In SEARCH, 17% of youth with T1D (n=3947) and 27% of T2D (n=552) respectively had poor glycemic control (HbA_{1c}> 9.5%). For both T1 and T2D, higher A1c was also associated with higher concentrations of apoB and LDL particle size [88], and elevated ACR [68], suggesting possible links early in the history of diabetes between glycemic control and future risk for both macro- and microvascular disease that require further study.

Cardiovascular (CV) Risk Profile. CV risk factors track from childhood to adulthood [89, 90] and risk factors measured in youth predict adult target organ damage [91 - 93]. Thus, an adverse risk profile among youth with diabetes may magnify the already three-fold excess risk for CV mortality associated with diabetes in adulthood [94]. In SEARCH, we found that T1 youth had a prevalence of overweight (22%) that was significantly higher than that of non-diabetic counterparts, and ~ 90% of youth with T2D were overweight or obese [95]. The prevalence of metabolic syndrome among SEARCH youth with T1D was 14%, and 92% for youth with T2D [96]. Further, among youth with T1D, 11% had elevated apoB, 8% had dense LDL, and 12% had elevated LDL-cholesterol. In contrast, among youth with T2D, 36% had elevated apoB, 36% had dense LDL, but only 23% had elevated LDL-cholesterol. Moreover, the prevalence of elevated blood pressure in youth with type 1 was 5.9%; minority ethnic groups, obese adolescents and youth with poor glycemic control were disproportionately affected. In contrast, 23.7% of adolescents with type 2 diabetes had elevated BP ($p<0.0001$) [97].

Psychosocial factors. Psychosocial factors are important to consider in the adaptation to and treatment of childhood diabetes [98 - 100]. Family conflict and communication have also been associated with HRQoL in youth with T1D [101] and with poorer metabolic control [102]. In addition, a higher level of parental fear of hypoglycemia was associated with poorer glycemic control in their child [103]. From SEARCH, youth from racial and ethnic minority groups had a higher rate of depressed mood than did NHWs [104]. Depressed mood was associated with higher HbA_{1c} [104] and among youth with T1D, poor glycemic control was associated with lower generic [105] and diabetes-related health-related quality of life (HRQoL) [106]. The SEARCH Cohort Study will provide urgently needed longitudinal studies in large and diverse cohort regarding the impact of psychosocial factors on the health of youth with diabetes.

Behavioral factors. Helgeson et al [107] reported high dietary fat intake among youth with T1DM. Regarding physical activity, a majority of youth with T1D from a Norwegian cohort did not meet physical activity recommendations [108], and lower

physical activity was associated with higher A1c and worse lipid profile [109]. From SEARCH, dietary intake of adolescents with T1DM is high in total and saturated fat, and low in fiber, fruits and vegetables compared to current nutrition recommendations [110], with similar patterns among those with T2D. In youth with T1D, a higher adherence to DASH diet was inversely related to hypertension [111]. Also, substantial proportions of youth with either T1 or T2D across race/ethnic groups engaged in less physical activity than recommended [6-8]. Of major concern, prevalence of current smoking ranged from 12-20% for T1D adolescents, and from 13-26% among T2D adolescents across race/ethnic groups [6-9].

Summary. The SEARCH Cohort Study will provide comprehensive information on the prevalence and incidence of key metabolic, psychosocial, and behavioral risk factors, and their association with acute and chronic complications of diabetes, and diabetes-related quality of life. These phenomena will be evaluated in a socio-cultural context, particularly considering race and ethnicity.

4.2.1.3. Effect of Barriers, Care Quality, and Transition to Adult Care on Outcomes

Timely receipt of high quality health care is important for children with special health care needs (CSHCN), [112-115] including diabetes. However, a chasm exists between ideal and actual care [116 - 118] among those of minority race/ethnicity and low socioeconomic status who continue to face barriers to quality health care [119 - 122] and health disparities, [123] including diabetes-related mortality [124].

Data from SEARCH demonstrate that a substantial proportion of parents report barriers to care including cost of care (41.2%) and medication (25.2%), not receiving family-centered care (31.3%), and problems communicating with doctors (43.3%) [125]. Being from a racial or ethnic minority group and having a lower income were associated with less access to care and reduced adherence to ADA guidelines for care. Further study is needed to elucidate the relationship of quality of care to outcomes, and specific barriers to care experienced by participant groups who most often do not receive recommended care.

To address this issue, we adapted a conceptual model describing children's interactions with the health care system and how barriers to high quality care reduce the likelihood of improved health outcomes of importance to diabetes [126], and incorporated this model into the overall conceptual framework of the SEARCH Cohort Study (see Figure 3, Section 4B.) Barriers to care interact in very complex ways with biological and social factors, sometimes as confounders, other times they act as mediators, and occasionally they can modify the associations of interest. Commonly, clusters exist of biological, social and system-related risks. Our model hypothesizes a direct effect of biological risk factors on outcomes, and further proposes that barriers to care, quality of care, transition of care, and behavioral risk

factors can affect biological factors over time, thereby altering outcomes. Finally, the model hypothesizes a link between socio-cultural factors (e.g. race/ethnicity) and both biological risk factors (e.g. dimensions of diabetes type) and mediators (e.g. barriers to care).

Transition of care from pediatric to adult health care is a dynamic process that seeks to meet the health care needs of each person as he or she moves from childhood to adulthood [(1)]. In contrast, 'transfer of care' denotes the single event of changing from a pediatric to an adult provider. Very little epidemiological research has been published that had examined the processes or outcomes associated with transition or transfer of care. Several publications describe transition of care focusing on specific programs for individuals with a chronic disease [(113 - 118)]. These studies are qualitative. They describe the average age of transfer of care as 18 years (range 13-25 yrs) [(121, 126 - 127)], deterioration in obtaining clinical care with a decrease in the frequency of health care visits and an increase in hospitalization rates [(11, 28, 128)], variation in glycemic control [(8, 120)], and no change in the frequency of adverse outcomes including hypoglycemia or diabetic ketoacidosis [(128, 129)]. This literature suggests that programs utilizing transition clinics had the greatest success [(122, 123, 130)]. Importantly, all of these studies describe experience of transition outside the US where health care systems are quite different [(119 - 134)]. In the United States, concerns about losing health insurance and the potential effect of under-insurance on young adults with chronic health conditions has been a major consideration in research on transition to adult care [(130)]. However, with the passage of comprehensive health reform in March 2010, young adults may continue on their parents' insurance until the age of 26 years if they do not have jobs that offer health insurance and if they can still be claimed as dependents on their parents' taxes, regardless of whether they are students or are employed. An opportunity exists to study how this new national policy may affect transition of care for young adults with diabetes by comparing SEARCH participants who transferred care before, versus after, health care reform is initiated.

Specifically from SEARCH, for individuals age 17 or older participating in the SEARCH 2001 prevalent cohort Quality of Care Survey, 66% of those with T1D reported seeing an adult provider as the main source of diabetes care, and 57% reported having discussed the transition to adult care with their health care provider. For T2D, 85% were seeing an adult provider, and 49% reported having discussed their transition of care. The median age of transition of care was 18 yr for T1D, and 19 yr for T2D.

Given the crucial role that high-quality care plays in health outcomes, understanding the effect of barriers to care and health-care quality on diabetes outcomes over time is critically important. Determining which barriers or aspects of quality affect outcomes

for which groups of individuals, how these processes interact with transition from pediatric to adult diabetes care, and whether and how new health insurance rules affect the transition process, would enable researchers to develop interventions to improve outcomes for youth with diabetes. Study of transfer of care before and after health care reform highlights a major strength of this proposal - the ability to test new research questions seamlessly within the existing structure SEARCH.

4.2.1.4. Summary of Significance of the SEARCH Cohort Study to the Field of Childhood Diabetes

Across a wide range of topics including biological, behavioral, and socio-cultural characteristics, processes of health care and quality of care, the SEARCH study has already substantially contributed to our understanding of the impact of diabetes in youth. The SEARCH Cohort Study will add estimation of complications in the modern era of treatment, and allow exploration of a wide variety of interacting biological, socio-cultural and health care factors that may alter the risk of such complications. Our findings will significantly inform clinical and public health practice and policy, as well as provide direction to new research, all targeted to reduce the impact of diabetes on the health and well-being of youth with diabetes.

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SEARCH Phase 3 Protocol - Section 5A
Registry Study
Case Ascertainment and Data Collection
Table of Contents

5. Case Ascertainment and Data Collection

5.1 AIM 1: TEMPORAL TRENDS

5.1.1. *Overview of Design, Methods and Data Collection*

Centers in SEARCH Phase 3 will continue to conduct population-based ascertainment of cases of diabetes in youth less than 20 years of age in the year of diagnosis for the period 2010 - 2014, using methods consistent with those employed in SEARCH Phase 1 and SEARCH Phase 2. This will involve identification, validation, confirmation of eligibility and uniqueness of cases, and registration of the case both locally with identifiers and centrally with the SEARCH 3 Coordinating Center (CoC) without identifiers. The 2010 - 2014 cases will have their medical records abstracted and will be asked to complete a brief survey. A sample of 2012 cases will be invited to an in-person research visit. Case registration will proceed without disruption in the transition from the end of SEARCH Phase 2 (September 29, 2010) until the full implementation of the SEARCH Phase 3 protocol. All data collection will be performed under standardized protocols by centrally trained and certified staff.

5.1.2. *Case Ascertainment Processes*

Ongoing Case Ascertainment: The case ascertainment, validation, eligibility, and deduplication protocol in SEARCH 3 will be the same as the one used in SEARCH 1 and 2 to ensure continuity and comparability across time and centers. SEARCH 3 will continue to use the reporting network of clinics and health care providers that was established previously as the primary approach to case-finding for incident cases of diabetes for the period 2010-2014. The case ascertainment approach involves existing validated pediatric diabetes databases, hospital and health plan databases, and other health care organizations. Center-specific case ascertainment methods are presented in Section 2.

Case Validation: Cases of diabetes will be validated based on provider reports, medical record reviews, or self-report of a physician diagnosis of (non-gestational) diabetes. A physician-diagnosed case of diabetes is established if any of the following criteria are met: (1) medical record review indicating a physician diagnosis of diabetes, (2) the diagnosis of diabetes is directly verified by a physician, (3) the physician referred a youth with diabetes to the study, or (4) the case was included in a clinical database that had a requirement for verification of diagnosis of diabetes by a physician.

Eligibility Criteria: Eligibility criteria will remain the same. As in SEARCH 1 and 2, the study will be confined to children/youth who, in addition to having an onset of physician-diagnosed of diabetes in the index year, are also are < 20 years of age on December 31 of the index year and 2) are resident of the population defined for geographically-based centers at any time during the index year, or a member of the

participating health plan for membership-based centers at diagnosis, and 3) are not active duty military personnel or institutionalized. Protected Health Information (PHI) will be obtained in order to validate and confirm eligibility and uniqueness of cases in keeping with HIPAA and the procedures and approvals required by the local IRB.

De-duplication: Duplicates will be identified using both electronic files and manually, both within and between case sources, using the name or initials, gender, date of birth, ethnicity, zip code, or other available information, in keeping with HIPAA requirements to use the least amount of PHI in conducting research. The number of duplicates identified will be used to estimate completeness of ascertainment with the capture-recapture method among the geographic centers.

Systematic re-ascertainment: A systematic case re-ascertainment process will be conducted in 2012 for cases incident in 2006-2010 and in 2014 for 2008-2012 cohorts. The purpose of re-ascertainment is to assure as complete ascertainment of diabetes cases as possible, especially those with T2D, who, due to different care patterns, we theorize are more likely to be missed by the SEARCH network prior to the close of the registration window. Additional cases will be registered with the center and the CoC with a flag to indicate that they were registered outside of the standard window.

Case Registration: Cases that are valid, eligible and unique will be registered by the center with information being uploaded to the CoC. Minimal information about the participant (age, gender, race/ethnicity, type of diabetes reported by clinician, center, date of diagnosis, zip code or county of residence, and birth date) will be uploaded to the CoC website in order to protect confidentiality. Names and addresses are not provided to the CoC. In cases where duplicates and cases that are not valid or eligible are identified at a later date, they will be unregistered by both the local center and the CoC.

