

APPENDIX C

EVALUATION OF MAJOR RESEARCH CONSORTIA, NETWORKS, AND RESOURCES

This Appendix includes evaluation of the major research consortia, networks, and resources supported by the *Special Statutory Funding Program for Type 1 Diabetes Research (Special Diabetes Program or Program)*. These sections were developed so that all the information on a single Consortium is found under that Consortium, rather than cross-referencing other sections of this Appendix. Therefore, information that is relevant to two different consortia will be repeated under each Consortium. This approach, although repetitive, was intentionally used so that complete information could be found in each Consortium's evaluation in a self-contained way. Consortium evaluations include the following sections:

- *Program Description*: The value added by the Consortium in the context of the overall research portfolio.
- *Highlights of Progress*: Examples of the progress achieved through spring 2010.
- *Anticipated Outcomes*: Description of anticipated future progress and the impact that the research effort could have on the health of people with type 1 diabetes.
- *Ongoing Evaluation*: Descriptions of regular oversight mechanisms, such as reviews by external evaluation panels.
- *Program Enhancements*: Descriptions of how the project has evolved over time to enhance research progress, based on input from external experts or from internal discussions within the program.

- *Coordination with Other Research Efforts*: Examples of how the research Consortium or network collaborates and coordinates its efforts with other research efforts to maximize and synergize progress.
- *Administrative History*: Programmatic details, including years of duration and agencies that support the Consortium.

In this Appendix, the consortia and networks are organized by Goal:³²

Goal I: Identify the Genetic and Environmental Causes of Type 1 Diabetes

- o Type 1 Diabetes Genetics Consortium
- o The Environmental Determinants of Diabetes in the Young
- o SEARCH for Diabetes in Youth
- o Type 1 Diabetes Mouse Resource

Goal II: Prevent or Reverse Type 1 Diabetes

- o Type 1 Diabetes TrialNet
- o Immune Tolerance Network
- o Cooperative Study Group for Autoimmune Disease Prevention
- o Standardization Programs: Diabetes Autoantibody Standardization Program, C-peptide Standardization, and Improving the Clinical Measurement of Hemoglobin A1c
- o Trial To Reduce IDDM in the Genetically At-Risk
- o Type 1 Diabetes–Rapid Access to Intervention Development³³

³² Many consortia are relevant to Goal VI (Attract New Talent and Apply New Technologies to Research on Type 1 Diabetes), so there is not a separate section on Goal VI.

³³ Also relevant to Goal V.

Goal III: Develop Cell Replacement Therapy

- o Beta Cell Biology Consortium
- o Non-Human Primate Transplantation Tolerance Cooperative Study Group
- o Clinical Islet Transplantation Consortium
- o Islet Cell Resource Centers
- o Integrated Islet Distribution Program
- o Collaborative Islet Transplant Registry

Goal IV: Prevent or Reduce Hypoglycemia in Type 1 Diabetes

- o Diabetes Research in Children Network

Goal V: Prevent or Reduce the Complications of Type 1 Diabetes

- o Epidemiology of Diabetes Interventions and Complications Study
- o Animal Models of Diabetic Complications Consortium
- o Genetics of Diabetes Complications
- o Diabetic Retinopathy Clinical Research Network

Goal I: Identify the Genetic and Environmental Causes of Type 1 Diabetes

TYPE 1 DIABETES GENETICS CONSORTIUM (T1DGC)

The T1DGC is organizing and implementing international efforts to identify genes that determine an individual's risk of developing type 1 diabetes. Teasing apart the multiple gene combinations that predispose someone to this complex disease requires analysis of a very large dataset covering thousands of patients and closely related family members who may or may not have developed the disease. The goal of the monumental first phase of the project, completed in FY 2007, was to recruit families particularly those with multiple siblings with type 1 diabetes, to join the study and to collect DNA samples for analysis. Later on, the Consortium also initiated collection of trio families, and cases and controls from populations with a low prevalence of disease. A Consortium database containing clinical, genetic, and medical history information has been established to facilitate the search for susceptibility genes. The database and centralized DNA repository have and continue to serve as a resource accessible to genetics researchers both within and outside the T1DGC.

HIGHLIGHTS OF PROGRESS

- Completed enrollment of over 2,800 families who have two or more siblings with type 1 diabetes and performed genome scans on these families.
- Completed enrollment of 500 families who have one member with type 1 diabetes and their parents, and 600 cases and 700 controls.
- Performed genome scans on all the 2,800 families who have two or more siblings with type 1 diabetes.
- Identified, with its collaborators, more than 40 genes or gene regions that are involved in type 1 diabetes.
- Established a Major Histocompatibility Complex fine-mapping project to study genes in this region involved in susceptibility to type 1 diabetes.
- Established a Rapid Response project to study candidate genes that could contribute to type 1 diabetes.
- Distributed samples and data to several investigators.
- Stored data and samples in NIDDK Central Repositories. These are available to scientists worldwide for application of the latest genetic technology to study DNA from this large and well-characterized set of affected families.

Anticipated Outcomes

The T1DGC is a large-scale, well coordinated effort to identify numerous genes and gene combinations that are important in predicting an individual's risk of developing type 1 diabetes or related autoimmune diseases. The T1DGC is building on the work of the Human Genome Project that spelled out the contents of human genes and the International HapMap Project that identified the points at which gene sequences differ from person to person. The T1DGC is resolving which of these genetic differences are significant for type 1 diabetes. In 2003, just three type 1 diabetes genes were known. Today, the T1DGC and its collaborators have identified more than 40 genes or gene regions that are associated with the disease.

As science progresses to the age of personalized medicine, clinicians may soon be able to determine the optimal treatment strategy for an individual based on his or her genetic background. With new insights into the genetic factors that play a role in type 1 diabetes, researchers may be able to identify with great precision those individuals at risk for the disease, and to develop and test prevention-oriented strategies. It is possible, for example, that certain therapies to delay or reverse the development of type 1 diabetes may be more effective in individuals with specific genetic changes that predispose to type 1 diabetes. Such new genetic knowledge could point the way toward better screening of newborns or to widespread screening of the general population to identify individuals at risk of developing type 1 diabetes. This knowledge would facilitate the design of more specific clinical trials for testing interventions specifically tailored to patients with similar risk profiles. These

are just a few examples of the enormously important, predictive and preemptive strides that can be envisioned and possibly attained by further understanding the genetic underpinnings of disease development.

Ongoing Evaluation

To ensure ongoing evaluation of the study design and the progress of the T1DGC, NIDDK established an External Evaluation Committee (EEC). The EEC is composed of investigators with scientific expertise relevant to research conducted by the T1DGC, but who are not members of the Consortium. The EEC meets annually to:

- Review activities that affect the operational and methodological aspects of the study (e.g., quality control procedures; performance of clinical networks, data coordinating center, and core laboratories).
- Review data to ensure its quality, provide input on procedures for analysis and data display, and provide input on interpretation and implication of results.
- Review proposed major modifications to the protocol or operations of the study for appropriateness, necessity, and impact on overall study objectives.

In addition, the T1DGC has been evaluated by an external panel of scientific and lay experts at an *ad hoc* evaluation meeting convened by NIDDK in January 2005. This meeting was an opportunity for external experts to evaluate progress and provide input on future research directions (for more information, see the Executive Summary and Appendix B). Through *ad hoc* evaluation meetings and regular meetings of the EEC, NIDDK continually seeks external input to inform current and future directions for the T1DGC.

Program Enhancements

Because of the evolving nature of science, consortia supported by the *Special Diabetes Program* have evolved over time and have undergone enhancements to take advantage of new technologies and research findings, and to accelerate progress. Some enhancements have been made in response to external input and others have been initiated by the consortium members. Examples of program enhancements for the T1DGC include:

- To increase coordination with the other human genetics consortia supported by the *Special Diabetes Program*, the T1DGC participated in a meeting with these consortia and developed new initiatives to coordinate future research efforts among these studies.
- The T1DGC also utilizes T1Dbase (<http://T1DBase.org>) as a Web-based tool to coordinate, manage, and interpret human, mouse, and rat genetics data. Use of T1Dbase has improved coordination of genetics research in mice and humans. Data on T1Dbase are open access and all software is open source in order to maximize its usage by the broad research community.

Coordination with Other Research Efforts

The T1DGC coordinates its efforts with multiple other type 1 diabetes research consortia and networks supported by the *Special Diabetes Program*. Collaboration, coordination, and resource sharing serve to synergize research efforts and accelerate research progress. Examples of coordination with other consortia are given below. For a summary of ongoing collaborative efforts, please see Appendix D.

Coordinating Patient Recruitment Efforts:

- All 14 Type 1 Diabetes TrialNet clinical centers and 4 SEARCH for Diabetes in Youth (SEARCH) study sites are participating as recruitment centers for the T1DGC North American Network.
- T1DGC assisted TrialNet in establishing international recruitment sites.

Enhancing Data Comparison Among Studies:

- T1DGC, TrialNet, SEARCH, and The Environmental Determinants of Diabetes in the Young (TEDDY) are sharing information and reagents so that they can assess allele and haplotype frequencies of the same sets of genes including *Human Leukocyte Antigen* and other diabetes-predisposing genes. This coordination will permit comparisons of genetics data across all four studies, effectively increasing the power of each in learning which genes play a role in disease onset.
- T1DGC, TrialNet, and TEDDY share the same North American laboratory for measurement of autoantibodies (markers used to predict an individual's risk for developing type 1 diabetes). This coordination will permit direct comparison of results obtained in each study.
- Researchers in the Diabetes Autoantibody Standardization Program (DASP) provide tools that T1DGC laboratories use to standardize autoantibody data. Data standardization provides confidence that results are independent of the laboratory performing the measurements.

Coordinating Studies of Type 1 Diabetes Genetics:

- The T1DGC coordinates its research efforts with the other genetics consortia supported by the *Special Diabetes Program* (Epidemiology of Diabetes Interventions and Complications, Family Investigation of Nephropathy and Diabetes, and Genetics of Kidneys in Diabetes Study).

Sharing Samples, Data, and Resources with the Research Community:

- The T1DGC has developed a comprehensive public Web site with information on samples, data, and resources that are available to the scientific research community (www.t1dgc.org).

- The T1DGC is repositing samples and data in all three NIDDK Central Repositories (Biosample, Genetics, and Data Repositories). The Repositories were established to expand the usefulness of NIDDK-supported studies by allowing a broader research community to access these materials beyond the end of the study.

T1DGC Administrative History

Date Initiative Started	2002
Date <i>Special Diabetes Program</i> Funding Started	2002
Participating Components	NIDDK, NIAID, NHGRI, and JDRF
Web site	www.t1dgc.org

T1DGC consists of a coordinating center and four clinical recruitment networks in Asia-Pacific, Europe, North America, and the United Kingdom.

THE ENVIRONMENTAL DETERMINANTS OF DIABETES IN THE YOUNG (TEDDY)

Scientists directing six independent studies of environmental triggers of type 1 diabetes in the United States and Europe joined forces to create this international consortium. TEDDY is providing a coordinated, multidisciplinary approach to understanding the infectious agents, dietary factors, or other environmental conditions that trigger type 1 diabetes in genetically susceptible individuals. TEDDY investigators have screened newborns in the general population, as well as those who have a first-degree relative with type 1 diabetes. In this large-scale, long-term epidemiological effort, in which patient follow-up is estimated to continue through 2023, high-risk infants will be followed until they are 15 years of age. The TEDDY study is making progress toward amassing the largest data set and samples on newborns at risk for autoimmunity and type 1 diabetes anywhere in the world. To maximize the return on the investment in TEDDY, samples from the study will be made widely available to researchers worldwide.

HIGHLIGHTS OF PROGRESS

- Completed screening of 418,671 newborns from the general population.
- Completed recruitment of 7,487 newborns from the general population.
- Completed screening of 6,412 newborns with a first-degree relative with type 1 diabetes.
- Completed recruitment of 894 newborns with a first-degree relative with type 1 diabetes.
- Mapped the frequencies of genes that increase susceptibility to type 1 diabetes in diverse populations.
- Completed food composition database harmonization.
- Discovered significant differences in infant feeding practices between the United States and Europe and explored variability in infant nutrition within the U.S. population.
- Identified risk factors for why families drop out of the study.

Anticipated Outcomes

Until researchers know what causes type 1 diabetes, it is difficult to develop strategies to prevent it. Previous studies suggested that certain factors, such as early exposure to cereal or cow's milk, might predispose to type 1 diabetes. However, these studies were too small and too short to achieve statistically significant results, and no definitive environmental trigger of the disease has yet been identified. Therefore, TEDDY is a crucially important effort to tease out the environmental factors triggering disease onset. While it is a substantial

investment of time and resources to follow individuals for many years, it is only through a long-term, coordinated study such as TEDDY that researchers are likely to answer critically important questions about type 1 diabetes risk and onset.

Realization of study goals could have an enormously positive impact on public health efforts regarding disease prevention. For example, if a viral trigger is revealed, a vaccine could possibly be developed to prevent disease onset in genetically-susceptible individuals.

Alternatively, if a dietary component is found to be causative or protective, individuals at risk could take steps to either eliminate or add it to their diets. By pinpointing the constellation of type 1 diabetes disease genes (as is being done by the Type 1 Diabetes Genetics Consortium), environmental triggers (as is being done in TEDDY), and their cascading effects on the immune system (see Goal II), researchers may be able to entirely prevent or reverse disease onset. Combating the disease at the “front-end” is especially beneficial because early steps could preclude or arrest the development of disease complications—including kidney failure, blindness, lower limb amputations, heart attacks, and strokes. Research on the genetic and environmental causes of the disease thus offers the real hope of preventing type 1 diabetes.