Collection of Core Variables: 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, gender, diabetes type and race/ethnicity for the entire population of cases. This information is also critical in assessing possible response bias to the in person research visit. This information is called "core" information. The main sources of core data are medical records and the initial participant survey and are described in Table 5 - 1.

Medical Record Abstraction (MRA) serves the following purposes: a) validation of diabetes diagnosis; b) main source of core demographic and diagnostic information, and c) secondary data source for race/ethnicity information. In SEARCH 2, an additional set of items pertinent to clinical presentation was added to the medical record abstraction effort: weight/height at diagnosis, DKA at diagnosis and insulin use history. We will continue to collect these data through MRA in SEARCH 3 and will seek 100% completion.

Initial Participant Survey (IPS) contains key data, including the core information described above, and serves to: a) verify of case eligibility (e.g., residence in the year of diagnosis); and b) is the main source for self-reported race/ethnicity information. Additional information includes: symptoms at presentation, potential secondary causes of the diabetes, use of insulin and other medications, treatment history, family structure, usual language spoken, and contact information (for local use only). The IPS can be self-administered or interviewer-administered. The information can be collected online, by phone or in person, or at the beginning of the in-person research visit. To encourage participation in the IPS, a monetary incentive of $10.00 will be offered. We will continue to collect these data through IPS in SEARCH 3 (Table 5 - 1) and will seek 90% completion.

In-Person Research Visit (IPV): The IPV or "registry visit" in SEARCH 3 is designed to collect data on relevant dimensions of diabetes type (presence of autoimmunity, genetic susceptibility to autoimmunity, insulin sensitivity, insulin secretion) and data informing the clinical presentation of diabetes. We will also store (by separate consent) blood, serum, plasma and urine for future genetic and non-genetic analyses. In keeping with the time-stratified sampling approach initiated in SEARCH 2, only the incident 2012 cohort will be eligible to participate in the registry visit. An additional sampling approach will be implemented in SEARCH 3, in order to reduce participant burden and maximize study resources, without compromising the statistical power to detect trends in clinical characteristics over time. To maximize the number of minority participants and youth with T2D, eligible cases for SEARCH 3 registry visit are all cases >10 years old, regardless of ethnicity/race, all minority cases, regardless of age, all cases not T1, regardless of race or age, and 50% of NHW T1 cases <10 years old. Since some sites are not able to obtain race at the time of the assignment of the PID, if race is not available, all participants will be invited to the IPV. We will seek a 70% completion of the IPV among eligible youth.

Table 5-1: Summary of SEARCH3 Registry Data Collection			
	Eligible Cohorts	Core Variables	Clinical Presentation
MRA	2010-2014	Date of birth, date of diagnosis, sex, provider-determined diabetes type, race/ethnicity, residence in the year of diagnosis	Weight/height at diagnosis, DKA at diagnosis, insulin use, acanthosis nigricans, diabetes autoantibodies and c-peptide assessment
IPS	2010-2014	Date of birth, date of diagnosis, sex, self-reported race/ethnicity, residence in the year of diagnosis; health insurance; usual diabetes care, education of parents; youth > 18 yrs.	Treatment history, secondary diabetes, symptoms at presentation, acute complications, medications, family history, contact information; reported height, weight
IPV	2012		*Physical Exam*: height, weight, waist circumference, BP, acanthosis nigricans
			Medication Inventory: list of currently prescribed medications
			Lab/specimens: diabetes autoantibodies (GAD65, IA2), HbA_{1c}, fasting glucose, C-peptide, lipids, urinary albumin/creatinine (spot sample)
			Repository: serum, plasma, DNA (by separate consent) and urine for storage on 1st morning void

The content of the IPV for incident cases will be similar to SEARCH 1 and 2 (Table 5 - 1). However, unique to SEARCH 3, we will add a first morning void urine collection that the participant will bring to the clinic. Urinary albumin and creatinine will be measured to obtain an albumin/creatinine ratio on a spot urine sample. Samples will not be collected during the visit on participants who are pregnant or menstruating, have had a fever greater than 100 degrees in the past two hours, or who have taken an antibiotic in the past seven days for a urinary tract infection. A dipstick test will also be performed to test for the presence of blood or leukocytes by the central laboratory. Urine will also be stored (first morning void only) to assess other markers of nephropathy in the future. (8/11)

The following will be collected for the IPV incident cases: fasting blood and urine for laboratory measurements and storage, and a brief physical examination as outlined below.

- Blood measures: Diabetes autoantibodies (GAD65, IA-2); (ZNT8 will be added after the assay is standardized); HbA_{1c}, fasting glucose and C-peptide, lipids (total

cholesterol, HDL-Cholesterol, LDL-Cholesterol, triglycerides), HLA risk genotypes

- Urine measures (spot and first morning void): Urinary albumin and creatinine (from spot urine collection)
- Physical examination: Height, weight, blood pressure, assessment of acanthosis nigricans, waist circumference (NHANES and minimum waist methods) on participants who are 3 years of age or older at the time of the visit
- Medication inventory: List of currently prescribed medications.

SEARCH participants with an IPS will be invited to complete the IPV if they meet the following eligibility criteria. If <10 years of age and have type 1 diabetes, we will invite 50% of non-Hispanic White and 100% of all minority youth to participate in the IPV. All youth with type 2 diabetes will be invited to the visit. To encourage IPV participation, a remuneration of $80.00 in cash or gift cards will be offered. Some centers may offer assistance with transportation in order to facilitate these visits. We will seek to complete a 70% rate among those participants invited to the IPV (Table 5-2).

Table 5-2. Estimated Number of Cases Registered, and Participating in the IPS and IPV Per Year

Center	Estimated N Incident cases/year			Estimated N IPS/year	Estimated N IPV/year*
	NHW<10	Other	Total		
SC	70	206	276	248	179
OH	51	113	164	147	104
CO	132	244	376	338	236
CA	15	213	228	205	156
WA	75	154	229	206	145
Total	343	930	1,273	1,144	820

5.1.3. *Mortality Surveillance*

To address Aim 3 of this study, we will conduct surveillance of mortality including all-cause and cause-specific mortality in the incident cohorts. All centers will systematically identify deaths that occur between the date of diagnosis and December 31, 2010 among youth in the 2002-2008 incident cohorts (registered during SEARCH 1 and 2) using the National Death Index (NDI) as the primary source, plus individual case reports of deaths made to the study team during the course of the study. The NDI is a central computerized index of death record information from State vital statistics offices nationwide. By the spring 2012, the NDI will include death record information through 2010. Due to HIPAA and IRB considerations that preclude this activity from being done centrally, each center will submit their cases to the NDI. The NDI Plus service will be used so that any potential matches are returned with the cause of death codes. Subjects

who are known to be deceased will be submitted separately to obtain cause of death. Records will be searched for all years for which vital status cannot be confirmed. Death certificates and reports of deaths by immediate family members or the participant's health care provider will also be considered definitive evidence of mortality. Next of kin will not be contacted when a death is identified.

Based on the 9,448 incident 2002-2008 cases registered to date, we anticipate that we will have ≈ 46,863 person-years (p-y) of follow-up with a mean follow-up time of 5 years for the cohort (35,836 p-y for T1D; 9.144 p-y for T2D). P-Y of follow-up will be calculated from the date of diagnosis until the date of death or December 31, 2010. We will examine all-cause mortality as well as cause-specific mortality. Cause of death will be obtained from the codes on the death using a standardized international protocol. In the analyses of risk and cause of death using this population-based cohort, we will evaluate the association between mortality and cause-specific mortality by gender, age, race/ethnicity, and DM type. In addition, targeted exploratory subgroup analysis will be conducted to examine the associations between variables measured at SEARCH visits including history of acute complications.

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5. Data Collection

5.1. SEARCH COHORT STUDY VISIT METHODS

5.1.1. *Eligibility and Anticipated Sample Size*

Individuals registered in the SEARCH cohort with a diagnosis of non-gestational diabetes in incident years 2002-2005, 2006 and 2008 and who completed a SEARCH baseline in-person visit in one of the SEARCH clinical centers will be eligible for the new SEARCH Cohort Study once they have had diabetes for at least 5 years. We will determine an algorithm that optimizes duration of disease over the data collection years of the Cohort Study, considering both diagnosis year and the timing of the most recent SEARCH visit during the SEARCH 2 protocol. We anticipate that the average duration of diabetes will be 8-9 years (range 6-14 yrs diabetes duration), and the average age of participants at the time of the SEARCH Cohort Visit will be about 20 years (range 8-32 yrs old). Our goal is to have 80% of eligible members of the cohort attend the proposed SEARCH Cohort Study visit, for a total of **3145** participants with a Cohort Study visit.

Of the 20% not attending the research clinic visit, an additional 10% will be participate by completion of surveys by telephone or internet, for a total of 90% inclusion or **3550 individuals**. Based on proportions of youth in sub-groups of diabetes type and race/ethnicity, the anticipated numbers and characteristics of anticipated participants in the SEARCH Cohort Study data collection are displayed in Table 5-1.

Table 5-1. Anticipated Sample Size and Characteristics: SEARCH Cohort Study (2002 - 2006, 2008)

	SC		OH		CO		CA		WA		All	
Type Race/Ethnicity	80%	90%	80%	90%	80%	90%	80%	90%	80%	90%	80%	90%
Type 1												
NHW	405	456	386	434	711	800	98	110	410	461	2010	2261
Other	175	197	58	65	188	211	185	209	94	106	700	788
Type 2												
NHW	38	42	30	34	16	17	7	8	16	18	107	119
Other	106	120	42	47	79	95	83	97	18	23	328	382
ALL	724	815	516	580	994	1123	373	424	538	608	3145	3550

While we considered including the 2001 prevalent cases for whom we also have baseline visit data, their dates of diagnosis ranged from 1982-2001. Because of the secular changes in treatment regimens and clinical outcomes that have been observed in other studies, we determined it best to focus on a contemporary cohort with reasonable numbers of youth in each of the diagnosis years included, both for interpretability of findings from the proposed effort, and for potential future, continued follow-up.

5.1.2. *Retention Strategies*

We will continue to employ traditional, proven, cohort retention strategies including: birthday cards, study newsletters, updating contact information annually, utilizing internet-based search systems to locate individuals lost to follow-up, using cell-phone text messaging and e-mail, offering flexible study date appointments including home visits, offering assistance with transportation, mailing pre-visit instructions, a reminder call prior to the visit, acknowledgement of participation, and participant remunerations that are appropriate for the length and the respondent burden of the proposed study visit. Investigators and study personnel will also continue to solicit the support of diabetes providers to encourage on-going study participation. Communications with providers include letters, e-mail messages, telephone calls, newsletters, individual discussions, and group presentations of study goals and preliminary results.

We recently sought expert advice on marketing the study to youth and families affected by diabetes from the American Diabetes Association (ADA). Their three major recommendations were 1) to update the SEARCH public website to make it more appealing to youth and families, 2) to utilize social networking, such as Facebook and MySpace to communicate with parents and participants, and 3) focus on positive messages about the study. Pilot work on social networking strategies is currently planned. During the planning of SEARCH 3, we conducted a survey of a sample of individuals (n=30) who previously were non-responders to SEARCH visits. The most common barriers to participation were multiple demands of life and for youth specifically, not wanting to spend more time with diabetes-related activities. The most common reasons for potential future participation were a desire to help others, to participate in finding a cure for diabetes, and to increase our understanding of diabetes. New strategies will be informed by these findings. We have also increased monetary remuneration from $80 in the SEARCH 2 follow-up visit to $120 for participation in the SEARCH 3 Cohort Study research visit. SEARCH will develop online forms to complete questionnaires for the study to enhance study participation and reduce participant burden during the visit.

5.1.3. *Summary of Measurements*

Table 5-2 shows measures for the SEARCH Cohort Study. All data collection is performed under standardized protocols by centrally trained and certified staff.