Importantly, the studies of environmental factors that play a role in type 1 diabetes may also contribute to understanding the development of celiac disease, a digestive disorder caused by autoimmunity directed at gluten proteins in wheat and other grains. Celiac disease affects about 2 million Americans and like type 1 diabetes, rates of the disorder are rising. Some genes confer susceptibility to both celiac disease and type 1 diabetes, and many people have both diseases. Therefore, ongoing studies to identify environmental triggers of type 1 diabetes are also investigating development of celiac disease. These studies may uncover environmental factors initiating both disorders, benefiting not only people with type 1 diabetes, but also people suffering from celiac disease and other autoimmune diseases.

Ongoing Evaluation

To ensure ongoing evaluation of the study design and the progress of TEDDY, NIDDK established an External

Evaluation Committee (EEC) composed of scientific experts who are not participating in TEDDY. The EEC meets annually, in person or by conference call, to:

- Review activities that affect the operational and methodological aspects of the study (e.g., quality control procedures; performance of clinical centers, data coordinating center, and core laboratories);
- Review data to ensure its quality, provide input on procedures for analysis and data display, and provide input on interpretation and implications of results; and
- Review proposed major modifications to the protocol or operations of the study for safety, appropriateness, necessity, and impact on overall study objectives.

In addition, TEDDY has been evaluated by external panels of scientific and lay experts at *ad hoc* evaluation meetings convened by NIDDK in January 2005 and April 2008. These meetings were an opportunity for external experts to evaluate progress and provide input on future research directions (for more information, see the Executive Summary and Appendix B). Through *ad hoc* evaluation meetings and regular meetings of the EEC, NIDDK continually seeks external input to inform current and future directions for TEDDY.

Program Enhancements

Because of the evolving nature of science, consortia supported by the *Special Diabetes Program* have evolved over time and have undergone enhancements to take advantage of new technologies and research findings, and to accelerate progress. Some enhancements have been made in response to external input and others have been initiated by

the consortium members. Examples of program enhancements for TEDDY include:

- Because measurements of islet autoantibodies were not standardized, it was difficult to compare results across different TEDDY sites. To address this barrier, TEDDY scientists fostered development of an NIDDK Islet Autoantibody Measurement Harmonization Project. This effort is helping to standardize protocols for measuring autoantibodies not just within TEDDY, but within all NIDDK studies, and is thus having a far-reaching impact.
- It was recognized that materials being developed by TEDDY would be of use to other scientists studying type 1 diabetes, so the consortium expanded its public Web site to include the study protocol, manual of operations, study forms, and other study materials (www.teddystudy.org).
- To take advantage of new and emerging technologies, TEDDY developed a program and explicit guidelines for ancillary studies to facilitate access to TEDDY materials by researchers who seek to expand and embrace new technologies for inclusion into the TEDDY study group. The NIDDK developed an initiative to support investigator-initiated ancillary studies to ongoing research efforts, including TEDDY.
- TEDDY enhanced coordination with other type 1 diabetes research consortia studying newborns, such as the Trial to Reduce IDDM in the Genetically at Risk (TRIGR) and TrialNet.

Coordination with Other Research Efforts

TEDDY coordinates its efforts with multiple other type 1 diabetes research consortia and networks supported by the *Special Diabetes Program*, particularly those studying newborns.

Collaboration, coordination, and resource sharing serve to synergize research efforts and accelerate research progress. Examples of coordination with other consortia are given below. For a summary of ongoing collaborative efforts, please see Appendix D.

Coordinating Research Studies Involving Newborns:

- TEDDY investigators have met with researchers participating in other type 1 diabetes research studies involving newborns (TRIGR and TrialNet) to discuss opportunities for enhancing coordination and collaboration.
- TEDDY has shared the following materials with TrialNet investigators who are studying newborns in the Nutritional Intervention to Prevent Diabetes Study: genetic-screening procedures, data forms, and parts of the Manual of Operations concerning follow-up of high-risk children.
- TEDDY and TRIGR share the same Data Coordinating Center. This coordination has resulted in implementation of similar standards in data collection, entry, management of quality control, and analyses for both studies.
- TEDDY, TrialNet, and TRIGR have coordinated patient recruitment efforts to ensure that they are not adversely competing for patient participants in their studies.
- TRIGR and TEDDY investigators are considering collaborative efforts on recruitment after TRIGR accrual ends. Both groups are also considering a follow-up intervention protocol.

Enhancing Data Comparison Among Studies:

- T1DGC, TrialNet, SEARCH for Diabetes in Youth, and TEDDY are sharing information and reagents so that

they can assess allele and haplotype frequencies of the same sets of genes including *Human Leukocyte Antigen (HLA)* and other diabetes-predisposing genes. This coordination will permit comparisons of genetics data across all four studies, effectively increasing the power of each in learning which genes play a role in disease onset.

- TEDDY, T1DGC, and TrialNet share the same North American laboratory for measurement of autoantibodies. This coordination will permit direct comparison of results obtained in each study.
- TRIGR and TEDDY have implemented similar standards in data collection and entry. This coordination is permitting direct comparison between results obtained in each study relevant to nutrition and to diabetes-associated variants of certain immune system genes (*HLA* genes).

- TEDDY scientists have fostered development of the NIDDK Islet Autoantibody Measurement Harmonization Project. Common protocols have been developed optimizing the methods used to measure antibodies in TEDDY. Protocols and standards have been distributed to all laboratories measuring antibodies in NIDDK studies and these laboratories are using a standard protocol and common standards to measure study samples.

Sharing Samples, Data, and Resources with the Research Community:

- TEDDY is repositing biological samples and data into the NIDDK Central Repositories and will make the material available to the broad scientific community. The NIDDK has developed an initiative to support investigator-initiated ancillary studies to ongoing studies, including TEDDY.

TEDDY Administrative History

Date Initiative Started	2002
Date <i>Special Diabetes Program</i> Funding Started	2002
Participating Components	NIDDK, NIAID, NICHD, NIEHS, CDC, and JDRF
Web site	www.teddystudy.org
TEDDY is a consortium of six Clinical Centers and one Data Coordinating Center in the United States, Finland, Sweden, and Germany.	

SEARCH FOR DIABETES IN YOUTH (SEARCH)

Major impediments to diabetes research and efforts to improve public health include lack of uniform national information on the rates of childhood diabetes, whether these are changing over time, and the clinical course and evolution of different forms of diabetes in children and youth. While substantial increases in the incidence of type 1 diabetes have been reported in Europe, reliable data on changes over time in the United States, or even how many children in the United States have diabetes, were lacking. The SEARCH multicenter epidemiological study is identifying cases of diabetes in children and youth less than 20 years of age in six geographically dispersed populations that encompass the ethnic diversity of the United States. The study aims to identify the number of children and youth under age 20 who have diabetes; learn how type 1 diabetes and type 2 diabetes differ, including how they differ by age and race/ethnicity; learn more about the risk for acute and chronic complications of diabetes in children and youth; investigate the different types of care and medical treatment that these children and youth receive; and learn more about how diabetes affects the daily lives of children and youth in the United States. Now that the first baseline assessment of diabetes rates in children nationwide has been completed, the study is poised to evaluate trends in diabetes incidence and progression of the disease over time.

HIGHLIGHTS OF PROGRESS

- The SEARCH prevalence data indicate that at least 154,000 children/youth (1.8 per 1,000) in the United States have diabetes. Diabetes prevalence varies across major racial/ethnic groups:
 - ▶ In children 0-9 years of age, non-Hispanic whites had the highest prevalence (about 1/1,000) and type 1 diabetes was the most common form of diabetes across all race/ethnic groups.
 - ▶ Among adolescents and young adults, African American and non-Hispanic white youth had the highest burden of diabetes (about 1/300) and Asian/Pacific Islanders had the lowest (about 1/750). Prevalence of type 1 diabetes was 2.3/1,000 and was the most common form of diabetes in all racial/ethnic groups except in American Indian youth.
- The SEARCH incidence data indicated that annually 15,000 youth are diagnosed with type 1 diabetes. Diabetes incidence also varies across major racial/ethnic groups:
 - ▶ In children less than 10 years of age, most diabetes cases are type 1, regardless of race/ethnicity, and the incidence of type 1 diabetes is highest in non-Hispanic whites.
 - ▶ In older youth (10-19 years), the highest incidence of type 1 diabetes is in non-Hispanic whites; American Indian and Asian/Pacific Islanders have the lowest.
- Since 2002, approximately 5.5 million children less than 20 years of age (approximately 6 percent of the under 20 years U.S. population) with wide racial/ethnic, socioeconomic, and geographic representation, have been under surveillance at the SEARCH research centers each year to estimate how many children develop diabetes (incidence cases) per year by age, sex, race/ethnicity, and diabetes type.

- Over 10,000 children/youth with diabetes, and their families, have been surveyed for SEARCH and over 6,000 have participated in SEARCH in-person visits. Nearly 3,000 stored DNA specimens from these participants are being used to extend the genetic component of SEARCH.
- The SEARCH data demonstrated that about four out of five youth with antibody positive diabetes have clinically significant amounts of residual beta cell function within the first year after diagnosis. This finding emphasizes the importance of clinical trials aimed at preserving residual beta cell function after diabetes onset.
- Results from SEARCH determined that 17 percent of youth with type 1 diabetes have hemoglobin A1c (HbA1c) levels reflecting poor blood glucose control. African American, American Indian, Hispanic, and Asian/Pacific Islander youth with type 1 diabetes are significantly more likely to have higher HbA1c levels compared with non-Hispanic white youth. This indicates the need for more effective treatment strategies, and better technologies and approaches to assist youth with diabetes in managing the disease, especially for those in minority groups.
- The SEARCH data revealed that young people with type 1 diabetes were more likely to be overweight, but not obese, compared to youth who did not have diabetes, highlighting the need to understand the role of excess weight in the development of diabetes and its impact on treatment.
- The SEARCH data showed that youth with type 1 diabetes and suboptimal control of their blood glucose levels had abnormal lipid (fat) profiles—indicators of heart disease risk—even after a short duration of disease. Effective blood glucose control may help protect against these abnormalities, which provides further impetus for people with type 1 diabetes to implement early and intensive blood glucose control.
- The large population-based cohort and collaborative infrastructure built by SEARCH has created new opportunities for additional research into childhood diabetes, resulting in five completed and six currently ongoing ancillary studies.

Anticipated Outcomes

Research supported through the SEARCH consortium has led to numerous insights and further understanding of the natural history, complications, and risk factors of diabetes onset in childhood and adolescence. SEARCH has generated estimates of diabetes prevalence and incidence by age, sex, race/ethnicity, and diabetes type, and continues to assess the impact of quality of diabetes care in youth on short- and long-term diabetes outcomes, including quality of life. Ongoing yearly case

ascertainment will determine trends in incidence in the United States. Acquiring these data is important in order to ultimately design and implement public health efforts to prevent the disease once prevention strategies are identified. Furthermore, the data that are acquired in the SEARCH study regarding the natural history and risk factors of diabetes can inform the design of new prevention and treatment strategies. High prevalence of cardiovascular disease risk factors, including obesity, dyslipidemia, and hypertension, has been documented in

youth with type 1 diabetes, as well as youth with type 2 or hybrid diabetes. The need for identifying effective approaches to improve dietary intake in youth with diabetes has been clearly documented. By building on SEARCH findings, researchers may be able to design interventions that can prevent or delay disease onset in at-risk individuals and, of equal importance, to design interventions to reduce risk for both acute and chronic complications of diabetes.

Ongoing Evaluation

The SEARCH Steering Committee (SC) comprises the Clinical Center and Coordinating Center principal investigators and one additional co-investigator from each center, designated scientists from the collaborating government agencies (CDC, NIH), and the central laboratory principal investigator. The SEARCH SC holds monthly conference calls and has overall responsibility for assuring the scientific integrity and progress of the study. It is also charged with assuring equity of data access and promoting career advancement of junior scientists working with SEARCH. The SEARCH Planning and Coordinating Committee, comprised of the Study Chair and Vice-Chair, the Coordinating Center principal investigator, and the Principal Scientists of the funding agencies, meets weekly by phone to facilitate study progress particularly regarding publications, and assure overall study coordination. SEARCH has seven standing committees (Typology; Publications and Presentations; Ancillary Studies; Protocol Oversight; Recruitment and Retention; Quality of Care; Epidemiology; Project Managers).

To ensure ongoing evaluation of the study design and the progress of SEARCH, CDC and NIDDK have established an External Scientific Evaluation Committee (ESEC). The ESEC is comprised of investigators with scientific

expertise relevant to research conducted by SEARCH, but who are not members of the Consortium. The ESEC meets annually to:

- Review activities that affect the operational and methodological aspects of the study (e.g., quality control procedures; performance of research centers, data coordinating center, and central laboratory);
- Review data to ensure its quality, advise on procedures for analysis and data display, and provide input on interpretation and implications of results; and
- Review proposed major modifications to the protocol or operations of the study for appropriateness, necessity, and impact on overall study objectives.

Program Enhancements

Because of the evolving nature of science, consortia supported by the *Special Diabetes Program* have evolved over time and have undergone enhancements to take advantage of new technologies and research findings, and to accelerate progress. Some enhancements have been made in response to external input and others have been initiated by the consortium members. Examples of program enhancements for SEARCH include:

- To manage challenges in the interpretation and implementation of the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule, SEARCH increased the efforts of study personnel working with the Institutional Review Boards, conducting case ascertainment, and recruiting volunteers. SEARCH presented data on the impact of the HIPAA law in conducting epidemiological research involving children at an ad hoc meeting organized by the Institute of Medicine of the National Academies in May 2007.

- As a result of diabetes autoantibodies (DA) measurement data generated by several NIH-funded studies, including SEARCH, discrepancies in DA measurements were observed and led NIDDK to form a harmonizing committee to standardize DA measurements. The SEARCH laboratory is one of the six laboratories participating in the DA standardization program. In addition, DA for all SEARCH samples, including those previously assayed, are being measured using the new harmonized protocols.
- To make samples and data available to the scientific community for ancillary studies, SEARCH has developed a comprehensive public Web site with information on samples, data, and resources that are currently available to the scientific community (www.searchfordiabetes.org). The SEARCH Ancillary Study Policy provides a process whereby outside investigators can access the SEARCH samples in a way that ensures scientific integrity and appropriate communication and coordination across projects. A subcommittee has been created to specifically monitor available stored samples, and to track funded and planned future use in order to maximize and coordinate use of this important resource.
- To increase the retention rate of study participants, a subcommittee of the SEARCH Protocol Oversight Committee has been formed to regularly review recruitment and retention rates and to develop new approaches to enhance success in this arena. These retention efforts have resulted in close to 80 percent of SEARCH subjects participating in at least one follow-up visit.
- SEARCH investigators played a key role in organizing an international workshop on the classification of diabetes in children and young adults. Sponsored by NIDDK and CDC, the workshop brought together diabetes researchers to share data on prevalence, incidence and classification of diabetes in youth. The goal of the workshop was to share and disseminate the most up-to-date data and identify key gaps that need to be addressed with further research.
- SEARCH investigators are playing a key role in organizing an international workshop on surveillance methods for diabetes and its complications in children and adolescents. Sponsored by CDC and NIDDK, this workshop will explore approaches to the surveillance of diabetes in youth from registries and integrated data systems in several locations in the United States and other countries, and discuss their advantages and disadvantages. The goal of the workshop is to inform the development of a research agenda that specifically addresses epidemiology and surveillance of pediatric diabetes, and to foster the adoption and modification of national and international surveys.

Coordination with Other Research Efforts

SEARCH coordinates its efforts with multiple other type 1 diabetes research consortia and networks supported by the *Special Diabetes Program*. Collaboration, coordination, and resource sharing serve to synergize research efforts and accelerate research progress. Examples of coordination with other consortia are given below. For a summary of ongoing collaborative efforts, please see Appendix D.

Coordinating Patient Recruitment Efforts:

- Four SEARCH study sites are participating as recruitment centers for the Type 1 Diabetes Genetics Consortium (T1DGC) North American Network, and SEARCH is sharing its genetics samples with T1DGC.
- The Colorado, Cincinnati, Seattle, and South Carolina SEARCH sites are informing participants about Type 1 Diabetes TrialNet studies and referring them to the TrialNet coordinator for information on enrollment.
- Three SEARCH sites (Colorado, California, and Seattle) are assisting with recruitment from the Trial to Reduce IDDM in the Genetically at Risk (TRIGR) by providing brochures and other information about TRIGR to potential study participants.

Enhancing Data Comparison Among Studies:

- T1DGC, TrialNet, SEARCH, and The Environmental Determinants of Diabetes in the Young (TEDDY) are sharing information and reagents so that they can assess allele and haplotype frequencies of the same sets of genes including *Human Leukocyte Antigen* and other diabetes-predisposing genes. This coordination will permit comparisons of genetics data across all four studies, effectively increasing the power of each in learning which genes play a role in disease onset.

Coordinating Research Studies Involving Children:

- SEARCH, TrialNet, TEDDY, and T1DGC investigators directly collaborate.

SEARCH Administrative History

Date Initiative Started	2000
Date <i>Special Diabetes Program</i> Funding Started	2001
Participating Components	CDC, NIDDK
Web site	www.searchfordiabetes.org
SEARCH consists of a coordinating center, a central laboratory, and six research centers in California, Colorado, Hawaii, Ohio, South Carolina, and Washington state.	

TYPE 1 DIABETES MOUSE RESOURCE (T1DR)

This research resource, located at The Jackson Laboratory, was established to expand existing repositories for genetically altered mice to accommodate the many different mouse models that are important for type 1 diabetes research. In its second phase, this project was expanded in scope to include activities supporting the Animal Models of Diabetic Complications Consortium (AMDCC; described later in this Appendix). Animal systems that appropriately model type 1 diabetes and its complications are critical tools for identifying and testing new therapeutic approaches, and for supporting the translational research required to move new treatments from the laboratory bench to patients' bedside. It is also important that the broad scientific community have ready access to these animal models to facilitate their research efforts. The repository is enhancing access and ensuring the continued availability of these mouse models to the entire research community.

HIGHLIGHTS OF PROGRESS

- Collected and preserved over 199 stocks of mice important to diabetes research that have been made available for distribution to the scientific community.
- Over 6,000 mice have been shipped from the T1DR to over 840 researchers.
- Performed genetic and phenotypic quality control that further enhances research utility of mice used for research on diabetes and its complications.
- Generated 19 new mouse strains that are sensitized to the development of diabetes complications for use by the research community.

Anticipated Outcomes

Animal models of type 1 diabetes can significantly facilitate the translation of laboratory research findings to clinical research. For example, techniques for gene discovery in small model organisms are much more powerful than in humans. Discovery of diabetes-causing genes in animal models will foster research on corresponding genes in human tissue samples and will thus help to uncover the pathways in which the genes function. Furthermore, animal models of the disease are important for testing promising therapeutic agents identified in the laboratory prior to testing in human clinical trials. Therefore, animal models are a crucial resource for translating laboratory results from

the bench to the bedside. The research community is taking advantage of the T1DR, as demonstrated by the fact that over 6,000 mice have been distributed to 840 researchers. These mouse models continue to be critically important for conducting type 1 diabetes research and are being used by the broad diabetes research community.

Ongoing Evaluation

Activities and progress of the T1DR are monitored by an External Evaluation Committee (EEC) comprised of experts in mouse genetics, mouse husbandry, and rodent models of type 1 diabetes. Members of the EEC are not affiliated with the T1DR or with The Jackson Laboratory. The EEC meets annually to:

- Review status of importation and distribution of stocks, identify and make recommendations for new strains to be solicited, and provide input on procedures to advertise repository holdings.
- Review quality control of genetics data on repository strains, including genome scans, chromosome-of-interest studies, and incidence studies.

In addition, the T1DR was evaluated by an external panel of scientific and lay experts at an *ad hoc* evaluation meeting convened by NIDDK in June 2009. This meeting was an opportunity for external experts to evaluate progress and provide input on future research directions (for more information, see the Executive Summary and Appendix B). Through *ad hoc* evaluation meetings and regular meetings of the EEC, NIDDK continually seeks external input to inform current and future directions for the T1DR.

Program Enhancements

Because of the evolving nature of science, consortia supported by the *Special Diabetes Program* have evolved over time and have undergone enhancements to take advantage of new technologies and research findings, and to accelerate progress. Some enhancements have been made in response to external input and others have been initiated by the consortium members. Examples of program enhancements for T1DR include:

- In its second phase, the T1DR was expanded in scope to include activities supporting the AMDCC to facilitate the production, phenotyping, repositing and

distribution of strains that are important for type 1 diabetes complications research.

- The T1DR has made enhancements to ensure that investigators are able to obtain animals for study at their research institution. A subset of the T1DR protocols involves development of mouse strains that may be physiologically brittle and difficult to ship to investigators for further study. In circumstances where it is determined that strains may not survive shipment as adults, younger cohorts are developed specifically for shipment. In the most severe cases where shipment of live animals may not be feasible, the T1DR has developed protocols to support shipment of embryos to investigators for expansion at the investigator's institution for further study.

Coordination with Other Research Efforts

In coordination with other NIH-sponsored mouse repositories, the T1DR serves as an archive for mouse models generated by all scientists engaged in research relevant to type 1 diabetes. In its second phase, the scope of the T1DR was expanded to include activities supporting the AMDCC, thus providing coordination of activities relating to animal models of diabetes complications. The T1DR also services many basic science consortia engaged in type 1 diabetes research, such as the Beta Cell Biology Consortium (BCBC). Mouse models distributed from these NIH-supported repositories support translational research relevant to pancreas development, autoimmunity, and transplantation. For a summary of ongoing collaborative efforts, please see Appendix D.

T1DR Administrative History

Date Initiative Started	2001
Date <i>Special Diabetes Program</i> Funding Started	2001
Participating Components	NIDDK (NCRR also supported first project phase)
Web site	http://type1diabetes.jax.org/
T1DR is located at The Jackson Laboratory, Bar Harbor, ME.	

Goal II: Prevent or Reverse Type 1 Diabetes

TYPE 1 DIABETES TRIALNET (TRIALNET)

TrialNet is an international network of investigators, clinical centers, and core support facilities that recruits patients and conducts research to advance knowledge about type 1 diabetes, and to test strategies for its prevention and early treatment. TrialNet supports the development and implementation of clinical trials of agents aimed at preventing the disease in people at risk for type 1 diabetes and slowing the progression of disease in newly diagnosed patients. The network's Natural History Study will enhance understanding of how the disease develops in individuals at risk and will thus help in the formulation of future trials. Biological samples collected from study volunteers are being stored at the NIDDK Central Repositories, and these valuable resources are being made available to the broader scientific community for further research on type 1 diabetes.

HIGHLIGHTS OF PROGRESS

- Completed the Diabetes Prevention Trial Type-1 (DPT-1) clinical trial of insulin for the prevention of type 1 diabetes in individuals at moderate and high risk for disease development, which showed that oral or injected insulin administration did not delay or prevent the disease in relatives of people with type 1 diabetes. However, in a subset of the moderate-risk patients studied (those with high levels of insulin-reactive autoantibodies), protection may have been observed. Because this result was not definitive, TrialNet has launched a new trial to further evaluate the role of oral insulin in delaying or preventing type 1 diabetes in this subset of people (see below).
- Determined that rituximab slows progression of type 1 diabetes in newly diagnosed patients. Rituximab treatment temporarily depletes B cells of the immune system and has been approved by the U.S. Food and Drug Administration for treatment of B cell non-Hodgkin's lymphoma and some autoimmune disorders, such as rheumatoid arthritis. Scientists tested whether four separate infusions of rituximab shortly after diagnosis could slow disease progression. After 1 year, people who had received the drug produced more of their own insulin, had better control of their diabetes, and did not have to take as much exogenous insulin to control their blood glucose levels, compared to people receiving placebo. The finding will propel research to find drugs targeting the specific B cells involved in type 1 diabetes because drugs such as rituximab that broadly deplete B cells can increase the risk of infection.
- Launched an oral insulin prevention trial in relatives of people with type 1 diabetes. As described above, a subset of individuals in the DPT-1 with high levels of insulin-reactive autoantibodies may have been protected from type 1 diabetes development with oral insulin administration. This suggestive result is being rigorously tested in TrialNet to determine if oral insulin could prevent or delay development of type 1 diabetes in this group of people.

- Completed a pilot study to test the role of omega-3 fatty acids in preventing type 1 diabetes, called The Nutritional Intervention to Prevent (NIP) Diabetes Study. The study was based on observations from epidemiologic studies that children who have received more omega-3 fatty acid (such as from fish)—either in the womb or during the first year of life—have a lower risk of developing type 1 diabetes. The pilot study demonstrated that increasing omega-3-fatty acids in breast milk through maternal supplementation or directly in formula or foods significantly increased blood levels of this substance. While measurable differences in omega-3 fatty acids were achieved, there was no difference in the immune marker studied so a full trial will not be launched.
- In addition to launching the two prevention studies already mentioned (oral insulin and NIP Diabetes Study), TrialNet has planned two other prevention studies: (1) a study of an anti-CD3 monoclonal antibody; and (2) a study evaluating glutamic acid decarboxylase (GAD)-alum vaccine.
- TrialNet launched the Natural History Study, which was begun to identify risk factors associated with development of type 1 diabetes and to document disease characteristics and progression. The Natural History Study will also identify and maintain a pool of individuals who would be candidates for participation in clinical trials. The first phase of the Natural History Study involves identification of those at risk by using a blood test for the presence of diabetes-related autoantibodies to screen close relatives of people with the disease. Thus far, over 74,000 individuals have been screened. The study plans to screen people at a rate of about 20,000 individuals per year. Participants are being offered enrollment in diabetes prevention and early intervention studies as they become available.
- TrialNet has begun or approved eight studies in new-onset type 1 diabetes to evaluate the effect of distinct interventions targeting an array of mechanisms putatively involved in the development of type 1 diabetes, including immunosuppressive agents (mycophenolate mofetil [MMF] and daclizumab), therapies directed at B cells (rituximab, described above), therapies directed at co-stimulation (CTLA-4 Ig [abatacept]), antigen-specific therapy (GAD-alum vaccine), and therapies aimed at improving beta cell function and/or mass (a study evaluating early aggressive, meticulous glycemic control facilitated by use of a continuous glucose sensor augmented insulin pump). In addition to the ongoing or approved trials, TrialNet accepts new proposals throughout the year, and received 15 new protocol proposals for consideration in 2009. TrialNet centers also participate in new-onset trials led by the NIAID-led Immune Tolerance Network (ITN), including those testing anti-CD3 (teplizumab) and thymoglobulin, as well as a phase 1 study examining the combination of IL-2 and rapamycin.
- The network completed a clinical study to compare reliability of two tests for beta cell function—the Mixed Meal Tolerance Test (MMTT) and intravenous Glucagon Stimulation Test (GST). Residual beta cell function (insulin secretion) in people with type 1 diabetes is known to result in improved glycemic control, reduced hypoglycemia, and reduced risk for complications. In insulin treated patients with diabetes, beta cell function is currently best measured by determining levels of human C-peptide. C-peptide is useful as an outcome measure in clinical trials: for example, trials testing agents to preserve beta cell function in new-onset diabetes. There are different ways

to stimulate insulin production and, concomitantly, C-peptide production, but it has not been clear which of these conditions is optimal for enabling C-peptide measurement. The MMTT/GST clinical trial compared the reliability and burden on patients of two test conditions for stimulating insulin/C-peptide: one, MMTT, is a liquid meal; the other, GST, is an injection of the hormone glucagon. Results of this study showed that the MMTT test is superior. This knowledge has helped to inform the design of future type 1 diabetes clinical trials to prevent or reverse type 1 diabetes in which C-peptide must be measured to determine if the intervention is successful.