Table 5-2. Summary of Data Available from SEARCH 1 and SEARCH 2 for Incident Cases Eligible for the SEARCH Cohort Study, and Measures Proposed for the SEARCH Cohort Study
Brief Medical Record (e.g., DM type, Dx date)
Medical Record Validation of Self-Report (subset)
Demographics and socioeconomic status indicators
Family Medical History
Health Questions - Serious acute complications (hypoglycemia, DKA), - Medications - Hospitalization - Other processes of care including transition - Quality of care - Family structure - Quality of life (PedsQL) Additional for age > 10 yr: - Tanner stage (age < 18 yr) - Parent and Participant Education - Diet (food frequency questionnaire) - Physical activity - Tobacco Use, Secondhand smoke - Alcohol - Depressive symptoms (CES-D) - Pregnancy
Hypoglycemia Fear Survey
Diabetes Family Interaction Scale
Diabetes Eating Problems Survey
Expansion of transition from pediatric to adult care (processes, satisfaction and type of transition)
Physical Exam (anthropometry, BP, acanthosis)
Retinopathy, retinal vessel caliber (fundus photos)
Peripheral Neuropathy (MNSI)
Cardiac autonomic neuropathy (HRV)
Arterial stiffness (PWV, Alx)
Laboratory Fasting glucose, DAA (GAD65, IA2, ZnT8 (once assay is standardized), fasting C-peptide, lipids (total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides), A1c; apoB, LDL particle size and density, cystatin-c CRP, IL-6, DGUC Rf, fibrinogen, adiponectin, leptin, creatinine, random and first morning void for urinary albumin and creatinine, storage of plasma, serum, DNA; storage of first morning void urine

5.1.4. *Risk Factors for Complications: Dimensions of Diabetes*

In addition to diabetes type as established by the health care provider, we assess markers of autoimmunity (diabetes autoantibodies, GAD65, IA2; plus the addition of the recently identified ZnT8 antibody [1] once assays are standardized) and fasting c-peptide [2, 3] and fasting glucose.

5.1.5. *Risk Factors for Complications: Other Laboratory, Physical Exam, and Health Behaviors*

A1c is the primary marker of glycemia. Lipid profile includes total, LDL- and HDL-cholesterol, and triglycerides. Additionally, we will measure apolipoprotein B, and LDL particle size and density, as well as adipocytokines (CRP, IL-6, fibrinogen, adiponectin, leptin) shown in Table 5-2 using existing SEARCH laboratory methods. Standardized anthropometry methods include height, weight, waist circumference; systolic and diastolic blood pressure; and evaluation for acanthosis nigricans all follow existing SEARCH protocols [3, 4]. Assessment of health behaviors all follow current SEARCH protocols, including dietary intake by food frequency [5], physical activity, alcohol, and active and passive smoking as previously described [6].

5.1.6. *Retinopathy*

SEARCH will obtain retinal images using a non-mydriatic fundus camera. Consistent with NHANES retinal photos [7], two 45-degree images are taken of each eye: the first image is centered on the optic nerve and the second centered on the macula. This device can measure vessel anatomy which is important because retinal arteriolar and venular calibers diameter have been associated with selected markers of atherosclerosis, stroke and coronary heart disease in adult populations [8, 9]. Among adults with T2D, retinal vessel caliber was independently associated with risk of incident nephropathy, lower extremity amputation, and stroke mortality [10]. In young Australian individuals with T1D, retinal vessel measurements were associated with duration of diabetes, gender, A1c, blood pressure and cholesterol, and these associations were observed even among those without DR [11].

As for the SEARCH pilot effort, we will utilize the expertise of the Ocular Epidemiology Reading Center (OERC) at the University of Wisconsin-Madison, an internationally recognized center of excellence diabetic retinopathy research [12]. The OERC will grade the images for presence and severity of DR, macular edema and retinal vessel caliber.

5.1.7. *Nephropathy*

Microalbuminuria has been the mainstay of diabetic nephropathy prediction modeling. However, recently its validity and robustness has been questioned [13], with increasing recognition of non-proteinuric diabetic kidney disease [14, 15], the tendency of microalbuminuria to regress more often than progress, and about 1/3rd of microalbuminuric patients never progressing to proteinuria [16, 17]. Nonetheless, patients who develop persistent microalbuminuria have about 5 times the risk of progressing to overt nephropathy compared to those who are normoalbuminuric at a baseline observation at least 5 years after diabetes diagnosis [18]. The first two phases of SEARCH collected random urine samples. The pitfalls of random urines, especially in adolescents who are susceptible to benign orthostatic proteinuria (frequency of 2-5%), are well

appreciated. However, for the SEARCH Cohorts Study, we will continue to collect a random urine sample during the visit for longitudinal analysis. Unique to SEARCH 3, we will add a first morning void sample that the participant will bring to the clinic. Urinary albumin and creatinine will be measures to obtain an albumin/creatinine ratio. Samples will not be collected during the visit on participants who are pregnant or menstruating, have had a fever greater than 100 degrees in the past 24 hours, or who have taken an antibiotic in the past seven days for a urinary tract infection. A dipstick test will also be performed to test for the presence of blood or leukocytes. Urine will also be stored (first morning void only) to assess other markers of nephropathy in the future. (08/2011)

Serum cystatin C has been associated not only with renal function, but also positively associated with coronary calcification among individuals with T1D [19]. Serum cystatin C [20, 21] and creatinine will be measured for calculation of estimated glomerular filtration rate (eGFR) using the new Schwartz equation for children [22]. Serum creatinine will be used to calculate eGFR in subjects over the age of 18, using the CKD EPI equation which has been demonstrated to be more precise than the modification of Diet in Renal Disease (MDRD) equation at higher GFRs [23]. eGFR will be used to monitor change in filtration function of the kidney. All three equations will be used in those 14-18 yrs, as there has been little investigation regarding the appropriate age or developmental stage to change from equations traditionally used for children, to those for adults. The limited precision of creatinine and cystatin C based estimation of GFR in the normal ranges are recognized. However, these methods may provide useful information on changes in GFR which are predictive of important outcomes [24].

5.1.8. *Markers of Macrovascular Disease: Vascular Dysfunction*

While there is great concern regarding the extent to which diabetes mellitus increases CVD risk, very little is known about the early stages of this process as they progress in adolescents and young adults. Vascular dysfunction occurs early in the atherosclerotic process and it is associated, among others, with obesity, hypertension and insulin resistance [25]. Since atherosclerosis is known to progress in a non-uniform fashion throughout the vascular tree [26], multiple methods have been developed to evaluate vascular function non-invasively. Non-invasive methods to study vascular function include, among others, assessment of arterial stiffness.

5.1.8.1. Measurement of arterial stiffness

The SphygmoCor CPVH System from AtCor Medical (Lisle, IL) is a portable system to measure arterial stiffness by pulse wave velocity (PWV), augmentation index (Aix) by non-invasive arterial tonometry, and heart rate variability (HRV).

5.1.8.1.1. **Pulse wave velocity (PWV)**

PWV is measured with a SphygmoCor CPVH System from AtCor Medical (Lisle, IL). ECG leads are applied to the chest, then distance from the lowest portion of the sternal notch to the carotid, radial, femoral & foot (dorsalis pedis or posterior tibial) artery sites is measured to the nearest 0.1 cm 3 times using a tape measure, averaged and entered into the software. Next, a pressure wave form is obtained for the proximal site. Finally, a second arterial waveform is recorded from the distal artery. The waveforms are gated by the R-wave on the simultaneously recorded ECG. PWV is the difference in the carotid-to-distal path length divided by the difference in R-wave-to-waveform foot times. The average of 10 measurements is used in the analyses to cover a complete respiratory cycle. An average of three PWV values is used for the analysis of the different PWV of the arm (carotid-radial) trunk (carotid-femoral) and lower extremity (carotid-foot minus carotid-femoral). Reproducibility of the SphygmoCor device has been published previously. Bland-Altman analyses of reproducibility yielded repeatability coefficient for aortic PWV of 2.34m/sec (for mean value of 8.15±3.01 m/sec) with between-observer values of 2.50 m/sec. This demonstrates excellent agreement at an average PWV near 5 m/sec measured in healthy children.

5.1.8.1.2. **Augmentation index (AIx)**

For AIx, the SphygmoCor tonometer is placed over the right radial artery and data are collected as previously described [27, 28]. The pressure waves are calibrated using systolic and diastolic BP obtained in the same arm. The device then analyses the pulse wave using a validated generalized transfer function [29]. Wave forms collected over an 8-second period are averaged to produce peripheral and corresponding central (ascending aortic) pressure waveforms. Ascending aortic pressure and AIx are derived from the central pressure waveform. Aix is the difference between the main outgoing wave and the reflected wave (RW) of the central arterial waveform, expressed as a percentage of the central pulse pressure. It provides a measure of systemic arterial stiffness. Since AIx is affected by heart rate (HR), values are adjusted to a standard HR of 75 beats/minute (AIx75). An average of 3 measures is used. The inter-observer difference for AI was found to be 0.23 ± 0.66% and the intra-observer difference was 0.49 ± 0.93% as compared to an average AI in healthy children of greater than 3%.

5.1.9. *Markers of Neuropathy*

While there is substantial evidence of the epidemiology of neuropathy in adult diabetes patients, there is limited information available on the prevalence and determinants of neuropathy among youth with diabetes. Given the large sample size, racial and ethnic

diversity and sizeable numbers of youth with Type 2 diabetes, the SEARCH for Diabetes in Youth Study presents a unique opportunity to understand the natural history of diabetic neuropathy (both peripheral and autonomic). Data to be collected during this visit include: 1) the Michigan Neuropathy Screening Instrument (MNSI), which includes a brief questionnaire, physical exam inspection, vibration sense, reflex test and monofilament test for peripheral neuropathy; and 2) cardiac autonomic neuropathy assessment using electrocardiogram analyses.

5.1.9.1. Peripheral neuropathy methods

The Michigan Neuropathy Screening Instrument (MNSI) is designed to screen for the presence of peripheral diabetic neuropathy. The MNSI is designed to be used in an outpatient setting and will be administered by trained technicians. The first part of the screening instrument consists of 15 self-administered "yes or no" questions on foot sensation including pain, numbness and temperature sensitivity. A higher score (out of a maximum of 13 points) indicates more neuropathic symptoms. The questions were chosen from among those in the Neuropathy Screening Profile that showed the highest degree of specificity and sensitivity for diabetic neuropathy among normal subjects and those with a variety of neuromuscular disorders [(30)] and have been recently validated [(31)]. The second part of the MNSI is a brief physical examination involving 1) inspection of the feet for deformities, dry skin, hair or nail abnormalities, callous or infection, 2) semi-quantitative assessment of vibration sensation at the dorsum of the great toe using a 128 Hz tuning fork, 3) grading of ankle reflexes and 4) monofilament testing with a 10 g Semmes-Weinstein monofilament using a standard protocol. Subjects with an MNSI score $\geq$ 2, together with reduced/absent vibration sense, ankle reflexes, and monofilament testing will be considered to have diabetic neuropathy on screening. Other combinations of results will also be evaluated.

5.1.9.2. CAN methods

Measurement of HRV will be performed by trained and certified technicians. The protocol is based on the software housed in the Sphygmacor instrument (ATCOR Medical: http://www.atcormedical.com/). A resting ECG will be completed for 5-10 minutes. Resting HRV time parameters that are captured include: HRV range, maximum, minimum; standard deviation, percent of consecutive beat-to-beat intervals that are greater than 50 milliseconds long (pNN50), Triangular index, and the root mean squared successive mean standard deviation (RMSSD), a measure of vagal index. Resting frequency parameters captured include: low frequency max (Hz); High freq max (Hz); LF:HF ratio, LF power normalized; HF power normalized, Total power (ms^2).

5.1.10. *Acute complications*

Acute complications studied will be severe hypoglycemia and DKA. Severe hypoglycemia is defined as a hypoglycemia event requiring assistance of another person [32]. For diabetic ketoacidosis, occurrence will be recorded as a) emergency department visit or b) hospitalization. This aligns well with prior publications on acute complications, and data frequently recorded in patient surveys and medical records [33]. Current data are not available on comparing self report of acute events to medical records or administrative data. By separately collecting data on ED visits and hospitalizations, we will be positioned to conduct a validation sub-study of self-report of acute complications.

5.1.11. *Diabetes treatment regimen and related technologies*

Diabetes Treatment Regimen and Related Technologies will be assessed, to include oral hypoglycemic agents, insulin regimen (including use of continuous subcutaneous insulin infusion, CSII), and glucose monitoring (including actions taken as a result of actual glucose values). With the recent introduction of continuous glucose monitoring (CGM) into clinical practice, we also query use of these devices [34, 35].

5.1.12. *Psycho-social factors*

We will use the Pediatric Quality of Life Inventory (PedsQL) [36] and the Center for Epidemiologic Studies-Depression (CES-D) scales [37]. The CES-D scale will be administered to all youth ≥ 10 years of age at the time of the visit [38]. We will add psychosocial measures that are specific to the goal of *achieving and maintaining good glycemic control*. One barrier to attaining this goal is fear of hypoglycemia. The Hypoglycemia Fear Survey (HFS) includes a "worry subscale" and a "behavior subscale" [39] with versions developed to use with children with type 1 diabetes (HFS-C) [40] and their parents (HFS-P) [41]. Additionally, we will administer the Diabetes Family Interaction Scale to assess diabetes-specific family conflict [42].

We will administer the Diabetes Eating Problem Survey-Revised (DEPS-R) and single item, "I take less insulin that I should." Youth with diabetes are at high risk of disordered eating behaviors (DEB). Amongst individuals with diabetes, insulin restriction is a unique strategy to induce weight loss. Concurrent DEB and type 1 diabetes carries significant metabolic consequences in young adulthood including poor glycemic control and increased risk of micro-vascular complications. [43, 44] We propose inclusion of these 17 items to the SEARCH 3 visit to provide valuable data about prevalence of co-morbid DEB in patients undergoing transition of care.

5.1.13. *Socio-cultural factors*

We will query household income, per capita income, family structure, preferred language, migration status, and parental and participant-attained education.

5.1.14. *Processes of care*

We will query the type and frequency of seeing health care providers (for diabetes and for primary care), processes of diabetes self-management training, and recent hospitalizations. Quality of Care is assessed based on ADA guidelines for pediatric and adult diabetes care in terms of testing frequency for A1c, blood pressure, lipids, and urine albumin [45]. We will use questionnaire instruments used in SEARCH Phases 1 and 2 to assess quality of care. Receipt of services will be measured by self-report by parents (patient age <18) or adult patients (age ≥ 18).

5.1.15. *Barriers to care*

Barriers to care will be measured via items from the Consumer Assessment of Healthcare Providers and Systems survey (CAHPS 3.0) Supplemental Item Set for Children with Chronic Conditions and one additional item to assess foregone care (care not received that parents thought was necessary) [46]. We will assess access, cost, and interaction barriers.

5.1.16. *Transition to adult care: assessment of care will be assessed in four topic areas*

i) Topic 1: Preparation for transition - We will use select questions from the National Survey of Children with Special Health Care Needs to answer key questions about preparation for transition. Using these questions will allow comparison between National Survey and SEARCH. These questions would only be asked of those who are still in Pediatric DM care. We will consider adding some of these questions to the survey for youth ≥ 10 years of age in addition to administering to the parent/guardian of youth ≥10.

ii) Topic 2: Determining that a change from pediatric to adult provider has occurred. We will use the SEARCH Annual Health Questionnaire used in SEARCH Phase 2 to address this topic. An analysis from SEARCH data showed that 55% of respondents reported a change in provider between the age of 17 and 24 with a mean age for transfer of 19.1 years with SD 1.7 years. These data suggest that the participants in SEARCH 2 understood the questions that dealt with transition.

iii) Topic 3: Satisfaction with Care: We will use existing questions from the SEARCH Quality of Care survey (based on CAHPS survey) to assess satisfaction with care provider for both pre and post transition subjects.

iv) Topic 4: Transition experience for those who have changed care providers. We will add 3 questions about the transition process for those who reported a change in provider.

5.1.17. *Validation sub-study: comparison of participant responses and medical records*

Participant/parent self-report of medical events and health care received is imperfect. Self-report may be limited by several factors, including the desire to give the correct or socially-desirable response, recall of events, and awareness of the services received. Further, recall accuracy may vary based on sociodemographic characteristics, such as education and income and the age of the respondent. In a study that compared recall of ambulatory care services by adults with chronic health conditions with medical record review, the authors suggested that recall of "memorable" services, such as blood pressure measurement, may be substantially better than for more invisible services, such as specific tests being done using a blood sample [47].

It is not feasible to conduct complete medical record reviews on all SEARCH Cohort Study participants. Therefore, we will conduct a sub-study to validate self-report of key medical events and selected markers of health care quality against clinical medical information in the medical record. Specifically, we will validate episodes of acute hypoglycemia requiring medical assistance (ED visit or hospitalization), DKA, ED visits, and hospitalizations. To evaluate the validity of these data elements, we will use information in the medical record (including information stored in electronic health records and clinical databases) to assess the frequency of these services compared to the frequency reported on the survey. A random sample of 25 charts for each center (total of 1250 records) will be reviewed to assess the concordance. With this number we can estimate 95% confidence intervals for the true concordance rate within +/- 20% for each site, and overall, if we find that the sites have consistent levels of concordance, we can estimate the 95% confidence interval for the true concordance within +/-8%. In addition to examining the concordance rates, we will examine kappa statistics both within sites and overall t o see what level of agreement exists.

5.2. EXPANSION OF REPOSITORY OF BIOLOGICAL SPECIMENS

The Northwest Lipid Metabolism and Diabetes Research Laboratories (NWRL) has been the Central Laboratory for the SEARCH for Diabetes in Youth Study since its inception. In addition to performing analysis, the laboratory has stored, processed, and retrieved serum, plasma, urine and DNA samples collected from study participants for analysis at NWRL and other laboratories participating in SEARCH ancillary studies. From the SEARCH Cohort Visit we will supplement this repository with additional stored plasma, serum, urine and DNA. Through the well-established SEARCH Ancillary Study policies, we encourage investigators outside of the SEARCH team to utilize this resource.

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SEARCH Phase 3 Protocol - Section 6A
Registry Study
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6. Statistical Considerations

6.1. TEMPORAL TRENDS IN INCIDENCE OF DIABETES (Research Questions 1.1 & 1.2)

SEARCH has ascertained each new case of T1D and T2D in its surveillance areas since 2002, allowing us to estimate the incidence of diabetes over time. We will continue this surveillance in SEARCH 3, and a primary objective is to assess the significance of changes in the incidence of T1D and T2D over time, overall and by levels of important characteristics such as age, sex, and race/ethnicity, and to determine if the changes over time vary by these characteristics.

Chi-square tests will be used to determine if the incidence of diabetes changes over time, overall and by characteristics of interest. The chi-square test is robust against a large range of possible differences; however, it is not particularly powerful for detecting specific patterns. While numerous patterns of change are possible (consistently increasing, consistently decreasing, increasing then decreasing, decreasing then increasing, etc.), we are primarily interested in detecting consistently increasing or decreasing changes over time. The Cochran-Armitage trend test will be used to determine if the changes over time are increasing or decreasing. In a more general framework, weighted linear regression and logistic regression will be used to assess changes in diabetes incidence over time. These models allow us to assess the effects of characteristics of interest and to determine if the trends differ by levels of the characteristics (e.g., younger vs. older age-groups, NHW vs. minority, males vs. females).

Approximately 5,000,000 youth less than 20 years of age live in the SEARCH surveillance area. About half are female, 60% NHW, 14% AA, 16% Hispanic, and the rest A/PI or AI. Using our initial incidence estimates [(1)] and assuming the population remains constant over time, we will be able to detect a slope of 0.13 (or 0.7% annual change) in the overall incidence of T1D. This slope is well within the range previously reported in the literature: an annual increase of 3.9% (95% CI 3.6-4.2) in Europe [(2)] and 2.3% (95% CI 1.6-3.1) in Colorado [(2)]. Importantly, given the large population and the relatively long period of surveillance (13 years), we will have adequate power to detect changes in incidence of T1D by age groups even smaller than those previously reported, for example, among Colorado youth: 3.5% (2.1-4.9) for age-groups 0-4 years; 2.2% (1.0-3.5) for 5-9 years 1.8% (1.0-2.7) for 10-14 years and 2.1% (0.5-3.7) for 15-17 years [(2)]. Moreover, we will be able to detect reasonable slopes in the incidence of T1D among the major racial/ethnic groups: 0.81% annual change for NHW [2.7% (1.9-3.6) previously reported (2); 2.2% for AA; 2.1% for Hispanics (1.6% (0.2-3.1) previously reported [(2)]. We will also be able to detect a slope of 0.13 (or 1.35% annual change) in the overall incidence of T2D in youth 10 and older, and reasonable slopes by sex, age-group and major racial/ethnic groups. There are no published

trends in incidence of T2D in youth, in the U.S. or worldwide, to provide comparison for our estimates.

Regression models will also be used to assess differences in the slopes by demographic characteristics (i.e, covariate by time interactions). Table 6.1 shows the differences in slopes of T1D and T2D, by demographic characteristics, which we can detect in 2014 (e.g., males vs females, NHW vs minority, and 0-9 vs 10-19 for T1D or 10-14 vs 15- 19 for T2D) with 80% power at the 5% two-sided level of significance, assuming a variety of slopes. For slopes ranging from 0.2 to 0.5 the detectable differences between groups are almost identical. We see that for T1D, using data through 2014, we can detect a difference in slopes of 0.28. The detectable differences in the slopes of T2D diabetes are slightly larger because of the smaller denominator (youth 10 and older), but not much larger since there is a lower incidence of T2D. Note that the most conservative estimates are shown in Table 6.1 (e.g., NHW vs minority for T1D as the denominators differed most for these groups); detectable differences were similar for other group comparisons.

Table 6.1 - Differences in slopes detectable with 80% power in 2014 (between genders, races, and age groups)

Slope 1*	Slope 2*	Difference
T1D		
0.20	0.47	0.27
0.30	0.58	0.28
0.40	0.68	0.28
0.50	0.78	0.28
T2D		
0.20	0.52	0.32
0.30	0.63	0.33
0.40	0.74	0.34
0.50	0.84	0.34

* Slope 1 is the observed slope in one group (e.g., males; NHW; etc) and Slope 2 is the observed slope in the other group (e.g., females; Other; etc)

6.2. TEMPORAL CHANGES IN CLINICAL CHARACTERISTICS (Research Question 1.3)

Another research question focuses on assessing potential temporal changes in the demographic and clinical characteristics of youth with diabetes over time. Analysis of variance (for continuous measures like age and HbA_{1c}) and logistic regression (for dichotomous measures like prevalence of autoimmunity) will be used to assess changes in these outcomes over time. Time will initially be entered as a categorical variable to check for any differences over time. Time will then be considered continuously to check for consistent changes over time (slopes). Time by covariate interactions will be assessed to

determine if the slopes differ by level of important covariates (e.g., does the change in age over time differ for males and females). In Table 6.2, we show the slopes that can be detected with 80% power using the data through 2014, assuming that 1) onset age will be available each year and data for the other measures will be available for cohorts incident in 2002-2006, 2008, and 2012; 2) the sample sizes for onset age and for variables of interest among T2D youth will remain constant; and 3) the sample size for variables of interest among T1D youth will remain constant between 2002 and 2008 and will be 5/6(N) for 2012 (due to sampling only 50% of the NHW age <10 years). For example, there are about 970 incident T1D cases per year with an IPV in our surveillance area. The mean age of newly diagnosed T1D cases in 2002 was 9.4 years with a standard deviation of 4.7 years. Using data through 2014, we can detect a yearly change in onset age of 0.031 years (e.g., 9.4 in 2002 vs 9.0 in 2014). Approximately 84% of T1D had evidence of autoimmunity in 2002. With a sample size of approximately 440 for diabetes autoimmunity each year it is collected, we'll be able to detect a change of 0.6% per year (e.g., 84% in 2002 vs 90% in 2012).

Table 6.2 - Changes in Clinical Presentation, By Type, Detectable with 80% Power in 2014

Variable	Mean (SD)	N per year	Detectable change
T1D			
Onset Age (years)	9.4 (4.7)	970	0.031
BMI-z	0.6 (1.0)	500	0.015
HbA_{1c} (%)	7.9 (1.6)	470	0.025
Insulin Sensitivity	10.3 (3.3)	430	0.054
FCP (ng/ml)	0.5 (0.5)	470	0.008
Autoimmunity (%)	84% (36%)	440	0.006
DKA (%)	30% (46%)	760	0.006
T2D			
Onset Age	14.3 (2.8)	250	0.037
BMI_z	2.1 (0.7)	85	0.026
HbA_{1c}	7.5 (2.4)	85	0.088
Insulin Sensitivity	4.6 (2.8)	75	0.109
FCP (ng/ml)	3.3 (1.9)	85	0.069

6.3. INFORMING SUSTAINABLE SURVEILLANCE

To address this aim, we are proposing to provide consultation and support to the CDC and the NIH for the development of low-cost, sustainable public health surveillance systems for diabetes in children. Based on our experience we know that efficient and complete ascertainment of cases of T2D in youth, and ascertainment of cases of diabetes in older youth present significant challenges. We are proposing two approaches to better understand the

underlying systems of care in order to define best practices for case ascertainment. The first builds on data that has been collected over the past 10 years of the SEARCH study as well as data to be collected in SEARCH 3; the second compares data collected by one of the existing six SEARCH centers - a HMO (KPSC) - with analogous data collected by a large integrated multi-payer system (UNC).