- Completed a T cell Validation Study to learn which T cell assays are most reliable and reproducible in identifying differences between people with and without type 1 diabetes. The first study involved the evaluation of blinded samples from the same people by four T cell laboratories in North America and a parallel test of one of the assays in the United Kingdom. Samples were drawn on two occasions to compare reproducibility, sensitivity, and specificity. The first validation study demonstrated that several of the assays were able to distinguish people with type 1 diabetes from healthy control individuals. This study represents the first blinded evaluation of T cell assay reproducibility in a large multicenter network with ongoing external quality control of all assays, an essential component for multicenter clinical trials. TrialNet hopes to continue to use this process to assess new biomarkers of disease progression.

Anticipated Outcomes

TrialNet is an international clinical research network focused on individuals at risk for or newly diagnosed with type 1 diabetes. Its efforts span the time period from birth in those at high genetic risk to the development of signs of increased risk (for example, autoantibodies), when prevention strategies are particularly urgent, and on through the time soon after diagnosis, when residual beta cell function may afford a unique opportunity for interventions to mitigate disease severity. TrialNet hopes to identify agents that safely delay or prevent the onset of type 1 diabetes, sparing those at risk from developing this devastating disease. TrialNet is also hoping to identify agents that can modulate the immune system of recently diagnosed patients so as to preserve remaining beta cell function and thus make it easier for them to control glucose levels and reduce their burden of

complications. In addition to providing direct benefit to newly diagnosed patients, new-onset trials are expected to identify agents that have low risk of serious side effects and have promise for preventing or delaying onset of type 1 diabetes in at-risk populations.

In addition to the conduct of clinical trials, TrialNet's extensive recruitment and frequent sampling and metabolic testing of individuals at risk for or with new-onset disease is facilitating research into biomarkers of disease progression. Other clinical studies conducted by TrialNet have improved the tests and strategies for future type 1 diabetes clinical trials, for example, showing that MMTT is superior to GST for stimulating insulin production. The infrastructure of TrialNet is also used to enhance other efforts supported by the *Special Diabetes Program*, such as aiding the Type 1 Diabetes Genetics

Consortium (T1DCG) with identification of families with two siblings affected with type 1 diabetes and collection of samples for genetic studies from these families.

There is a rigorous process for consideration of studies proposed for conduct through this coordinated clinical research infrastructure. This involves review by experts in diabetes, immunology, safety/ethics, clinical trials, study design and analysis. As new therapeutic agents are identified through additional studies supported by the *Special Diabetes Program*, TrialNet's standing infrastructure will be indispensable for the testing of these promising agents in patients. Furthermore, TrialNet makes resources available to the broader scientific community. For example, they make available serum, RNA, and peripheral blood mononuclear cell samples from people enrolled in the Natural History Study for validation of new biomarkers of type 1 diabetes. They also invite the broad community to submit proposals for ancillary studies as an adjunct to ongoing protocols. The knowledge gained from TrialNet's Natural History Study will help to spur the design of new prevention and treatment approaches. TrialNet's current position of strength is the result of years of effort in outreach to the diabetes care and research communities, intensive training in research procedures, including sample collection and storage for mechanistic assays (in collaboration with the ITN), and the establishment of close collaborative ties among clinical diabetes and immunology researchers. TrialNet scientists also take proactive roles in critically reviewing, identifying, and prioritizing promising candidates for trials, considering both clinical feasibility and scientific merit.

Ongoing Evaluation

TrialNet is led by an Executive Committee consisting of study leadership from the Chairman's Office, the Coordinating Center, NIDDK, and NIAID. This committee provides ongoing oversight, discusses issues related to trial conduct, and coordinates various Study Group activities. The TrialNet Steering Committee, comprised of the principal investigator and a co-investigator from each clinical center, principal investigator from the Coordinating Center and each major laboratory, and representatives from NIDDK, NIAID, NICHD, and JDRF, meets two times yearly to evaluate proposed and ongoing protocols and to reach consensus for TrialNet activities. A Data and Safety Monitoring Board (DSMB), appointed by NIDDK, NIAID, and NICHD, reviews diabetes protocols from TrialNet, the ITN, and the Autoimmunity Centers of Excellence. The DSMB meets at least four times per year to monitor protocol progress and reviews all safety issues. A TrialNet External Evaluation Committee (EEC), appointed by NIDDK, provides expert input and external review of overall TrialNet activities yearly.

TrialNet's intensive, streamlined protocol review process involves five separate committees: (1) Scientific Review Committee (with veto power), (2) Clinical Feasibility Committee, (3) Infectious Disease Safety Review Committee, (4) Ethics Committee, and (5) Intervention Strategies and Prioritization Committee (which meets last and considers reports of the other four committees). Several of these committees include outside experts. Protocols may be advanced from these committees for approval by the Steering Committee. Once a protocol is approved, associated mechanistic studies to improve

understanding of pathophysiology underlying the disease are developed by a Mechanistic Studies Committee. Following Steering Committee approval, NIH seeks external input (from the DSMB and/or the EEC) to decide whether to move forward with protocol implementation.

In addition, TrialNet has been evaluated by external panels of scientific and lay experts at *ad hoc* evaluation meetings convened by NIDDK in January 2005 and April 2008. These meetings were an opportunity for external experts to evaluate progress and provide input on future research directions (for more information, see the Executive Summary and Appendix B). Through *ad hoc* evaluation meetings and regular meetings of the EEC, NIDDK continually seeks external input to inform current and future directions for TrialNet.

Program Enhancements

Because of the evolving nature of science, consortia supported by the *Special Diabetes Program* have evolved over time and have undergone enhancements to take advantage of new technologies and research findings, and to accelerate progress. Some enhancements have been made in response to external input and others have been initiated by the consortium members. Examples of program enhancements for TrialNet include:

- Shortly after TrialNet began, it was recognized that the international community had much to contribute to the network both intellectually and logistically. With the agreement of NIDDK, the JDRF solicited applications for international clinical centers to join TrialNet. Three European sites and one Australian site are fully represented on the Steering Committee. These sites have contributed to the screening of
- people for the Natural History Study, enrollment of participants into the new-onset intervention studies and into the Oral Insulin Prevention Study, and in mechanistic studies.
- The initial protocol review process relied heavily on primary review at the level of the Steering Committee. After a few years, the protocol submission and review process was modified to facilitate thorough and rapid review and prioritization of protocols before coming to the Steering Committee for formal consideration.
- For those proposals approved for inclusion in TrialNet, initiating investigators have joined investigators with special expertise in the network to form a Protocol Development Team to expedite protocol development. This includes staff from the Chairman's Office, the Coordinating Center, and NIDDK. The Team was convened to lead the development of all protocols and to coordinate activities of the individual committees that oversee each protocol. A common template is used, and institutional review board (IRB) and regulatory issues are considered early in the process to expedite protocol development.
- At the end of the initial 7 year grant period, Clinical Center cooperative agreement PIs were asked to re-compete for funding and center status, and affiliated sites were invited to join the competition to become new centers. This competition led to the selection of 14 outstanding centers, 12 of which were continuations of prior cooperative agreements, and 2 new centers that were formerly TrialNet affiliates. All of the centers successfully competed by demonstrating exceptional recruiting ability and scientific knowledge and innovation that will improve TrialNet now and into the future.

- In addition to a re-competition of TrialNet centers, the TrialNet biostatistics and data coordinating center, which was formerly funded by a cooperative agreement, was converted to a contract and was competed in an open contract Request for Proposals issued in 2008. A new contract was awarded to the University of South Florida Data Coordinating Center, which offered strengths in operational efficiency and electronic database capabilities. The coordinating center transition was accomplished during the latter part of 2008 and 2009. The network looks forward to many more years of strong biostatistical capability and leadership, and efficient data and network coordination.

Coordination with Other Research Efforts

TrialNet coordinates its efforts with multiple other type 1 diabetes research consortia and networks supported by the *Special Diabetes Program*. Collaboration, coordination, and resource sharing serve to synergize research efforts and accelerate research progress. Examples of coordination with other consortia are given below. For a summary of ongoing collaborative efforts, please see Appendix D.

Coordinating Patient Recruitment Efforts:

- TrialNet and the ITN jointly introduced and advertised the TrialNet Natural History Study, the ITN Insulin B chain Vaccine Study, the ITN Anti-CD3 Study, the ITN Thymoglobulin Study and the ITN IL-2/Rapamycin Study.
- North American TrialNet centers participated as recruitment centers for the T1DGC North American Network. TrialNet investigators supplied the T1DGC with 74.8 percent of the affected sib-pair or trio families collected in North America.
- T1DGC assisted TrialNet in establishing international recruitment sites.
- TrialNet, The Environmental Determinants of Diabetes in the Young (TEDDY), and the Trial to Reduce IDDM in the Genetically At-Risk (TRIGR) have coordinated recruitment efforts to ensure that they are not adversely competing for patient participants in their studies.

Coordinating the Conduct of Clinical Trials:

- TrialNet and DirecNet are jointly performing the Metabolic Control Study, a study evaluating early aggressive meticulous glycemic control facilitated by use of a continuous glucose sensor-augmented insulin pump.
- TrialNet collaborates with the ITN to facilitate implementation of clinical trials designed by ITN. More than 90 percent of ITN type 1 diabetes study participants have been recruited and followed at TrialNet sites. Conversely, the ITN assists TrialNet with sample collection, RNA purification, PBMC isolation, sample tracking, storage, and analysis of mechanistic samples. A coordinating committee facilitates the TrialNet-ITN interactions and a common DSMB is used for type 1 diabetes studies. Representatives from the ITN serve as full members of the TrialNet Mechanistic Study Committee.
- Protocols potentially of interest to TrialNet and ITN are considered by both consortia to assess the possibility for joint sponsorship.
- TrialNet communicates regularly with the Clinical Islet Transplantation Consortium on clinical and mechanistic issues.

Enhancing Data Comparison Among Studies:

- TrialNet, TEDDY, and T1DGC share the same North American laboratory for measurement of autoantibodies. This coordination will permit direct comparison between results obtained in each study.
- TrialNet uses laboratories certified through the HbA1c Standardization Program.
- The C-peptide Standardization Program included the TrialNet C-peptide measurement laboratory in its international comparison and harmonization efforts, which will continue with the development of the reference standards needed to harmonize the assay into the future.
- TrialNet has been an active participant in an NIDDK-led program to standardize and harmonize autoantibody measurements in all NIDDK-sponsored research networks, as well as the CDC-led Diabetes Autoantibody Standardization Program (DASP).
- T1DGC, TrialNet, SEARCH for Diabetes in Youth, and TEDDY are sharing information and reagents so that they can assess allele and haplotype frequencies of

the same sets of genes including *Human Leukocyte Antigen* and other diabetes-predisposing genes. This coordination will permit comparisons of genetics data across all four studies, effectively increasing the power of each in learning which genes play a role in disease onset.

Coordinating Research Studies Involving Newborns:

- TrialNet investigators meet with investigators participating in other type 1 diabetes research studies involving newborns (TEDDY and TRIGR) to discuss opportunities for enhancing coordination and collaboration.
- TEDDY has shared the following materials with TrialNet investigators who are studying newborns in the NIP Diabetes Study: genetics-screening procedures, data forms, and parts of the Manual of Operation concerning follow-up of high-risk children. Through concerted action to define exclusive study geographic areas, investigators in the two studies have also avoided direct competition for eligible study participants.

TrialNet Administrative History

Date Initiative Started	2001
Date <i>Special Diabetes Program</i> Funding Started	2001
Participating Components	NIDDK, NIAID, NICHD, NCRR, NCCAM, JDRF, ADA
Web site	www.diabetestrialnet.org

TrialNet is conducting clinical trials with researchers from 18 Clinical Centers in the United States, Canada, Finland, United Kingdom, Italy, and Australia. In addition, more than 150 medical centers and physician offices participate in TrialNet.

IMMUNE TOLERANCE NETWORK (ITN)

The ITN is an international consortium of over 80 scientists and physicians dedicated to evaluating therapies to reduce autoimmunity and other adverse immune responses by inducing, maintaining, and monitoring “immunological tolerance” in humans for islet, kidney, and liver transplantation; autoimmune diseases; and allergy and asthma. The goal of immune tolerance research is to identify and evaluate strategies to “re-educate” the immune system in a highly specific manner to prevent graft rejection or disease-causing immune responses. Examples of autoimmune processes targeted by the ITN include those that destroy insulin-producing beta cells in type 1 diabetes, or the immune responses that destroy transplanted islets. It is important, however, that these strategies not dampen the body’s normal infection-fighting immune mechanisms. Particular trials may be conceived by the ITN itself, or by scientists and physicians not initially affiliated with the ITN, but who are invited to submit clinical trial proposals. The ITN then assists investigators with study development, implementation, monitoring, and analysis; access to cutting-edge technologies; and a wide range of other expert scientific, regulatory, and technical support. Clinical trials are augmented by mechanistic studies designed to uncover basic biological features of immune tolerance which will, in turn, help guide the design of future clinical trials.

HIGHLIGHTS OF PROGRESS

- *Conducting the first multicenter trial of islet transplantation:* Nine sites in North America and Europe successfully replicated the “Edmonton protocol” for islet transplantation in the ITN’s multicenter study from 2001-2006. The “Edmonton protocol” was a revolutionary new procedure developed in Canada that greatly improved the outcomes for islet transplantation in a relatively small single-site study. The ITN study showed that it was possible to replicate the Edmonton study at multiple islet transplantation research centers. While most people experienced a gradual loss of transplanted islet function over a period of years, even those individuals who retained only partial islet function and did not remain “insulin-free” benefited greatly from improved post-transplant glycemic control. The study played a critical role in defining the challenges, obstacles, and feasibility of moving islet transplantation into the therapeutic arena.
- *Determining that autoantibody titers may predict islet transplant success:* Among the aberrant immune processes that occur in type 1 diabetes is the production of “autoantibodies” that recognize beta cell components. Autoantibody levels were measured pre-transplant in patients enrolled in the ITN multicenter study of the “Edmonton protocol.” Investigators found that pre-transplantation levels of autoantibodies to two beta cell proteins correlate indirectly with long-term graft survival and insulin-free status following the transplant. If confirmed, this result may lead to the development of predictive biomarkers of graft survival. It also underscores the need to abrogate both the immune reactivity to transplanted (foreign) donor cells and the ongoing autoimmune response.
- *Completing a pilot study testing novel vaccine for new-onset type 1 diabetes:* A pilot study tested an insulin-B chain peptide vaccine designed to preserve function of insulin-producing beta cells in newly diagnosed patients.

People who received the vaccine exhibited an increase in insulin autoantibody levels and developed T cell responses to the insulin B-chain peptide, clear indications of humoral and antigen-specific cellular responses to the vaccine. Evidence of the induction of antigen-specific regulatory T cells that might impede disease progression was also observed in treated patients.

- *Completing trials testing anti-T cell therapies for treating new-onset type 1 diabetes:* A number of promising anti-T cell therapies are being evaluated in type 1 diabetes, including the anti-CD3 monoclonal antibody, hOKT3gamma1(Ala-Ala). This antibody was shown to prolong the “honeymoon” phase for up to 2 years in a small study of recently diagnosed type 1 diabetes patients. The ITN is currently evaluating this agent in an expanded, multicenter phase II study of 83 people using a modified dose schedule designed to prolong beta cell preservation. In addition, the ITN is enrolling a 66 person, multicenter, placebo-controlled study of antithymocyte globulin which showed promising rates of insulin remission in a pilot study in Europe.
- *Launching a phase I trial using a novel cocktail to promote regulatory T cells:* Interleukin-2 (IL-2) and sirolimus have been used successfully to suppress autoimmune destruction of islets in non-obese diabetic (NOD) mice. The data suggest that the combination therapy promotes the development and survival of regulatory T cells known to suppress autoimmunity. This ITN trial is assessing the safety of this combination in order to provide a foundation for testing its effectiveness in individuals with recent-onset type 1 diabetes.
- *Demonstrating that a combination of assays detects type 1 diabetes with high sensitivity and specificity:* ITN investigators showed that no single assay (such as an autoantibody test or any of several other types of assays) distinguishes non-diabetic individuals from those with type 1 diabetes. However, the combination of an autoantibody test and two types of assays for T cells identified a high proportion of patients with type 1 diabetes with no false positives.
- *Supporting an active pipeline of new studies to assess immunomodulatory interventions for treating new-onset type 1 diabetes:* ITN will open a multicenter phase II study of Alpha-1 Antitrypsin (AAT) in 2010. AAT has shown promising results in NOD mice leading to a sustained reversion from hyperglycemia to normal glucose values in some animals. AAT, which is currently approved for use in patients with genetic deficiencies of AAT production, is believed to play a role in dampening inflammatory responses. Two additional studies are in earlier stages of clinical trial development and other projects are completing preclinical toxicology studies.

Anticipated Outcomes

The ITN is adding to knowledge of the autoimmune response in type 1 diabetes and testing strategies for blocking destruction of beta cells. ITN research on assays of the immune system to detect those at risk may help in the early identification of research participants and lead

to improved outcomes via earlier intervention. Research on tolerance-inducing agents brings hope of arresting the autoimmune destruction of beta cells; while the overall goal is maintenance of residual function, preservation of at least some insulin producing cells would facilitate glucose control with less risk of hypoglycemia. For

those who undergo islet transplantation, modulation of the immune system is necessary, not only to block the diabetes-specific autoimmune reactions that destroy beta cells, but to prevent the general immune rejection that can occur with any transplanted tissue. When donor cells or organs are transplanted, the patient's immune system recognizes these as foreign. Consequently, immunosuppressive drugs are necessary to prevent transplant rejection. However, long-term immunosuppression carries an increased risk of infections and certain types of cancer and many drugs that are effective in suppressing the immune system are also toxic to beta cells. As another potential treatment strategy, scientists are exploring whether beta cells can be coaxed to regenerate to levels that will restore insulin production. If effective, such a treatment would also require blocking of the autoimmune response. The ITN's research may lead to immunosuppression-free protocols or to drugs with narrower specificity to blunt unwanted immune responses. Thus, these efforts hold promise for improving the lives of people with type 1 diabetes and for those at risk.

Ongoing Evaluation

The ITN's principal decision-making body is the Network Steering Committee (NSC), a group of approximately 20 leaders in the field of immune tolerance, transplantation, asthma, allergy, autoimmunity, clinical trial design, and bioethics who evaluate clinical trial proposals, conduct annual strategic assessments, and oversee the ITN research portfolio and policies. NSC recommendations are subject to prioritization and final approval by the Network Executive Committee, which consists of ITN Directors, additional experts, and NIAID staff. Day-to-day management of ITN operations is carried out by the ITN Director and his deputies. In addition, the ITN

and NIAID leadership convene for periodic meetings to establish milestones, assess progress, and conduct long-range planning. Meetings are held with industry cosponsors and potential partners on an as-needed basis. The majority of ITN/industry collaborations are supported through Clinical Trial Agreements executed between pharmaceutical or biotechnology companies and NIAID.

Concepts for ITN clinical trials are promoted through one of two pathways: the ITN's open call for proposals to the research community or via NSC annual strategic assessments. Strategic Assessment groups, assembled for each of the ITN clinical emphasis areas, are composed of NSC members and external experts in the respective fields. They are tasked with reviewing the ITN portfolio in their area, and identifying promising strategies for discussion and prioritization by the NSC. Each year, several of these are selected for feasibility assessment and protocol development. Studies selected for implementation are developed by the principal investigator, in collaboration with the ITN Clinical Trials Group, the ITN Tolerance Assay Group, and industry partners. NIAID provides regulatory, medical affairs, and project management support. NIAID contractors provide clinical monitoring, statistical data management, and drug distribution services for ITN trials. Study Management Teams—consisting of study investigators, ITN clinical, assay, and operations staff, NIAID project managers, contractors, and industry representatives—oversee the implementation of the study and meet regularly over the course of the trial to review study progress in relation to predefined milestones. The ITN Clinical Trials Group provides operations staff in charge of clinical project management, while the ITN Tolerance Assay and Data Analysis Group ensures the

integrity of the associated mechanistic studies. The ITN also provides data analysis services for mechanistic studies, data warehousing, study logistics, and patient recruitment support for all trials.

The ITN type 1 diabetes projects were evaluated by external panels of scientific and lay experts at *ad hoc* evaluation meetings convened by NIDDK in January 2005 and April 2008. These meetings provided an opportunity for external experts to evaluate progress and provide input on future research directions (for more information, see the Executive Summary and Appendix B). Through *ad hoc* evaluation meetings and regular meetings of Committees described above, NIAID continually seeks external input to inform current and future directions for the ITN.

Program Enhancements

The *Special Diabetes Program* has had a significant impact on ITN studies and has stimulated and enhanced the development and conduct of additional clinical trials in early onset type 1 diabetes. Without the support of the *Special Diabetes Program*, many of the studies that are currently planned or ongoing within the Network could not have been conducted.

These resources have enabled the ITN and other NIAID contractors (statisticians, and those responsible for data management, site monitoring, etc.) to dedicate staff to this mission.

Coordination with Other Research Efforts

The ITN coordinates its activities with multiple other type 1 diabetes research consortia and networks supported by the *Special Diabetes Program*. Collaboration, coordination, and resource sharing serve

to synergize research efforts and accelerate research progress. Examples of coordination with other consortia are given below. For a summary of ongoing collaborative efforts, please see Appendix D.

Coordinating Patient Recruitment Efforts:

- The ITN and TrialNet jointly introduced and advertised the ITN Insulin B-chain Peptide Study and the TrialNet Natural History Study.

Collaborating To Enhance Islet Transplantation Efforts:

- Islet Cell Resource Centers isolated and supplied human islets to the ITN Multi-centered Islet Transplantation Trial clinical sites.
- The Collaborative Islet Transplant Registry archives trial results.
- The Clinical Islet Transplantation (CIT) Consortium and ITN are sharing expertise and coordinating efforts in the planning of immunologic assays in CIT trials. ITN core labs will perform selected assays in CIT trials.
- The CIT Consortium, the ITN, and the Non-Human Primate Transplantation Tolerance Cooperative Study Group (NHPCSG) are interested in using similar reagents for islet transplantation or as immune modulators for the treatment of type 1 diabetes.
- The ITN shares information about scientific priorities and pre-clinical research needs with the NHPCSG and both organizations benefit from shared information about study outcomes.
- ITN priorities for pre-clinical testing of new therapeutics are considered in evaluating NHPCSG Opportunities Pool applications. Several ITN high-priority strategies have been funded as pilot projects.

Sharing of Other Resources and Information:

- ITN collaborates with TrialNet to facilitate implementation of clinical trials designed by ITN. Many ITN type 1 diabetes study participants have been recruited and followed at TrialNet sites. A coordinating committee facilitates the TrialNet-ITN interactions and a single DSMB reviews many NIDDK and NIAID type 1 diabetes clinical trials. The TrialNet chairman is a member of the ITN Steering Committee.
- Protocols potentially of interest to ITN and TrialNet are considered by both consortia with the opportunities for joint sponsorship.
- ITN-supported investigators have used the Type 1 Diabetes-Rapid Access to Intervention Development program for production and pre-clinical testing of novel reagents.
- TRIGR and the ITN are coordinating their efforts in the area of T cell assays.

ITN Administrative History

Date Initiative Started	1999
Date <i>Special Diabetes Program</i> Funding Started	2001
Participating Components	NIAID, NIDDK, and JDRF
Web site	www.immunetolerance.org
The ITN consists of over 80 world leaders in the clinical and basic sciences of immune tolerance from academic research institutions around the world.	

COOPERATIVE STUDY GROUP FOR AUTOIMMUNE DISEASE PREVENTION (PREVENTION CENTERS)

The Cooperative Study Group for Autoimmune Disease Prevention (Prevention Centers) is a collaborative program of investigators that supports research on the development of new prevention and treatment strategies for autoimmune diseases and evaluates these approaches in pilot and clinical studies. The Prevention Centers aim to create improved models of disease pathogenesis and therapy to better understand immune mechanisms. Ultimately, these models will provide opportunities to test new prevention strategies and validate new tools for human studies. The Centers also support projects, such as the development of surrogate markers for disease progression and/or regulation, designed to encourage rapid translation of discoveries from animal models to human clinical trials.

HIGHLIGHTS OF PROGRESS

- *Identifying insulin as a primary target for the autoimmune response in the non-obese diabetic (NOD) mouse model of diabetes:* Mice have two insulin genes, and generation of a NOD mouse lacking the insulin 1 gene revealed that it is required for development of insulinitis and diabetes. Subsequent experiments showed that diabetes did not develop in NOD mice engineered to produce a slightly altered insulin molecule not recognized by the mouse's immune system. This research suggests that autoimmune reaction against insulin may be a critical initiator of the pathway toward beta cell destruction.
- *Launching the NOD Roadmap Project on the NOD mouse model of type 1 diabetes:* This study has generated a comprehensive time course of disease in the NOD mouse model of type 1 diabetes, cataloguing phenotypes, transcripts, and histochemistry through multi-institutional collaborations. Initial transcript data and analysis are posted on an open source Web site. Ongoing work on this project will refine this analysis by focusing on gene expression in small groups of cells in the pancreas. This project lays an extensive groundwork for future investigations into the mechanisms underlying the pathogenesis of type 1 diabetes in this model and the extension of these results to human diabetes.
- *Demonstrating the role of the Deaf1 gene in the development of type 1 diabetes:* As part of the NOD Roadmap project, scientists found that cells in the murine pancreatic lymph nodes make two forms of a gene called *Deaf1*. One form encodes full-length, functional *Deaf1* protein, while the other encodes a shorter, nonfunctional variant. Additional experiments in mice suggested that the functional form of *Deaf1* may control the production of molecules needed to eliminate immune cells that can destroy insulin-producing cells in the pancreas, thus preventing type 1 diabetes. Researchers also found that levels of the variant form of *Deaf1* were higher in people with type 1 diabetes compared to levels in people without the disease. The research suggests that the development of type 1 diabetes may be due to increased levels of the *Deaf1* variant protein in pancreatic lymph nodes, which may, in turn, lead to reduced production of molecules that are required to "educate" the immune system not to attack the body's own cells, including the insulin-producing cells of the pancreas.