6.4. EVALUATING CASE ASCERTAINMENT STRATEGIES: ANALYSIS OF SEARCH REGISTRY DATA

For research question 2.1, we will evaluate (a) whether a longer period of calendar time is required to ascertain cases of youth with T2D or older youth with any type of diabetes than youth with T1D and younger youth; (b) whether any calendar time difference in ascertainment by diabetes type and age can be accounted for by the time from clinical diagnosis to hospitalization or receipt of specialty care services; and (c) if there are temporal changes in observed differences in time to case ascertainment. Date of diagnosis, date of birth, sex, clinical diabetes type, type of health care provider (pediatric endocrinologists, pediatricians, family practice physicians, adult endocrinologists) and the system in which each youth with diabetes received their care (community clinic, university based health system, managed health care organization) around the time of diagnosis are obtained from the medical record, the IPS, or administrative data sources at the time of case validation. Calendar time from date of diagnosis to date of case registration will be calculated in months so that time from diagnosis to registration can be compared by type within each category as well as within type by age category.

Using this information from SEARCH registered cases we will be able to quantify the timing and completeness of case ascertainment under a variety of scenarios. For example, we can simulate specific ascertainment scenarios to compare the completeness of ascertainment of youth with T1D versus T2D by age category if a system relied solely on pediatric endocrinology and hospital-based surveillance networks as compared to if a system that relied on these sources plus primary care providers. We will identify efficient ways to optimize ascertainment of youth with T1D or T2D, using data collected to date by the SEARCH study and through the 2011 incident cohort. This approach goes beyond examining variation by study centers and takes advantage of the diversity within and between the existing SEARCH study centers which conduct ascertainment state-wide (SC, CO), in defined regions (WA, OH), from enrollees in managed health care organizations (CA), and from enrollees in IHS facilities.

6.5. MORTALITY ANALYSIS COMPONENT

Crude mortality rates per 1,000 person-years (p-y) will be calculated, and Poisson and Cox proportional hazards regression analyses will be used to evaluate predictors of mortality (e.g., DM type, race/ethnicity, insurance type). Using the mortality rate of 2.50/1,000 p-y from the Chicago DM registry cohort study [3], we estimate that we will have 117 deaths in the SEARCH cohort. We will calculate the Standardized Mortality Ratio (SMR) comparing the SEARCH cohort to mortality data from the geographic areas from which the SEARCH sample participants are drawn, accounting for the demographic distribution of the cohort with DM.

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6. Statistical Considerations

There will be four main analytic approaches: 1) estimation of incidence rates of complications (Aims 1 and 2); 2) estimation of prevalence of complications (Aims 1 and 2); 3) longitudinal evaluation of predictors of outcomes and conditions, including consideration of potential mediators and moderators (Aims 1, 2 and 4); and 4) evaluation of mortality rates, including comparison with age-comparable non-diabetic youth (Aim 3). Here we provide selected examples to illustrate analytic strategies and to provide key information regarding sample size and detectable differences.

6.1. STATISTICAL ANALYTIC METHODS

6.1.1. *Incidence Rate Estimation*

Because all SEARCH Cohort Study participants will have had at least one previous SEARCH in-person visit, we will be able to define a group of participants who were free from the event of interest (i.e., normotensive) at "baseline". Multiple logistic regression methods will be employed to examine the incidence rates of binary measures (e.g., hypertension) of interest. Predictors can include categorical or continuous variables. A continuous variable that measures the time between visits for each participant (to account for the fact that individuals will have different lengths of follow-up) and the predictor- by-time interaction will be included. Next, we will expand the logistic regression model to include other participant level characteristics (e.g., SEARCH clinical center, age, and gender [a "demographically adjusted model"]). We will then expand the model to adjust for other covariates. In addition, we will examine potential interactions; if significant interaction is present, analyses will be performed stratified by that characteristic.

6.1.2. *Prevalence Estimation*

Some of the outcomes of interest will not have been measured during SEARCH 1 or 2, such as outcomes including retinopathy and neuropathy. Therefore, prevalence of these outcomes will be estimated. Models to evaluate cross-sectional associations of risk factors will use logistic regression and will proceed as described above to account for potential confounding or effect modification.

6.1.3. *Longitudinal Models*

All participants in the SEARCH Cohort Study will have already had at least one in-person visit during SEARCH 1 and 2, and ~75% of the 2002-2005 incidence cases have at least 2 in-person visits per the SEARCH 2 protocol. Since SEARCH 2 also included longitudinal data (there are over 2000 SEARCH participants already with at least one follow-up visit), our team developed a plan for modeling longitudinal data. Specifically, we will use longitudinal mixed effects analysis of covariance models that always include duration of diabetes as a time-varying covariate. This approach correctly models the varying durations of disease prior to the initial SEARCH in-person visit, and the varying

durations of time allowed via the SEARCH data collection windows between the initial and subsequent visits.

The initial model will examine outcomes (measured previously between 1 (baseline) and 4 times (baseline, 12, 24, 60 mo visits) and once during the SEARCH Cohort Study visit), the predictor of interest (e.g., DM type), the duration of diabetes at each measurement time and the predictor-by-diabetes duration interaction. These models will then be expanded to include demographic information (e.g., sex) that would be considered as fixed/non-time varying effects. In addition, based on our experience with performing these longitudinal analyses on the SEARCH 2 cohort, we also propose to consider treating the exposure (predictor) of interest as a time-varying covariate in these models as well. This will allow the time-varying correlation of the predictor to the outcome of interest to be modeled correctly. We will also consider adding other time-varying covariates (e.g., BMI z-score) into these models as needed to examine the specific relationships being studied. These mixed effects models also are flexible to allow for potentially non-linear relationships to be modeled over time, and 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. 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 repeated measurements, an unstructured covariance matrix can often provide for the most efficient estimation of model parameters.

For analysis of longitudinal discrete outcomes (e.g. transfer of care from a pediatric to adult provider), we will use the generalized estimating equation (GEE) approach to fit logistic or log-linear models that account for the dependency between repeated measures. GEE techniques allow estimation of model parameters and their 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, and between the marginal mean and covariates.

6.1.4. *Mediation Modeling*

For some of the analyses described above we will need to carefully assess the potential effects of mediators on the relationships we are examining. We will use mediation models as described by Baron & Kenny [(1)] in which a series of ANCOVA models are fit regressing: 1) outcome on exposure (Model 1); 2) mediator on exposure (Model 2); and 3) outcome on both mediator and exposure (Model 3). A change in the estimate of the exposure effect from Model 1 to Model 3 is evidence of mediation. We will use bootstrap methods for significance testing of the mediation effect and for calculating confidence intervals [(2)].

What is particularly exciting about using the SEARCH Cohort study is that potential mediator data will be measured at least at two time points. For instance, we can examine potential differences in access to care (a potential mediator) at particular points in time in relation to outcomes of interest. In addition we can form models that incorporate several potential mediators simultaneously (e.g., access to care and physical activity). Procedures, such as examining eigenvalues, discussed in Belsley, Kuh, and Welch [(3)] and Kleinbaum, Kupper and Muller [(4)] will be used to identify problems with multicollinearity and appropriate steps will be taken to reduce the problem.

6.1.5. *Missing Data Considerations*

We utilize the sequential data collection of the SEARCH protocol to statistically adjust for potential selection bias related to response rates or other reasons for missing data. Variables determined to predict loss to follow-up will be included in our predictive models in order to satisfy the conditions for the data to be considered "Missing at Random" (MAR) [(5)]. 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). A growing body of literature describes two alternative approaches to handle this potential problem: explicit modeling of the censoring mechanisms [(6 - 12)] and pattern-mixture models [(13)]. 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 [(14)]. This will provide useful information to allow us to understand the potential limitations we may have to interpret results in the presence of informative censoring.

6.2. POWER ANALYSIS

Based on our calculations from SEARCH 1 and 2 we anticipate that at least 3,288 subjects will participate in the SEARCH Cohort Study in-person visit, and therefore the calculations below use that sample size as the starting value for estimating power and detectable differences.

6.2.1. *Incidence Rate Estimation*

To estimate power for this component we first had to estimate the proportion of participants who would be free of the condition at their initial in-person visit during SEARCH 1 and 2. Table 6-1 shows the expected sample sizes available for comparing incidence rates between subgroups under two scenarios: 1) proportion in subgroups are 86% versus 14% (the proportions of T1D and T2D), and 2) proportion in subgroups are 65% versus 35% (the proportions of NHW and all others).

Table 6-1: Expected Sample Sizes Available for Comparing Incidence Rates between Subgroups Under Two scenarios

	Scenario 1		Scenario 2	
Outcome (% of participants **free** of condition at initial SEARCH visit)	Subgroup A (86%)	Subgroup B (14%)	Subgroup A (65%)	Subgroup B (35%)
	Expected number of participants free of outcome at initial visit			
Hypertension (92%)	2504	423	1893	1019
Obese (bmi-z $\geq$ 95th%ile) (76%)	2069	349	1564	842
High LDL ($\geq$ 100) (57%)	1511	262	1173	631
High ACR ($\geq$30 (90%)	2450	414	1852	997
Hypoglycemia in last 6 months (91%)	2477	418	1872	1008
DKA in last 6 months (85%)	2314	391	1749	941

Using this table we can determine detectable differences for each outcome/group comparison for a variety of plausible scenarios for incidence rates. Table 6-2 illustrates detectable differences assuming a two group continuity corrected chi-square test for a variety of scenarios with alpha=0.05 (2-sided).

Table 6-2. Detectable Differences in Selected Outcomes Assuming a Two-Group Continuity Corrected Chi-square Test for a Variety of Scenarios with Alpha=0.05 (2-sided)

	Scenario 1: Example T1 vs. T2		Scenario 2: NHW vs. Other	
Outcome	Incidence Rate for T1	Detectable Rate for T2 (Power)	Incidence Rate for NHW	Detectable Rate for Other Race/Ethnic Group (Power)
Hypertension	6%**	10% (80%)	6%**	10% (96%)
	12%	18% (88%)	12%	17% (95%)
Obese	5%	10% (90%)	9%	14% (95%)
	10%	16% (86%)	19%	25% (91%)
High LDL	23%	32% (84%)	14%	20% (89%)

	33%	43% (85%)	24%	31% (87%)
High ACR	9%	15% (93%)	5%	8% (86%)
	19%	26% (87%)	10%	14% (87%)
Hypoglycemia in last 6 months	11%	17% (90%)	23%	28% (82%)
	21%	28% (86%)	33%	39% (88%)
DKA in last 6 months	15%	21% (81%)	9%	13% (87%)
	25%	32% (80%)	19%	24% (84%)
** First incidence rate reflects observed incidence rate in SEARCH 1 and 2 for follow-up visits already measured.				

Based on this table, we see, for instance, that there is 90% power to detect a difference between Type 1 and Type 2 participants on their rate of incident obesity if the rate of incident obesity is 5% in the Type 1 group and 10% or higher in the Type 2 group. Likewise, there if the rate of obesity were 9% in the NHW group then there is 95% power to detect a "Other" race/ethnic group rate of 14% or higher. The above calculations should be conservative since when we adjust for participant level characteristics in our models we should reduce variability and increase precision as we estimate the difference in incidence rates between groups.

6.2.2. *Prevalence Estimation*

Unlike the incidence rate comparison, all SEARCH Cohort Study participants can be used for the prevalence rate analyses since the incident rate calculations need to remove participants who have the outcome present at visit 1 from the analyses. With this in mind we estimate that there will be 3166 participants available to contribute to prevalence rate estimates. Based on this, Table 6-3 shows a variety of scenarios for detectable differences comparing groups (i.e., type 1 vs type 2, non-Hispanic white vs others, etc) using a chi-square test to compare groups with alpha=0.05 (2-sided).