- *Enhancing the autoimmune disease prevention research enterprise:* The Centers launched new autoimmune disease prevention projects through pilot projects. Over one-third (36 percent) of the innovative high-risk and pilot/feasibility projects awarded using the Prevention Centers' special opportunities funds have matured into NIH Research Project Grants. Notably, seven of these pilot projects were awarded to young investigators, who subsequently have converted them into self-supporting, career-establishing grants. In addition, several large programs and major initiatives were launched or initially supported through this pilot program.
- *Developing new tools to predict and monitor disease onset and progression:* Developed biological tools to identify certain types of T cells that can attack beta cells based on recognition of the beta cell protein GAD65. These tools are "MHC class II tetramers," which are constructed to contain a segment of the GAD65 protein. Researchers can use these tools to retrieve, quantify, and characterize GAD65-reactive T cells from patients and individuals at risk for the disease. Such T cells are a potential marker of early disease, and this research will increase understanding about the destructive autoimmune response that underlies type 1 diabetes. In addition, the Centers developed tools for using proteomics technology that can facilitate detection of autoantibodies and other markers of autoimmune disease.
- *Characterizing the functional properties of cells called "CD4⁺CD25⁺ regulatory T cells:"* These cells help protect against autoimmune disease by suppressing the activities of autoreactive T cells. Investigators also have identified functional defects in this T cell subset in humans with autoimmune disease.
- *Demonstrating the mechanisms by which blockade of a particular molecular interaction between immune cells can prevent or modulate the course of diabetes and other autoimmune diseases:* In these studies, scientists administered to mice an agent that blocked the interaction between two important molecules. One molecule, called CD154, exists on the surface of many T cells, and another molecule, called CD40, is present on other types of immune cells. One of their findings was that blocking the CD154-CD40 interaction resulted in induction of a novel type of cell that is able to prevent the onset of type 1 diabetes in mice.

Anticipated Outcomes

Autoimmune diseases are significant contributors to the burden of chronic illness. The ultimate goals of autoimmune disease research are to understand the body's aberrant immune responses and to "re-educate" the body to become tolerant to the antigens and tissues that are the targets of an attack without impairing the immune system's ability to fight infection. To this end, the Prevention Centers support a multidisciplinary program of investigators focused on understanding

the immune mechanisms that underlie the process of autoimmunity, determining novel approaches to modulation of the immune system, and applying this knowledge to the prevention of autoimmune diseases.

In people with type 1 diabetes, the immune system attacks insulin-producing beta cells in the pancreas, prohibiting the body from absorbing glucose. Investigators funded by the Prevention Centers are working to identify and characterize cells of the immune

system, such as certain types of T cells, which attack and destroy the body's beta cells causing type 1 diabetes. Another research focus is to define the beta cell molecules that are targeted for autoimmune attack. Prevention Centers investigators have discovered that insulin is a primary target of this process in a mouse model. Researchers funded by the Prevention Centers also are examining how other aspects of the immune system, or experimental manipulations that alter the immune system, may confer protection against autoimmunity. For example, their research in mice suggests that the functional form of Deaf1 plays a role in the production of molecules needed to eliminate immune cells that can destroy insulin-producing cells in the pancreas. This research is helping to identify new markers of disease susceptibility and progression and opportunities for novel treatment strategies.

Ongoing Evaluation

The Prevention Centers' progress and study design are monitored and evaluated on an ongoing basis through Steering Committee meetings, annual all-investigator meetings, and external evaluations. The Prevention Centers Steering Committee meets to discuss ongoing pilot projects and new pilot proposals as well as the overall progress of the group. External reviewers attended the 2005 all-investigator meeting to provide feedback on the accomplishments and direction of the program.

In addition, the Prevention Centers have been evaluated by external panels of scientific and lay experts at *ad hoc* evaluation meetings convened by NIDDK in January 2005 and June 2009. These meetings were an opportunity for external experts to evaluate the progress and provide

input on future research directions (for more information, see the Executive Summary and Appendix B). Through *ad hoc* evaluation meetings and all-investigator meetings, NIAID continually seeks external input to inform current and future directions for the Prevention Centers.

Program Enhancements

Because of the evolving nature of science, consortia supported by the *Special Diabetes Program* have evolved over time and have undergone enhancements to take advantage of new technologies and research findings, and to accelerate progress. Some enhancements have been made in response to external input and others have been initiated by the consortium members.

Examples of program enhancements for the Prevention Centers to encourage applications from the most talented scientists as well as submissions by young investigators include:

- NIAID created a Web site for the Prevention Centers to advertise funding opportunities: <http://www3.niaid.nih.gov/about/organization/dait/CSGADP.htm>. After the Web site's implementation, the percentage of projects awarded to investigators new to the program rose from 58 percent of projects in the previous funding period (FY 2001-2005) to 73 percent in the current funding period (FY 2006-2009).
- The Steering Committee emphasizes young investigators when selecting innovative projects. For the current funding period (FY 2006-2009), 38 percent of innovative project awards were made to new investigators, compared to 21 percent during the previous period.

Prevention Centers Administrative History

Date Initiative Started	2001
Date <i>Special Diabetes Program</i> Funding Started	2001
Participating Components	NIAID, NIDDK, JDRF
Web site	www.niaid.nih.gov/about/organization/dait/Pages/CSGADP.aspx
This Consortium consists of six centers in the United States.	

STANDARDIZATION PROGRAMS: DIABETES AUTOANTIBODY STANDARDIZATION PROGRAM (DASP); C-PEPTIDE STANDARDIZATION; AND IMPROVING THE CLINICAL MEASUREMENT OF HEMOGLOBIN A1c (HbA1c)

The purpose of these programs is to develop and implement standardization programs designed to improve the measurement of: (1) aberrant molecules called “autoantibodies,” which are predictive of type 1 diabetes; (2) C-peptide as an indicator of insulin production; and (3) HbA1c as an indicator of glycemic control. Such improvements and standardization are greatly advancing both research and patient care.

DASP

DASP seeks to improve the measurement of autoantibodies in blood that are predictive of type 1 diabetes, and to decrease laboratory-to-laboratory variation. Autoantibody production reflects abnormal and destructive immune system functioning. A normal immune system is designed to fight infections; one part of this complex process is the production of antibodies that target infectious agents. The immune system of a person who has—or is developing—type 1 diabetes, however, also makes “autoantibodies” that recognize insulin and other beta cell-derived molecules. Autoantibodies are currently the best predictors of the onset of type 1 diabetes before the appearance of increased blood glucose and clinical symptoms. In combination with genetic screening, autoantibody tests are used to identify individuals at elevated risk of developing type 1 diabetes and to characterize autoimmunity. DASP sets of serum samples are used as standards to evaluate the performance of diabetes laboratories throughout the world and serve as reference materials for developing new methods and technologies. They also have been used for the NIDDK Islet Autoantibody Measurement Harmonization Project, which is helping all the major research consortia standardize protocols for measuring autoantibodies. DASP also provides training and information to guide other laboratories in improving their performance.

DASP standardized assays are critical for research on all forms of diabetes in children because they are helpful in distinguishing type 1 and type 2 diabetes.

C-peptide Standardization Program

This program aims to establish reliability in measurements of C-peptide, which is a byproduct of insulin production by beta cells and thus useful as a marker of beta cell function. In people taking insulin as therapy for diabetes, C-peptide is used to assess insulin production from the beta cell. In clinical trials of agents designed to prevent the disease in at-risk persons, or to preserve beta cell function in individuals with new onset type 1 diabetes, C-peptide is being used as the key outcome measure. Residual beta cell function is associated with better glycemic control, lower risk of hypoglycemia, and lower risk of long-term diabetic complications.

National Glycohemoglobin Standardization Program (NGSP; HbA1c Standardization Program)

The purpose of the NGSP is to achieve standardization and reliability in measurement of HbA1c, a component of blood that is a good surrogate measure of long-term blood glucose control and, as such, reflects risk of diabetic complications. Clinical guidelines for controlling blood glucose to reduce diabetes complications set targets for control of blood glucose as assessed by this key test based on results from two landmark clinical trials:

the Diabetes Control and Complications Trial (DCCT) for type 1 diabetes and the United Kingdom Prospective Diabetes Study for type 2 diabetes. By successfully standardizing HbA1c testing so that clinical laboratory results can be related directly to the results of the DCCT, this program is enabling health care providers and patients to accurately and meaningfully assess glycemic control and risks for complications. The standardization of HbA1c measures is essential to public health efforts, such as those of the National Diabetes Education Program (NDEP), to improve diabetes control nationwide so that the public can reap the benefits of clinical trials

proving that complications can be delayed or prevented. This effort also allows researchers to better define diabetes control and evaluate risk for complications, as well as foster comparison of results across multiple studies worldwide. The NGSP consists of a Steering Committee and a Laboratory Network. The NGSP network interacts with manufacturers and laboratories to assist with calibration and to certify methods as traceable to the DCCT. The NGSP also works with the College of American Pathologists to assign HbA1c values to proficiency testing specimens for better evaluation of HbA1c results in clinical laboratories.

HIGHLIGHTS OF PROGRESS

- DASP conducted and presented workshop evaluations of key international diabetes laboratories in 2000, 2002, 2003, 2005, 2006, and 2009.
- DASP validated improvement of two different technologies for measuring autoantibodies.
- DASP documented improvement in performance of the insulin autoantibody assay for laboratories with consistent participation in the DASP Training Program.
- DASP created laboratory reference materials (blood samples) from type 1 diabetes patients and healthy people that are available to ensure assay quality and to support further technology development.
- DASP sets of serum samples have been used for the NIDDK Islet Autoantibody Measurement Harmonization Project. This effort is helping to standardize protocols for measuring autoantibodies within numerous research consortia, and is thus having a far-reaching impact.
- Accurate measurement of antibodies through DASP have allowed improved characterization of childhood diabetes in the SEARCH for Diabetes in Youth study (see Goal I) and an appreciation of the existence of hybrid forms of diabetes with characteristics of both type 1 and type 2. Accurate antibody measurement has also benefitted enrollment in the NIDDK's Treatment Options for Type 2 Diabetes in Youth (TODAY) clinical trial. More precise measures have allowed more patients to enroll into the trial because eligibility excluded those with autoimmunity, and previous assays were non-specifically falsely identifying some potential participants as having autoimmunity.
- DASP validated the fourth major diabetes autoantigen, zinc transporter 8 (ZnT8) in DASP 2007 and DASP 2009. DASP 2010 will evaluate polymorphic ZnT8 dimer and trimer constructs.

- A new non-radioactive assay format, the Luminescent Immunoprecipitation System (LIPS) demonstrated the potential for good performance in DASP 2009 and the availability of LIPS reagents will be expanded to additional laboratories in DASP 2010.
- The C-peptide program evaluated the stability of C-peptide and effects of common interferences. The program is coordinating international laboratory comparisons of C-peptide measurement to harmonize the measurement technologies and to improve precision and reliability of results. Results of two comparisons have been published in *Clinical Chemistry*, in 2007 and 2008. In the latest comparison trial, two isotope-dilution liquid chromatography–mass spectrometry was used as a reference method to assign values to serum-sample calibrators, which helped to reduce the imprecision among methods and laboratories. This research is crucial for optimizing measurement techniques and harmonizing methods, which will enable the use of C-peptide endpoints in large multicenter clinical trials, and potentially, for clinical monitoring.
- The HbA1c standardization program has improved the standardization and reliability in measures of HbA1c so that clinical laboratory results can be used by health care providers and patients to accurately and meaningfully assess blood glucose control and risks for complications. Building on this success, the American Diabetes Association (ADA) recently recommended HbA1c as a more convenient approach to diagnose type 2 diabetes.
- Standardization of the HbA1c test supported the development of a national education campaign on “knowing your HbA1c number.” The campaign is sponsored by the NDEP, which is a partnership of NIDDK and CDC.
- Building on the success of the HbA1c standardization program, NIDDK was able to launch a new campaign highlighting the importance of using accurate methods to test HbA1c in people who have sickle cell trait or other inherited forms of hemoglobin. Results have been published in *Journal of Diabetes Science and Technology* in 2009 and in *Clinica Chimica Acta* in 2010.
- Standardized HbA1c is the key outcome measure in studies testing efficacy of new drugs for diabetes treatment and is the basis for U.S. Food and Drug Administration approval of new diabetes medications.
- The CDC HbA1c laboratory and the NGSP have participated in efforts of the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) to develop a “higher level” reference method for measuring HbA1c. This reference method was approved by the IFCC and is now the basis for uniform standardization of HbA1c assays worldwide. The IFCC Working Group also developed a mathematical equation to facilitate comparison among results obtained by this IFCC reference method and the NGSP, as well as with methods in Sweden and Japan.
- For HbA1c measurements, between 1996 and 2006, there was an increase in the number of methods and laboratories certified by the NGSP as traceable to the DCCT. Methods and laboratories are certified each year.

In 2005, the NGSP certified 63 HbA1c diagnostic methods and 41 laboratories. Nearly all laboratories worldwide are using methods that are traceable to and certified by the NGSP.

- Proficiency testing data also showed a decrease in the variability of HbA1c measurements among laboratories.

Anticipated Outcomes

The autoantibody, C-peptide, and HbA1c standardization programs are extensive efforts to improve laboratory measures of critical markers for type 1 diabetes risk and disease progression. While key to research, the importance of these efforts extends beyond research to diagnosis and treatment of all forms of diabetes. Standardized assays are required for the success of multicenter clinical studies as different participating laboratories must be able to obtain measurements that are comparable and can be meaningfully analyzed together. Research progress will also be enhanced when the results of different trials are based on standardized measures to facilitate comparison. Patients and their health care practitioners will be better able to ascertain what a given blood test means in terms of health risks and treatment plans when test results are sufficiently reliable for comparison with relevant research studies. As a result of research toward standardizing autoantibody testing and identifying new biomarkers for predictive assays, those at risk for type 1 diabetes may be diagnosed earlier, permitting earlier intervention to diminish disease severity. Improved measurement techniques for C-peptide will impact research on agents that can preserve beta cell function, particularly in those with new-onset diabetes. C-peptide measurements are increasingly used in both government-funded and industry trials, since FDA has recently accepted C-peptide preservation as an important outcome measure of benefit for new-onset clinical trials. Improvements in HbA1c

testing have enabled the ADA to recommend the test as a more convenient approach for diagnosing type 2 diabetes. Thus, the standardization programs are already having wide-reaching implications for researchers, clinicians, and patients.