Table 6-3: Scenarios for Detecting Statistical Differences in Prevalence of Retinopathy and Neuropathy

Outcome	316/2849		473/2692		2112/1049 (Anticipated NHW vs. Other Race Split)	
	Percentage with trait in smaller group					
	10%	20%	10%	20%	10%	20%
	Detectable Difference (Power)					
Retinopathy	.16 (81)	.28 (86)	.15 (82)	.27 (89)	.14 (89)	.25 (88)
	5%	15%	5%	15%	5%	15%
Neuropathy	.10 (85)	.22 (83)	.09 (84)	.21 (85)	.08 (88)	.20 (93)

Based on this table, we see that there is 81% power to detect a difference between Type 1 and Type 2 participants on their prevalence of retinopathy: 10% in the Type 1 group and 16% or higher in the Type 2 group, a realistic potential comparison given early pilot findings of 18% of youth with evidence of DR among the first 38 evaluated.

6.2.3. *Longitudinal Models Component*

For the purposes of estimating the sample size needed to detect a significant difference with sufficient power, calculations were based on comparing measurements after adjusting for visit 1 data. These calculations need to account for the proportion of the variance in the outcome that is explained by the visit 1 values. Although our full longitudinal models will incorporate all intermediate time points into the final analysis, our power calculation is based on examining the difference in the outcome of interest adjusting only for the visit 1 assessment of the outcome. Therefore, these power calculations will be conservative, since the additional information provided by the intermediate assessments of outcome measures are not included.

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

The following formula was used to describe the minimum detectable difference in terms of standard deviations between the participants in groups (i.e., Type 1 versus Type 2). In the formula, r2 is the percent of the variance of the follow-up outcome explained by the visit 1 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 (i.e. systolic blood pressure), n_1 is the number of participants in the Type 1, k is the ratio of n_1/n_2 (sample size in type 1 and type 2 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 1 and 2, standard deviations for systolic blood pressure, BMI - Z-scores and LDL cholesterol were estimated as 12.7, .85 and 29, respectively. Using these numbers, Table 6-4 describes the detectable differences if there were 450 participants in the Type 2 group and 2711 in the Type 1 group.

Table 6-4: Detectable Differences in Systolic Blood Pressure, BMI Z-Score and LDL-Cholesterol Given 450 Type 2 Participants 2711 Type 1 Participants				
Detectable Differences with 80% Power	Correlation Between Baseline and Follow-Up Measures			
Sample Size (n_1/n_2) (2711/450)	.50	.65	.75	.86
Systolic Blood Pressure	1.57 mmHg	1.38 mmHg	1.20 mmHg	0.95 mmHg
BMI (Z-Score)	.11 (SD)	.09 (SD)	.08 (SD)	.06 (SD)
LDL-Cholesterol	3.58 mg/dl	3.14 mg/dl	2.73 mg/dl	2.18 mg/dl

As can be seen, if the correlation between the baseline and follow-up measurements is moderate (.50) then we have 80% power to detect a difference of 1.51 mmHg for the Type 1 versus Type 2 comparison of blood pressure change. As stated above, these estimates should be conservative because 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.

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SEARCH Phase 3 Protocol - Section 7
Data Management
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7. Data Management

The most popular method of developing a data management system is to use remote data entry through a web-based interface. This method was used for the SEARCH Phase 1 and 2 and will continue to be used in SEARCH Phase 3. The WFUSM SEARCH Coordinating Center (CoC) data management system operates on a web browser 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 SQL Server data warehouse. Front-ends were built using HTML and ColdFusion 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, centers are encouraged to use a recent standards-compliant browser such as Firefox, Safari, Opera or Internet Explorer.

In this model, the clinic staff uses a PC to access the study website and enter the data directly. 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 and/or reports are generated at the time of data entry to alert the project managers of outstanding data entry issues.

7.1. QUALITY CONTROL

The WFUSM SEARCH CoC is responsible for developing and implementing quality control (QC) procedures. QC techniques are incorporated into each phase of the study from case ascertainment, recruitment and registration of persons with diabetes through data acquisition, reading and/or interpretation of the results and their analyses and publication. The CoC 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.

7.2. DATA ENTRY

A web-based application for study data entry was implemented for SEARCH in Phase 1 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.

7.3. ELECTRONIC FORMS

Electronic forms will be used for SEARCH Phase 3. 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 participant ID, the staff member is given a list of forms that can be entered or edited. After the selection is made, the form is displayed and any existing information is 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 is housed at the individual study centers. Data will reside on the database server at the CoC in a Windows SQL Server database.

7.3.1. *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. Reports of these errors are provided 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.

7.3.2. *On-site Monitoring*

Center visits to the SEARCH study centers are conducted based on a timeline developed by the SEARCH Protocol Oversight Committee. Clinics may be selected for extra center 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 centers is poor, the Protocol Oversight Committee may recommend a special center visit for of the Center to assist in identification and correction of data quality issues. Center visits 1) provide a means for continual training, retraining and reinforcement of standard study procedures; 2) enhance communication between the study centers 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 center visits. These center visits include auditing of data collection/entry results received by the CoC for randomly selected participants. The study centers and laboratories are sent a list of the randomly selected participants and requested to have the clinic records and participant 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 participant 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 center visit. An audit visit summary is presented to the Protocol Oversight Committee. The review of ten participant records at each center visit should be adequate, unless the study center has been targeted for more extensive review due to previous problems.

7.3.3. *Clinic Performance Monitoring*

The SEARCH CoC will continue to provide feedback to clinic staff through the internal website with regard to clinic performance in ascertainment of IPS, participant 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.

7.3.4. *Server Management and Data Center (Security)*

The servers involved in this project are contained within a secure data center with environmental controls which detect abnormal conditions such as power outages, high heat or humidity, and loud sound. In the event of an abnormal condition, the system contacts three (3) individuals to notify them of the alerts.

The data center has several secure access points that are accessible only by a badge reader. Only authorized staff will have accessible badges to these areas. The building is surrounded by a 10 foot fence with a gate access through badge control. The outside building door is accessed through badge control. The data center room is housed in a locked computer room that is accessed through badge control. Each of these access controls is in place 24 hours a day and seven days a week.

All servers have uninterruptible power supplies (UPS). The building has a backup generator that will automatically initiate in the event of a power failure.

The computer room is equipped with fire suppression equipment. This equipment is tested on a scheduled timetable by the institution. The entire Data Center is fire-protected by a clean agent system which is backed up by a dry-pipe pre-action sprinkler system. The Data Center room is located on the second floor of the building in an area with no windows and has a raised floor to protect against flooding.

The system is protected by a Cisco firewall and is located in a secure DMZ. Servers are protected by institution supported and maintained intrusion detection software as well as by SecureIIS which monitors incoming server traffic.

7.3.5. *Backups (Disaster Recovery)*

Nightly backups, moved offsite regularly, will be made of all data and stored in secure fireproof cabinets. The backup schedule consists of full monthly backups and nightly incremental backups. Backup tapes are kept indefinitely and therefore tapes are not rotated. Backup tapes are handled by two system administrators. Tapes are transported to offsite storage in locked containers and are stored in file proof cabinets.

Tapes are identified by unique bar code labels accessible only by the systems administrators. This is the only information on the tape label.

The backup system stores the information for each bar code with details of directories/files backed up that includes the date and time of backup. The backup system, when needing to restore files, will identify which tape is needed based on the bar code label. Only designated system administrators can restore the backup tapes.

Tapes are transported by one of two identified tape custodians. The tapes are put in a metal, locked box and then transported from the data center to the offsite storage facility. At all times during the transport, one of the tape custodians is present with the locked box of tapes.

7.3.6. *Tracking and Monitoring of Laboratory Data*

Study centers log each shipment of specimens sent to central laboratory by use of barcode labels that it will attach to all samples prior to shipment. Once samples are received at the central lab, they are scanned into the central laboratory database. This same process

is used when the Central Laboratory sends samples to an outside laboratory for testing. 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.

7.3.7. *Tracking and Reporting of Study Data*

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 centers. In addition, a variety of online reports are constructed for use by the study centers, 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.

7.3.8. *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.

7.3.9. *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 SEARCH clinical centers.

7.3.10. *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 participant 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.

Data will be released to the funding agencies in a timely fashion. The SEARCH Steering Committee will develop a plan for the sequential release of data during the study and will the release of the final dataset according to federal guidelines.

Data will be transmitted electronically between the SEACH CoC and the Ocular Epidemiology Reading Center and the Central Laboratory.

7.3.11. *Data Destruction*

7.3.11.1. 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.

7.3.11.2. 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.

7.3.11.3. Destruction of paper records

Paper records containing confidential information should be destroyed using a secured method and not depositing into standard trash receptacles.

7.3.11.4. 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 is fairly easy for computer specialists to do "hard drive," using commercially available software applications. When properly applied, these tools prevent the reconstruction of any data formerly stored on the hard drive. Floppy disks, data stored on CD-ROM’s, or on back-up tapes should be physically destroyed.

7.3.11.5. 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.

SEARCH Phase 3 Protocol - Section 8A
Registry Study
Human Subjects
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8. Human Subjects

8.1. GOALS

In this section, we will outline the study's plans to:

a. to obtain the highest level of informed, voluntary participation from eligible persons with diabetes and their parents/guardians (if they are <18 years of age);

b. to follow all local and national human subjects regulations;

c. to respects the wishes of the person with diabetes and their parent/guardian, regarding participation, continuation in study, and receipt of clinically relevant test results;

d. to protect confidentiality;

e. to ensure safety of participants relative to completion of the study measures; and,

f. to ensure fair and equal treatment of all participants and their parents/guardians when applicable.

8.2. OVERVIEW: BACKGROUND INFORMATION

SEARCH Phase 3 will be conducted in two components, a Registry Study and a Cohort Study. Both components will be completed at all five SEARCH clinical centers, and the Coordinating Center and Central Laboratory will be the same for both components. No individual will be excluded on the basis of gender or race/ethnicity. Since the focus of this study is to learn more about the impact of diabetes on people who are less than 20 years of age at the time of diagnosis, this study includes children, adolescents, and young adults. This study does not involve fetuses, neonates, prisoners, or institutionalized individuals. Young women, who are pregnant and eligible for the study, will not be scheduled to participate in an in-person visit (IPV) until at least six weeks after the completion of the pregnancy.

The SEARCH Registry Study will involve ascertainment of cases diagnosed in the calendar years 2010 - 2014. Registered cases in all five incident years will be asked to complete an initial participant survey (IPS). The survey will be used to validate a diagnosis of diabetes, to confirm study eligibility, and to obtain essential core data elements. For the incident years 2011 and 2013, potentially eligible participants will be invited to participate in a baseline (IPV). Cases of secondary diabetes or any other specific types of diabetes, however, will be excluded from the study visit. Local study personnel will send study newsletters and conduct other local activities in order to try to maintain contact with these cases to allow for recruitment of these persons for future ancillary studies.

Based on previous SEARCH incidence data, we anticipate approximately 1,316 new cases of diabetes to occur per year in the base populations of these five centers. Therefore, we anticipate a total of approximately 6,000 new cases to be identified and registered for the

period throughout the grant period. This includes the 2010 cases that would be identified and registered starting September 30, 2010. We will attempt to have an IPS completion rate of 90% of all registered participants. We also anticipate approximately 1,700 participants will be involved in the IPV for the 2011 and 2013 incident years.

8.3. PROTOCOL DEVELOPMENT AND MAINTENANCE

The study protocol will be standardized across five centers. Information will be obtained from multiple sources: Medical Records, IPS, IPV (including physical exam, questionnaires, laboratory studies of blood and urine). Forms used for data collection will be distributed to the Study Centers 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 but no personal (such as name, social security number, medical record number, contact information, etc). Subject identifiers will be maintained in a separate file, which is maintained and protected locally.

Methods of recruitment and data collection may vary between centers. Centers will obtain local IRB approval, and follow local IRB regulations.

Model consent, assent forms and subject recruitment material will be prepared by the human SEARCH human subjects committees, translated into Spanish by a certified translator before sending to the centers so that they can be further customized and submitted for approval by the local IRB committees.

The Coordinating Center will be responsible for obtaining approval for the Federal Office of Management and Budgets for the conduct of the study.

8.4. CENTER SPECIFIC GUIDELINES

Each of the five centers 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 participant'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. All Spanish translations will be done by certified translators. Materials will be provided in additional languages as determined by the local study population demographics. No potentially eligible subject will be excluded based on language.

8.5. RECRUITMENT AND METHODS TO ENTER STUDY

The goals of recruitment are to maximize enrollment while respecting the voluntary nature of clinical research. Recruitment will take place at a number of levels: person with diabetes and their family, community (e.g., diabetes support groups, school nurses, and television/newspaper) and health care providers. Methods of recruitment will vary by center. All recruitment materials will be developed in collaboration with the CoC and may be customized by local centers. Recruitment materials will require local IRB approval. Also,

centers 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 local study personnel contact information. They will be assured that the SEARCH study will not interfere with their relationship with their participants. Each center will have a provider network that will be specific to that center. Centers will use existing methods (with enhancements over time when applicable) to conduct efficient, timely surveillance of incident cases of diabetes. Identifiers will be maintained by the local SEARCH personnel and not submitted outside the local center.

8.6. 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.

8.7. RESEARCH MATERIALS

All incident cases of diabetes in the study clinical center areas age less than 20 years will be invited to complete the IPS and, of those who complete an IPS whose diabetes is not known to be secondary to other conditions, will be invited to participate in the IPV.

8.7.1. *Case Registration*

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

8.7.2. *Collection of Core Variables*

A minimum amount of demographic and clinical information will be collected for all registered cases in order for the study to be able to provide population-based rates of diabetes mellitus by age, gender, diabetes type and race/ethnicity for the entire population of cases. This information is also critical in assessing possible response bias to the in person research visit. This information is called "core" information.

8.7.3. *Medical Record Abstraction (MRA)*

The Medical Record Abstraction (MRA) serves the following purposes: a) validation of diabetes diagnosis; b) main source of core demographic and diagnostic information, and c) secondary data source for race/ethnicity information. Additional set of items pertinent to clinical presentation will be collected: weight/height at diagnosis, DKA at diagnosis, insulin use history.

8.7.4. *Initial Participant Survey (IPS)*

The Initial Participant Survey (IPS) contains key data, including the core information described above, and serves the following purposes: a) verification of case eligibility (e.g., residence in the year of diagnosis); b) main source for self-reported race/ethnicity. Additional information includes: symptoms at presentation, potential secondary causes of the diabetes, use of insulin and other medications, treatment history, family structure, usual language spoken, and contact information (for local use only).

8.7.5. *In-Person Research Visit (IPV)*

The IPV for of SEARCH 3 was designed to collect data on relevant dimensions of diabetes type (presence of autoimmunity, genetic susceptibility to autoimmunity, insulin sensitivity, insulin secretion) and data informing the clinical presentation of diabetes in youth. Only cohorts incident in 2011 and 2013 will be eligible to participate in the IPV. To maximize the number of minority participants and youth with T2D, cases that will be eligible to participate in the SEARCH 3 IPV are 100% of minority youth, regardless of age and type, 100% of youth age ≥10 years at diagnosis, regardless of race/ethnicity and type, and 50% of NHW youth age < 10 years who have type 1 diabetes. The content of the IPV will be similar to SEARCH 1 and 2 and will consist of collection of fasting blood and urine for laboratory measurements and storage and a physical examination.

- Measurements made to inform dimensions of diabetes type are DA (GAD65, IA-2 with the proposed addition of the novel ZnT8 antibody, once assays are standardized);
- Validated insulin sensitivity index (waist circumference, HbA_{1c}, triglycerides);
- Urinary albumin and creatinine;
- Standard lipid measures;
- HLA risk genotypes and fasting C-peptide (FCP) (plasma glucose will be measured in order to interpret FCP);
- The IPV physical examination, conducted on children over the age of 3 years, 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. Height will be measured in centimeters using a

stadiometer. Weight will be measured in kilograms using an electronic scale. Blood pressure will be measured using the aneroid sphygmomanometer. The NHANES and natural waist methods will used to measure waist circumference.

8.8. STUDY DATA

Each newly diagnosed case will be assigned a unique SEARCH identification number and this SEARCH identification number will be used in order to link data across multiple visits. Each of the five SEARCH centers will maintain person's 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 SEARCH Coordinating Center (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 centers will enter into a Limited Data Use Agreement with the CoC in compliance with the Standards of Privacy of Individually Identifiable Health Information as outlined by the HIPAA privacy rules. Local access to person's 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 as de-identified to the HIPAA standard. Laboratory personnel are not able to identify individuals based on the information sent to them.

8.9. CONSENT FORMS

The model consent and assent forms developed by the SEARCH study staff 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 of age at the time of the survey or study visit. Participants 18 years of age 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 consent to release test results to health care provider(s)

i) Availability of information

j) Right to withdraw

k) Additional elements of consent

l) Any additional text required by the Center

m) Witnessing and signatures

8.10. ASSENT

The age of assent and the method of obtaining assent will be defined and conducted in accordance with the guidelines of the local IRB.

8.11. PARTICIPANT REMUNERATIONS

Participants will receive monetary compensation commensurate with level of involvement and effort. Participant remunerations will be of equal monetary value across centers, with the amount noted in earlier sections of the study protocol. However, the way this remuneration is distributed, e.g., type of gift certificates, checks, etc., will vary across centers, and will be in accordance with local IRB and financial regulations.

8.12. PARTICIPANT SAFETY

Participant safety will be monitored through center specific guidelines. Study-related adverse events will be documented on the Event Reporting Form and submitted to the Coordinating Center. An external reviewer will review all events reported on the Event Reporting Form and report findings to the SEARCH Protocol Oversight Committee.

8.13. RESULTS

Participants (or their parent/guardian if <18 years of age) will be given all clinically relevant test results based on samples collected during their study visits. Transmission of results will be based on the age of the participant at the time that the results become available. If the participant's parent agreed to have the samples drawn but the participant is at least 18 years of age when the results become available, then the participant will be notified of the results.

Participants (or their parent/guardian if <18 years) will be asked whether or not they wish their diabetes and/or primary care provider(s) to receive their clinically relevant test results such as: HbA_{1c}, lipid profile, C-peptide, DAA, microalbumin, and glucose. 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, 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 participant or his/her parent/guardian if <18 years of age, as well as the provider if permission was given at the time of the study visit.

Information from interviews (general interviews and supplemental interview conducted with youth ≥ 10 years) will NOT be shared with parents or guardians with one exception. If the alert value for the Centers for the Epidemiologic Studies of Depression (CES-D) scale is reached, the center personnel will offer participants (and their parent/guardian if <18 years of age) assistive referrals.

Participants who are ≥ 10 years at the time of the interview will be administered a supplemental survey. This survey includes questions related to eating disorders. Parents will be allowed to review the survey before it is completed by their child and will be asked to waive their right to review their child's answers. If they refuse to waive their rights to review, the supplemental survey will not be administered. Youth ≥ 10 years will also be asked to complete the CES-D scale as described above.

8.14. PARTICIPANT RISKS AND BENEFITS

For all centers, potentially-eligible participants will be identified by a network of reporting health care providers. Some centers may also identify potential cases by linkage of confidential clinical and administrative data systems such as those generated based on information in the electronic medical record. Participant identification and registration will be conducted in a manner that is HIPAA-compliant and according to the requirements of the local IRB and minimizes the risk of loss of privacy.

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. Some centers may also mail survey or linkage to the survey on-line as a part of this introductory letter. After mailing this introductory letter, a designated member of the local research team or a survey research company working in collaboration with the study center may call the parent/participant to complete the IPS. Consent requirements for completion of this survey will be governed by the local IRB.

Participants who are eligible to participate in the IPV will be contacted and 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 IPV, 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 IPV 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.

8.14.1. *Protection Against Risk*

To minimize the possibility of risks associated phlebotomy experienced medical staff will obtain the blood samples in accordance with local or state guidelines. A 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 may 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 (< 70 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 $\geq$ 70 mg./dl. If the blood glucose level is above 300 mg./dl., study personnel will be trained to check urinary ketones.

After the blood sample is obtained, their blood glucose level will be measured using their meter or one provided by the local staff and 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 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.

The CES-D scale is administered to identify participants who may be at increased risk for 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: 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 attempt to seek and obtain consent from these participants. Samples will not be tested if consent cannot be obtained or is explicitly denied. All clinically relevant results will be reported to the participant. Any future contact with participants will be based on their age at the time of contact. If the participant's parent agreed to have the sample stored but the participant is at least 18 years of age when additional consent is requested, then the participant will be contacted for this additional consent.

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 attempt to seek and obtain consent from these participants. Samples will not be tested if consent cannot be obtained or is explicitly denied. All clinically relevant results will be reported to the participant. Transmission of results will be based on the age of the participant at the time that the results become available. If the participant's parent agreed to have the samples drawn but the participant is at least 18 years of age when the results become available, then the participant will be notified of the results.

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 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 PHI will be used or disclosed in compliance with the Health Insurance Portability and Accountability Act (HIPAA). A limited amount of 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 five 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 plan to request a Certificate of Confidentiality from the appropriate federal entity. We applied for and received a Certificate of Confidentiality in SEARCH 1 and 2.

8.14.2. *Potential Benefits of the Proposed Research to the Participants 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.

Potential risks to study participants are minimal and reasonable in relation to the anticipated benefits to society from the knowledge that will be gained from this study.

8.14.3. *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 that are developing diabetes seems to be increasing over time.

This is a large, multi-center study that will be well-represented by youth from a variety of racial/ethnic backgrounds. The information obtained in this study will help clinicians and researchers better understand the prevalence and incidence of childhood diabetes, the characteristics of persons with 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.

Potential risks to study participants are minimal and reasonable in relation to the importance of the knowledge that is expected to be gained from this study.

8.14.4. *Data and Safety Monitoring Plan*

Even though this study is not a clinical trial, an internal Protocol Oversight Committee (POC) has been established for SEARCH to: 1) oversee personnel training and certification procedures to assure consistency of measurements among all 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 reviews the activities of the studies, based on reports from the POC. The external monitor will provide interim and annual safety reports to the Director of the Coordinating Center and the POC. 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 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, the Coordinating Center, 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.

8.15. REPOSITORY

Testing related to diabetes is limited to basic testing as mentioned in Section 6A and 6B. 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.

8.15.1. *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.

8.15.2. *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.

8.15.3. *Sample Maintenance*

8.15.3.1. 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 Principal 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 for his or her study center.

8.15.3.2. Sample Destruction

Individual participants (or their parents if participants are < 18 years old) when sample destruction is desired) 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). Any analyses done on their samples before the data the request is received will remain in the study dataset.

8.15.3.3. Use of Repository Samples

Samples will be made available (with Executive Committee approval) 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 which require a review by the Ancillary Studies Committee. Distribution of samples by the laboratory will be only by direction of the executive committee.

8.16. 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 Ancillary Studies Committee and the Executive Committee. Publications based on Ancillary Studies must be approved by the Publications and Presentations Committee. Involvement in the ancillary studies will vary by study center. Each ancillary study will require separate IRB approval, and a separate source of funding.

8.17. 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. Participants are asked at each visit if they would like to be contacted for future studies. Annual contact will be made with participants or their parent/guardian (if ≤ 18 years of age) to update information such as address and telephone numbers. Participants who withdraw from the study will not be contacted for future studies.

SEARCH Phase 3 Protocol - Section 8B
Cohort Study
Human Subjects
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8. Human Subjects

8.1. GOALS

In this section, we will outline the study's plans to:

a. to obtain the highest level of informed, voluntary participation from eligible persons with diabetes and their parents/guardians (if they are <18 years of age);

b. to follow all local and national human subjects regulations;

c. to respects the wishes of the person with diabetes and their parent/guardian, regarding participation, continuation in study, and receipt of clinically relevant test results;

d. to protect confidentiality;

e. to ensure safety of participants relative to completion of the study measures; and,

f. to ensure fair and equal treatment of all participants and their parents/guardians when applicable.