Ongoing Evaluation

Ongoing evaluation of the research and progress of the Standardization Programs is carried out as described below.

DASP: DASP efforts are managed by the Immunology of Diabetes Society (IDS) Autoantibody Standardization Committee, CDC, and NIDDK. The activities and progress are reviewed by IDS participants at the workshop presentations at the IDS meetings, and additional input is periodically sought from the IDS president and other prominent scientists in the field.

C-peptide: The C-peptide standardization program has project oversight from CDC. In addition, a C-peptide Standardization Advisory Committee provides input on research studies and assists in evaluation of results.

HbA1c: The effort to improve and standardize the measurement of HbA1c is divided between CDC and the NGSP (with CDC support) at the University of Missouri. The CDC and the NGSP Laboratory also participate as members in the IFCC Reference Laboratory Network for HbA1c Measurement.

In addition, these programs were evaluated by an external panel of scientific and lay experts at an *ad hoc* evaluation meeting convened by NIDDK in January 2005. This meeting was an opportunity for external experts to evaluate progress and provide input on future research directions (for more information, see the Executive Summary and Appendix B). Through *ad hoc* evaluation meetings and regular meetings of the Committees described above, CDC and NIDDK continually seek external input to inform current and future directions for these standardization programs.

Program Enhancements

Because of the evolving nature of science, Standardization Programs supported by the *Special Diabetes Program* have evolved over time and have undergone enhancements to take advantage of new technologies and research findings, and to accelerate progress. Some enhancements have been made in response to external input and others have been initiated by the consortium members. Examples of program enhancements for the Standardization Programs include:

- DASP is standardizing new autoantibodies as they are identified.
- Plans for future enhancements to the C-peptide harmonization effort include the establishment of reference methods and materials endorsed by the Joint Committee for Traceability in Laboratory Medicine and the World Health Organization. These methods and materials can be used to establish surveillance of commercial laboratory performance and achieve traceability goals.
- The HbA1c test has been examined in diverse populations both with regard to ensuring that commercial laboratories use tests that are valid in people with hemoglobinopathies and to look for

variation in HbA1c levels in different racial and ethnic groups in conjunction with the ADA decision to use HbA1c for diagnosis.

Coordination with Other Research Efforts

The Standardization Programs coordinate their efforts with multiple other type 1 diabetes research consortia and networks supported by the *Special Diabetes Program*. Collaboration, coordination, and resource sharing serve to synergize research efforts and accelerate research progress. Examples of coordination with other consortia are given below. For a summary of ongoing collaborative efforts, please see Appendix D.

Enhancing Quality and Standardization of Laboratory Measures in Multicenter Clinical Trials:

- DASP interacts with The Environmental Determinants of Diabetes in the Young, Type 1 Diabetes Genetics Consortium, Type 1 Diabetes TrialNet, and SEARCH for Diabetes in Youth autoantibody labs, by providing laboratory materials and proficiency testing to facilitate their autoantibody measurements.
- The C-peptide program included two laboratories from TrialNet in an international comparison effort, the results of which illustrated the need to identify and minimize the major sources of variation in C-peptide measurements in multicenter, multi-laboratory clinical studies.
- TrialNet, Epidemiology of Diabetes Interventions and Complications, and other clinical studies supported by the *Special Diabetes Program* use laboratories certified through the NGSP.

Improving and Developing Technology:

- Because of limitations associated with autoantibody testing, DASP is working with NIDDK-supported

investigators studying proteomics and type 1 diabetes, and collaborating with the Pacific Northwest National Laboratory, to find new biomarkers to improve diagnosis of and prediction of risk for this disease. This collaborative project will use blood samples collected by DASP from newly diagnosed type 1 diabetes patients and healthy people. The samples will be analyzed with proteomic and metabolomic technologies: that is, large-scale

profiling and characterization of the component proteins and small molecules, respectively. Differences identified between samples from patients and healthy individuals can be further investigated for potential predictive or diagnostic value.

DASP Administrative History

Date Initiative Started	1998
Date <i>Special Diabetes Program</i> Funding Started	1998
Participating Components	CDC, NIDDK, and Immunology of Diabetes Society

C-peptide Standardization Program Administrative History

Date Initiative Started	2002
Date <i>Special Diabetes Program</i> Funding Started	2003
Participating Components	CDC, NIDDK, C-peptide Standardization Advisory Committee, and University of Missouri

HbA1c Standardization Program Administrative History

Date Initiative Started	1996
Date <i>Special Diabetes Program</i> Funding Started	1998
Participating Components	CDC, NIDDK, NGSP
Web site	www.ngsp.org

The HbA1c program is carried out at the CDC-supported NGSP, as well as the Reference Laboratory for HbA1c at CDC, both members of the IFCC Reference Laboratory Network for HbA1c; NIDDK also funds this effort.

TRIAL TO REDUCE IDDM IN THE GENETICALLY AT-RISK (TRIGR)

TRIGR is an international clinical trial to determine, for infants at risk for type 1 diabetes, whether weaning to extensively-hydrolyzed formula, as compared to standard cow's milk formula, will reduce the risk of developing diabetes-predictive autoantibodies and, ultimately, type 1 diabetes. Environmental factors, such as exposure during infancy to foreign proteins from food, may interfere with normal immune system development in genetically-susceptible individuals, and formula is usually the first foreign food given to infants as they are weaned from human breast milk. Standard cow's milk formula contains proteins that are intact and thus capable of inciting the immune system. Hydrolyzing proteins breaks them into very small pieces, which are much less likely to elicit an immune response, and prior research has suggested that weaning to hydrolyzed (versus intact-protein) formula may reduce risk of type 1 diabetes. The first phases of TRIGR are extensive, multi-national efforts to identify several thousand infants at risk for type 1 diabetes by recruiting pregnant women who have the disease, or an affected family member, and subsequent screening of the infants for diabetes-associated variants of certain immune system genes (*Human Leukocyte Antigen* genes). As part of the study, exclusive breastfeeding will be encouraged, but once this is no longer possible, babies will enter the intervention portion of the study by being randomly assigned to receive either standard or extensively-hydrolyzed formula (up to age 8 months). Follow-up monitoring will assess autoantibody development and diabetes incidence up to age 10 years.

HIGHLIGHTS OF PROGRESS

- Completed enrollment of 2,160 eligible newborns.
- Achieved 89 percent retention rate over the first 5 years of the study, which is greater than the planned retention rate of 80 percent.
- Achieved 94 percent study-wide protocol compliance (e.g., measuring visits, questionnaires, and blood samples).
- Had a successful intervention phase, which ended in mid-2007. Compliance with the intervention resulted with all planning parameters being met or exceeded.
- Found differences in infant feeding patterns between Europe and North America. In Europe, the first foods to be introduced were typically fruits and vegetables, whereas in North America, gluten-free cereals were introduced first.
- Found that the proportion of mothers with or without type 1 diabetes who initially breastfed their infants did not differ significantly. However, the duration of both exclusive and total breastfeeding was shorter among mothers with type 1 diabetes.
- Discovered that, although differences in early growth patterns were observed in Europe versus North America, in Canada versus the United States, and by maternal type 1 diabetes status, parameters were similar by 24 months of age. Early childhood growth elevations are consistent with the higher incidence of type 1 diabetes in Europe and Canada compared to the United States, and a lower incidence in children of mothers with type 1 diabetes.

Anticipated Outcomes

TRIGR is a large-scale, well-coordinated clinical trial to test the effect of a dietary intervention during infancy on the development of type 1 diabetes in genetically-susceptible individuals. If the results of this trial show that weaning to hydrolyzed infant formula, as compared to standard formula, reduces incidence of type 1 diabetes, then it will have validated a practical way to alter the course of autoimmunity development and reduce type 1 diabetes incidence in young children.

TRIGR builds on prior research in animals and on a pilot study in humans that investigated the association of different infant formulas with autoantibody appearance. It has been hypothesized that diabetes-related autoimmunity may be triggered when the immature gut of an at-risk infant encounters foreign dietary proteins. The use of extensively hydrolyzed formula during weaning would delay the introduction of more complex, intact foreign proteins. Thus, TRIGR may also shed further light on the role of the gut and its immune system in the development of type 1 diabetes. The potential for a dietary modification in infancy to reduce type 1 diabetes—along with biological data on the very large number of genetically susceptible infants being studied—makes the TRIGR study enormously beneficial to families at risk.

Ongoing Evaluation

To ensure ongoing evaluation of the study design and the progress of TRIGR, NICHD has established an External Data Safety Monitoring Board/Advisory Panel for this trial. Additional critical entities include the trial's International Coordinating Center, which integrates operations for all regions of the TRIGR Study Group, maintains and validates documents related to the operations of TRIGR, and is in charge of developing study forms and the

Manual of Operations. A Data Management Unit is responsible for data management systems; monitoring the study for protocol compliance, adverse events, and other issues; and data analysis and reporting. There are also a number of working committees focused on such topics as nutritional intervention, ancillary studies, and internal safety monitoring, among others.

In addition, TRIGR has been evaluated by external panels of scientific and lay experts at *ad hoc* evaluation meetings convened by NIDDK in January 2005 and April 2008. These meetings were an opportunity for external experts to evaluate progress and provide input on future research directions (for more information, see the Executive Summary and Appendix B). Through *ad hoc* evaluation meetings and regular meetings of the External Data Safety Monitoring Board/Advisory Panel, NICHD continually seeks external input to inform current and future directions for TRIGR.

Program Enhancements

Because of the evolving nature of science, consortia supported by the *Special Diabetes Program* have evolved over time and have undergone enhancements to take advantage of new technologies and research findings, and to accelerate progress. Some enhancements have been made in response to external input and others have been initiated by the consortium members. Examples of program enhancements for TRIGR include:

- To take advantage of new and emerging technologies, TRIGR developed a program and explicit guidelines for ancillary studies to facilitate access to TRIGR materials by researchers who seek to expand and embrace new technologies for inclusion into the TRIGR study group.

- TRIGR enhanced coordination with other type 1 diabetes research consortia studying newborns, such as The Environmental Determinants of Diabetes in the Young (TEDDY) and Type 1 Diabetes TrialNet.
- Because measurements of islet autoantibodies were not standardized, it was difficult to compare results across different studies. To address this barrier, an NIDDK Islet Autoantibody Measurement Harmonization Project was undertaken. This effort is helping to standardize protocols for measuring autoantibodies within all NIDDK studies, and is thus having a far-reaching impact. TRIGR will also be using the harmonized assay at the end of the study so that comparisons can be made.

Coordination with Other Research Efforts

TRIGR coordinates its efforts with multiple other type 1 diabetes research consortia and networks supported by the *Special Diabetes Program*. Collaboration, coordination, and resource sharing serve to synergize research efforts and accelerate research progress. Examples of coordination with other consortia are given below. For a summary of ongoing collaborative efforts, please see Appendix D.

Coordinating Research Studies Involving Newborns:

- TRIGR investigators have met with investigators participating in other type 1 diabetes research studies involving newborns (TEDDY and TrialNet) to discuss opportunities for enhancing coordination and collaboration.
- TEDDY and TRIGR share the same Data Coordinating Center. This coordination has resulted in implementation of similar standards in data collection, entry, management of quality control, and analyses for both studies.
- With the closure of the TRIGR accrual, two TRIGR sites began collaborative efforts on recruitment for TEDDY. Both groups are also considering a combined follow-up intervention protocol.

Coordinating Patient Recruitment Efforts:

- Two SEARCH for Diabetes in Youth sites assisted with TRIGR recruitment by providing brochures and other information about TRIGR.
- TRIGR, TrialNet, and TEDDY have coordinated recruitment efforts to ensure that they are not adversely competing for patient participants in their studies.

Enhancing Data Comparison Among Studies:

- TRIGR and TEDDY have implemented similar standards in data collection and entry.
- TRIGR and the Immune Tolerance Network are coordinating their efforts in the area of T cell assays.

TRIGR Administrative History

Date Initiative Started	2001
Date <i>Special Diabetes Program</i> Funding Started	2001
Participating Components	NICHD, Canadian Institutes of Health Research, European Foundation for the Study of Diabetes, European Union, JDRF, Netherlands Diabetes Foundation, and Mead Johnson
Web site	www.trigr.org
TRIGR is taking place at 77 sites in 15 countries including the United States, 12 European countries, Canada, and Australia.	

TYPE 1 DIABETES—RAPID ACCESS TO INTERVENTION DEVELOPMENT (T1D-RAID)³⁴

Promising ideas for novel therapeutic interventions can encounter roadblocks in movement from bench to bedside testing. Many investigators who have discovered a promising therapeutic agent in the laboratory do not have the resources or the background knowledge, for example, to “scale up” production of the agent for use in clinical trials. The T1D-RAID program was established to help overcome this major barrier to development of potential new therapeutics for type 1 diabetes and its complications. The program provides resources for pre-clinical development of drugs, natural products, and biologics that will be tested in clinical trials. The goal of T1D-RAID is to facilitate translation from the lab to the clinic of novel, scientifically meritorious therapeutic interventions for type 1 diabetes and its complications. T1D-RAID is not a grant mechanism and it does not sponsor clinical trials. Rather, it sponsors the work needed to get ready to do clinical trials. The program is assisting investigators by providing pre-clinical development steps, the absence of which may impede clinical translation.