8.2. OVERVIEW: BACKGROUND INFORMATION

SEARCH Phase 3 will be conducted in two components, a Registry Study and a Cohort Study. Both components will be completed at all five SEARCH clinical centers, and the Coordinating Center and Central Laboratory will be the same for both components. No individual will be excluded on the basis of gender or race/ethnicity. Since the focus of this study is to learn more about the impact of diabetes on people who are less than 20 years of age at the time of diagnosis, this study includes children, adolescents, and young adults. This study does not involve fetuses, neonates, prisoners, or institutionalized individuals. Young women, who are pregnant and eligible for the study, will not be scheduled to participate in an in-person visit (IPV) until at least six weeks after the completion of the pregnancy.

The SEARCH Cohort study will involve follow-up in-person visits for all participants diagnosed in incident years 2002-2005, 2006, and 2008 in SEARCH Phases 1 and 2 and who completed a baseline visit as part of the previous SEARCH protocol that have had diabetes for at least 5 years. Youth who were eligible for a baseline visit under the previous SEARCH protocol, but who declined to participate in this in-person visit or who explicitly refused further contact or are known to be deceased; will not be asked to participate in follow up visits for this study. The IPV will involve the collection of data from medical record review (in a subset of participants), a physical examination, self-reported data on health behaviors, health care, and psychosocial factors, and the assessment of diabetic retinopathy, neuropathy, nephropathy and markers of cardiovascular disease.

A total of 3,699 youth with diabetes who were diagnosed in incident years 2002-2005, 2006, and 2008 have completed a baseline visit thus far as part of the previous SEARCH protocol. Therefore, approximately 3,700 individuals will be eligible for a follow-up in-person visit.

8.3. PROTOCOL DEVEOPMENT AND MAINTENANCE

The study protocol will be standardized across five centers. Information will be obtained from multiple sources: Medical Records, IPS, IPV (including physical exam, questionnaires, and laboratory studies of blood and urine). Forms used for data collection will be distributed to the Study Centers 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 but no personal (such as name, social security number, medical record number, contact information, etc). Subject identifiers will be maintained in a separate file, which is maintained and protected locally.

Methods of recruitment and data collection may vary between centers. Centers will obtain local IRB approval, and follow local IRB regulations.

Model consent, assent forms and subject recruitment material will be prepared by the human SEARCH human subjects committees, translated into Spanish by a certified translator before sending to the centers so that they can be further customized and submitted for approval by the local IRB committees.

The Coordinating Center will be responsible for obtaining approval for the Federal Office of Management and Budgets for the conduct of the study.

8.4. CENTER SPECIFIC GUIDELINES

Each of the five centers 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 participant'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. All Spanish translations will be done by certified translators. Materials will be provided in additional languages as determined by the local study population demographics. No potentially eligible subject will be excluded based on language.

8.5. RECRUITMENT AND METHODS TO ENTER STUDY

The goals of recruitment are to maximize enrollment while respecting the voluntary nature of clinical research. Recruitment will take place at a number of levels: person with diabetes and their family, community (e.g., diabetes support groups, school nurses, and television/newspaper) and health care providers. Methods of recruitment will vary by center. All recruitment materials will be developed in collaboration with the CoC and may be customized by local centers. Recruitment materials will require local IRB approval. Also, centers 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 local study personnel contact information. They will be assured that the SEARCH study will not interfere with their relationship with their participants. Each center will have a provider network that will be specific to that center. Centers will use existing methods (with enhancements over time when applicable) to conduct efficient, timely surveillance of incident cases of diabetes. Identifiers will be maintained by the local SEARCH personnel and not submitted outside the local center.

8.6. 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.

8.7. RESEARCH MATERIALS

All eligible individuals (incident years 2002-2005, 2006, and 2008 who completed a baseline visit as part of the previous SEARCH protocol) will be invited to participate in a follow-up in-person visit (F-IPV) after. The person has had diabetes for at least five years. The F-IPV will include the following research material:

- blood specimens: diabetes autoantibodies (GAD65, IA2, ZnT8); HbA_{1c}; C-peptide, and lipid levels; creatinine; fasting serum/plasma for storage; DNA for storage; and urine for albumin/creatinine;
- physical examination: height, weight, waist circumference, blood pressure, and presence of acanthosis;
- measure of microvascular complications of the eye: retinal photographs, using a non-midriatic camera;
- measures of peripheral neuropathy: Michigan Neuropathy Screening Instrument (MNSI) physical assessment: foot inspection (visual and tactile), vibration sensation (tuning fork), ankle reflex, and monofilament testing of the great toe;
- measure of autonomic neuropathy: using SphygmoCor;
- measures of vascular function: arterial stiffness by pulse wave velocity and augmentation index by non-invasive arterial tonometry, both using SphygmoCor;

- surveys and questionnaires to obtain data related to co-morbidities and complications, medical and family history, medication inventory, diabetes education, diabetes home care, quality of care, quality of life, insurance, parental education, and composition of household and income additional data will be obtained from individuals who are 10 years of age or older: tanner stage, physical activity, diet, , tobacco use, and depression;
- contact information: name of the person and her/his parents or guardians and alternate contacts, addresses, phone numbers, and e-mail addresses.

8.8. STUDY DATA

Each newly diagnosed case will be assigned a unique SEARCH identification number and this SEARCH identification number will be used for the Cohort Study in order to link data across multiple visits. Each of the five SEARCH centers will maintain person's 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 SEARCH Coordinating Center (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 centers will enter into a Limited Data Use Agreement with the CoC in compliance with the Standards of Privacy of Individually Identifiable Health Information as outlined by the HIPAA privacy rules. Local access to person's 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 as de-identified to the HIPAA standard. Laboratory personnel are not able to identify individuals based on the information sent to them.

8.9. CONSENT FORMS

The model consent and assent forms developed by the SEARCH Study staff 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 of age at the time of the survey or study visit. Participants 18 years of age 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 consent to release test results to health care provider(s)

i) Availability of information

j) Right to withdraw

k) Additional elements of consent

l) Any additional text required by the Center

m) Witnessing and signatures

8.10. ASSENT

The age of assent and the method of obtaining assent will be defined and conducted in accordance with the guidelines of the local IRB.

8.11. PARTICIPANT REMUNERATIONS

Participants will receive monetary compensation commensurate with level of involvement and effort. Participant remunerations will be of equal monetary value across centers, with the amount noted in earlier sections of the study protocol. However, the way this renumeration is distributed, e.g., type of gift certificates, checks, etc., will vary across centers, and will be in accordance with local IRB and financial regulations.

8.12. PARTICIPANT SAFETY

Participant safety will be monitored through center specific guidelines. Study-related adverse events will be documented on the Event Reporting Form and submitted to the Coordinating Center. An external reviewer will review all events reported on the Event Reporting Form and report findings to the SEARCH Protocol Oversight Committee.

8.13. RESULTS

Participants (or their parent/guardian if <18 years of age) will be given all clinically relevant test results based on samples collected during their study visits. Transmission of results will be based on the age of the participant at the time that the results become available. If the participant's parent agreed to have the samples drawn but the participant is at least 18 years of age when the results become available, then the participant will be notified of the results.

Participants (or their parent/guardian if <18 years) will be asked whether or not they wish their diabetes and/or primary care provider(s) to receive their clinically relevant test results such as: HbA_{1c}, lipid profile, C-peptide, DAA, microalbumin, and glucose. 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, 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 participant or his/her parent/guardian if <18 years of age, as well as the provider if permission was given at the time of the study visit.

Information from interviews (general interviews and supplemental interview conducted with youth ≥ 10 years) will NOT be shared with parents or guardians with one exception. If the alert value for the Centers for the Epidemiologic Studies of Depression (CES-D) scale is reached, the center personnel will offer participants (and their parent/guardian if <18 years of age) assistive referrals.

Participants who are ≥ 10 years at the time of the interview will be administered a supplemental survey. This survey includes questions related to eating disorders. Parents will be allowed to review the survey before it is completed by their child and will be asked to waive their right to review their child's answers. If they refuse to waive their rights to review, the supplemental survey will not be administered. Youth ≥ 10 years will also be asked to complete the CES-D scale as described above.

8.14. PARTICIPANT RISKS AND BENEFITS

For all centers, potentially-eligible participants will be identified by a network of reporting health care providers. Some centers may also identify potential cases by linkage of confidential clinical and administrative data systems such as those generated based on information in the electronic medical record. Participant identification and registration will be conducted in a manner that is HIPAA-compliant and according to the requirements of the local IRB and minimizes the risk of loss of privacy.

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. Some centers may also mail survey or linkage to the survey on-line as a part of this introductory letter. After mailing this introductory letter, a designated member of the local research team or a survey research company working in collaboration with the study center may call the parent/participant to complete the IPS. Consent requirements for completion of this survey will be governed by the local IRB.

Participants who are eligible to participate in the IPV will be contacted and 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 IPV, 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 IPV 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.

8.14.1. *Protection Against Risk*

To minimize the possibility of risks associated phlebotomy experienced medical staff will obtain the blood samples in accordance with local or state guidelines. A 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 may 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 (< 70 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 $\geq$ 70 mg./dl. If the blood glucose level is above 300 mg./dl., study personnel will be trained to check urinary ketones.

After the blood sample is obtained, their blood glucose level will be measured using their meter or one provided by the local staff and 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 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.

The CES-D scale is administered to identify participants who may be at increased risk for 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: 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 attempt to seek and obtain consent from these participants. Samples will not be tested if consent cannot be obtained or is explicitly denied. All clinically relevant results will be reported to the participant. Any future contact with participants will be based on their age at the time of contact. If the participant's parent agreed to have the sample stored but the participant is at least 18 years of age when additional consent is requested, then the participant will be contacted for this additional consent.

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 attempt to seek and obtain consent from these participants. Samples will not be tested if consent cannot be obtained or is explicitly denied. All clinically relevant results will be reported to the participant. Transmission of results will be based on the age of the participant at the time that the results become available. If the participant's parent agreed to have the samples drawn but the participant is at least 18 years of age when the results become available, then the participant will be notified of the results.

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 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 PHI will be used or disclosed in compliance with the Health Insurance Portability and Accountability Act (HIPAA). A limited amount of 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 five 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 plan to request a Certificate of Confidentiality from the appropriate federal entity. We applied for and received a Certificate of Confidentiality in SEARCH 1 and 2.

8.14.2. *Potential Benefits of the Proposed Research to the Participants 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.

Potential risks to study participants are minimal and reasonable in relation to the anticipated benefits to society from the knowledge that will be gained from this study.

8.14.3. *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 that are developing diabetes seems to be increasing over time.

This is a large, multi-center study that will be well-represented by youth from a variety of racial/ethnic backgrounds. The information obtained in this study will help clinicians and researchers better understand the prevalence and incidence of childhood diabetes, the characteristics of persons with 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.

Potential risks to study participants are minimal and reasonable in relation to the importance of the knowledge that is expected to be gained from this study.

8.14.4. *Data and Safety Monitoring Plan*

Even though this study is not a clinical trial, an internal Protocol Oversight Committee (POC) has been established for SEARCH to: 1) oversee personnel training and certification procedures to assure consistency of measurements among all 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 reviews the activities of the studies, based on reports from the POC. The external monitor will provide interim and annual safety reports to the Director of the Coordinating Center and the POC. 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 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, the Coordinating Center, 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.

8.15. REPOSITORY

Testing related to diabetes is limited to basic testing as mentioned in Section 6A and 6B. 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.

8.15.1. *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.

8.15.2. *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.

8.15.3. *Sample Maintenance*

8.15.3.1. 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 Principal 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 for his or her study center.

8.15.3.2. Sample Destruction

Individual participants (or their parents if participants are < 18 years old) when sample destruction is desired) 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). Any analyses done on their samples before the data the request is received will remain in the study dataset.

8.15.3.3. Use of Repository Samples

Samples will be made available (with Executive Committee approval) 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 which require a review by the Ancillary Studies Committee. Distribution of samples by the laboratory will be only by direction of the executive committee.

8.16. 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 Ancillary Studies Committee and the Executive Committee. Publications based on Ancillary Studies must be approved by the Publications and Presentations Committee. Involvement in the ancillary studies will vary by study center. Each ancillary study will require separate IRB approval, and a separate source of funding.

8.17. 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. Participants are asked at each visit if they would like to be contacted for future studies. Annual contact will be made with participants or their parent/guardian (if ≤ 18 years of age) to update information such as address and telephone numbers. Participants who withdraw from the study will not be contacted for future studies.