HIGHLIGHTS OF PROGRESS

- Prepared lisofylline to meet product specifications for use in clinical trials. Lisofylline is now being tested in a clinical trial supported by the Clinical Islet Transplantation (CIT) Consortium (see Goal III) to determine if it can help to prevent recurrent autoimmunity after islet transplantation in humans.
- Established two master cell banks for manufacturing of a novel drug regimen (IL-2-Fc agonist and mut-IL 15-Fc antagonist) for a planned Immune Tolerance Network (ITN) (see Goal II) clinical study. Researchers in the Non-Human Primate Transplantation Tolerance Cooperative Study Group (NHPCSG) (see Goal III) demonstrated long-term survival of islets after transplantation when the animals were given the novel mixture of medicines that target the immune system. Based on these findings, the ITN approved a clinical trial to test this therapy in people with newly diagnosed type 1 diabetes to determine if the medicines can slow progression of disease.
- Stimulated the need for resources to do pre-clinical efficacy studies in type 1 diabetes and its complications. This resulted in the establishment of two contracts to provide preliminary and confirmation efficacy data in animal models (the T1D-Preclinical Testing Program [T1D-PTP]).
- Promptly terminated one project for a therapeutic for diabetic neuropathy after studies performed through the T1D-PTP failed to provide confirmation of efficacy previously provided by the principal investigator.
- Reviewed and referred six new potential projects to the T1D-PTP to conduct efficacy studies in animals to obtain stronger pre-clinical evidence prior to T1D-RAID investment.

³⁴ This program is also relevant to Goal V because it provides resources for therapies related to the complications of type 1 diabetes.

Anticipated Outcomes

Because clinical trials of agents to prevent, reverse, or treat type 1 diabetes and its complications are so important to realizing real improvements in the health and quality of life of patients, it is crucial to have a research continuum from the laboratory, where therapeutic agents are identified and initially tested, to the clinic, where agents are tested in patients. T1D-RAID provides a necessary resource that permits researchers to overcome the major barrier to moving promising agents from bench to bedside. T1D-RAID is already manufacturing agents for testing in type 1 diabetes clinical trials and is expected to produce several more. As more knowledge is gained about the underlying mechanisms of disease development, including genes and environmental factors that cause disease (see Goal I), as well as key immune system players (see Goal II), researchers could use this information to develop additional targets for disease prevention and treatment. Therefore, having the T1D-RAID resource in place will help to translate these new discoveries from the laboratory to the clinic, thereby accelerating the pace at which therapeutic agents can be used to prevent or treat type 1 diabetes.

Ongoing Evaluation

To determine which submitted requests are scientifically and technically meritorious, NIDDK specially convenes a T1D-RAID Review Panel consisting of outside experts from academia and industry who make recommendations to the Institute regarding whether a project should receive support. Final prioritization of the projects is made by NIDDK and takes into consideration the importance of the project to the NIH research agenda, portfolio diversity, and contract capacity. Investigators whose projects are supported are invited to present their

project to a joint NIDDK/NCI T1D-RAID team, at which time questions can be asked. The Project Development Team, consisting of NIDDK T1D-RAID program directors, NCI staff experts, the principal investigator, and other Institute staff as necessary, decide on the necessary tasks and exact next steps. The NCI identifies and assigns available contractors for the tasks based on their expertise, capacity, and the time frame. The contractors then perform the T1D-RAID-approved tasks under the direction of NIDDK and NCI staff.

Milestones for progression of the project are then set by the Project Development Team. Monthly meetings of the NIDDK/NCI T1D-RAID team review the progress and roadblocks on each project to ensure that projects are progressing and that information is widely shared among all members of the principal investigator's team and the NIDDK and NCI staff managing the T1D-RAID program. In the event that a T1D-RAID project is encountering problems or overrunning its project budget in a way that will not readily lead to a desired data endpoint, a status review group will be convened to consider the likelihood that further work in the project area will be fruitful. The investigator and NIDDK staff will present progress to date to extramural scientists knowledgeable in the area. Following the presentations, the review group will meet in closed session to determine whether T1D-RAID efforts should continue with new project milestones or the project should be concluded.

In addition, T1D-RAID has been evaluated by external panels of scientific and lay experts at *ad hoc* evaluation meetings convened by NIDDK in January 2005 and June 2009. These meetings were an opportunity for external experts to evaluate progress and provide input on future research directions (for more information, see the Executive Summary and Appendix B). Through *ad*

hoc evaluation meetings and other meetings described above, NIDDK continually seeks external input to inform current and future directions for T1D-RAID.

Program Enhancements

During the course of any long-term research project, adjustments need to be made to respond to a changing scientific landscape, which can include new and emerging areas of science and new discoveries that can inform future research directions. Because of the evolving nature of science, consortia supported by the *Special Diabetes Program* have also evolved over time and have undergone enhancements to take advantage of new technologies and overcome barriers to progress. Some enhancements have been made in response to gaps or opportunities identified by external input or by consortium members. Examples of program enhancements for T1D-RAID include:

- The inability to confirm the efficacy data provided in the original proposal submitted by an investigator was a concern of NIDDK and its reviewers and was resolved by the establishment of contracts by NIDDK to conduct animal efficacy studies.
- NIDDK program staff have worked closely with NIDDK's Technology Transfer Office to ensure that Material Transfer Agreements clearly establish ownership. NIDDK works with the principal investigator to ensure close communication in circumstances in which ownership of a project might change. This procedural change was established to

ensure freedom for T1D-RAID to conduct pre-clinical development activities if ownership of the project changes. It is possible, as a project progresses, that ownership of the project may change from one entity to another (e.g., a company transfers ownership of the material).

Coordination with Other Research Efforts

T1D-RAID is supporting the pre-clinical development of therapeutic agents that will be tested in clinical trials supported by the *Special Diabetes Program*. Therefore, this resource has been critically important in facilitating the translation of agents from bench to bedside, where they will be tested in people with type 1 diabetes. For a summary of ongoing collaborative efforts, please see Appendix D.

Facilitating Type 1 Diabetes Clinical Trials:

- T1D-RAID supported the manufacture of lisofylline, which is being tested in the CIT Consortium to determine if it can help reduce islet autoimmune destruction after islet transplantation.
- T1D-RAID is assisting in the manufacture and toxicology studies of a novel drug regimen (IL-2-Fc agonist and mut-IL 15-Fc antagonist), which will be tested in an ITN clinical trial. Researchers in NHPCSG demonstrated long-term survival of islets after transplantation when the animals were given this novel mixture of medicines.

T1D-RAID Administrative History

Date Initiative Started	2003
Date <i>Special Diabetes Program</i> Funding Started	2004
Participating Components	NIDDK, NCI
Web site	www.T1Diabetes.nih.gov/T1D-RAID/index.shtml

The T1D-RAID program was modeled after the NCI's RAID program and is a collaboration between NIDDK and NCI. The sponsors of approved requests to T1D-RAID gain access to the pre-clinical drug development contract resources of NCI's Developmental Therapeutics Program.

Goal III: Develop Cell Replacement Therapy

BETA CELL BIOLOGY CONSORTIUM (BCBC)

The BCBC is an international Consortium of investigators pursuing key challenges of enormous relevance to the development of therapies for type 1 diabetes by: (1) understanding how endogenous beta cells are made through the study of pancreatic development, with the hope of making pancreatic cells in culture; (2) exploring the potential of animal and/or human stem cells (embryonic³⁵ or adult) as a source of making pancreatic islets; and (3) determining the basic mechanisms underlying beta cell regeneration in the adult as a basis for producing new cellular therapies for diabetes. The BCBC is responsible for collaboratively generating necessary reagents, mouse strains, antibodies, assays, protocols, and technologies that are beyond the scope of any single research effort and that would facilitate research on the development of novel cellular therapies for diabetes.

HIGHLIGHTS OF PROGRESS

- Increased understanding of the events that occur during development that lead to the formation of pancreatic beta cells. This type of knowledge is being used in the development of strategies to generate beta cells from embryonic stem cells and/or other stem/progenitor cell populations, such as induced pluripotent stem cells.
- Identified progenitor cells in the adult mouse pancreas that form insulin-producing beta cells.
- Reprogrammed adult mouse exocrine cells into insulin-producing beta cells.
- Demonstrated spontaneous conversion of adult alpha cells into insulin-producing cells in beta cell-depleted mice.
- Developed a new mouse model for studying beta cell regeneration.
- Discovered a new marker for pre-clinical type 1 diabetes called ZnT8.
- Generated and/or listed on its Web site over 300 unique and useful resources of which 70 percent are publically available (those that are not remain in development and are released after validation and/or publication).
- Generated and/or validated more than 110 antibodies against markers expressed at different stages of stem cell to beta cell maturation and distributed more than 700 orders, to BCBC and non-BCBC investigators, since its inception. In a major development, a subset of these antibodies now allow researchers to obtain, for the first time, highly-purified fractions of the various endocrine cell types present in islets coming from human donors, including insulin-producing beta cells and glucagon-producing alpha cells.
- Created, for distribution to the scientific community, four PancChips (microarrays) that enable researchers to study genes expressed in the pancreas/islets of both humans and mice, as well as over 36,000 gene promoter regions in mice. Between 2002 and 2007, the core manufactured approximately 4,000 units of three different arrays, including over 2,300 that were shipped to investigators in 19 different countries.

³⁵ The NIH supports research using human embryonic stem cells within the NIH Guidelines for Human Stem Cell Research.

- Generated more than 50 new lines of genetically engineered mice or mouse embryonic stem cells to enable researchers to study pancreatic/islet cell development in animal systems. These mouse resources are available to the broad scientific community through a BCBC Web-based mouse database.
- Initiated <http://genomics.betacell.org>, previously known as EPConDB, a searchable database that provides sophisticated search tools for genes, their transcripts, and their profiles in expression studies. In addition, over 50 microarray studies related to the beta cell, and an additional 20, were extensively annotated and made available.
- Attracted new talent to beta cell biology through the Pilot and Feasibility (P&F) Program, funding seven new investigators.
- Attracted new talent to beta cell biology through the Seeding Collaborative Research in Beta Cell Biology (SCRBCB) Program. This mechanism permitted investigators outside the BCBC to collect preliminary data and form collaborative research teams prior to applying for full-scale grants during the BCBC re-competition.
- Stimulated productive collaborations among investigators with the Collaborative Bridging Project (CBP) which to date has supported 21 different short-term (1-3 years) projects. This program has yielded novel reagents and new methods, brought new skills and knowledge into the BCBC, and increased the number of formal collaborative interactions between BCBC participants by nearly 50 percent.

Anticipated Outcomes

The successful BCBC has made numerous scientific discoveries in the field of beta cell biology and accelerated progress toward the development of cell-based therapies for the treatment of type 1 diabetes. BCBC research has increased understanding of the developmental pathways required to produce a fully functioning pancreatic islet; the nature of stem/progenitor cells during normal pancreatic development and in the adult pancreatic islet; and the mechanisms of beta cell regeneration in the adult animal and human islet. With these insights and recent developments, the BCBC is shifting its efforts to take advantage of new emerging opportunities and increasing its focus on translational outcomes and scientific issues that stand in the way of developing new cell-based and regenerative therapies. First, the BCBC is working to reconstruct human type 1

diabetes in the mouse to produce a better animal model in which to study this disease. The model has two components: (1) type 1 diabetes patient-specific induced pluripotent stem cells that will differentiate into beta cells, blood stem cells, and cells of the immune system; and (2) a mouse recipient for the cells with genetic components of a human immune system. With these components, scientists expect the mouse to recapitulate the early events in the autoimmune destruction of human beta cells. This will allow them to study these events and test strategies to intervene in this process.

In addition, the BCBC will place a greater emphasis on studies of human cells and tissues to move new discoveries forward as quickly as possible. Efforts will be increased to generate beta cells from human embryonic stem cells,³⁶ to increase the human beta cell mass, and to uncover the mechanism to reprogram human

³⁶ The NIH supports research using human embryonic stem cells within the NIH Guidelines for Human Stem Cell Research.

adult cells into beta cells. Furthering basic research on beta cells will enhance efforts to produce an abundant supply of beta cells for transplantation and/or efforts to promote the generation of new beta cells within the body. The potential outcomes of BCBC research could permit scientists to grow islets in the laboratory for use in future research or clinical efforts. This knowledge could help scientists recreate an environment in the transplant patient that would optimize the success of the grafted islets, as well as make the treatment more widely available. Additionally, new knowledge could lead to the development of strategies to increase a person's beta cell mass *in vivo*, without the need for transplantation and immunosuppressive drugs.

The BCBC provides an infrastructure that is conducive to tackling these critical issues that can revolutionize type 1 diabetes research and, ultimately, the treatment of type 1 diabetes patients. BCBC researchers work collaboratively and are encouraged to share data and information on a regular basis through a coordinating center that organizes retreats, meetings, conference calls, and a comprehensive Web site. This rapid and efficient communication ensures that all members are aware of the "latest" research findings, and that they can tailor their own research endeavors to build upon that knowledge. Furthermore, research through this Consortium and in the broader scientific community is also accelerated by having core facilities that produce key laboratory reagents (e.g., mouse models, antibodies, microarrays). This easy access to resources means that more time is spent performing real experiments, rather than preparing reagents to do the experiments. The *Special Diabetes Program* has facilitated the establishment of this multifaceted, interdisciplinary, collaborative, team-science approach to bring together leading experts in beta cell

biology to address fundamental questions about this important area of science, which is key to combating type 1 diabetes.

Ongoing Evaluation

The Executive Committee (EC), consisting of four NIDDK staff members and three BCBC investigators, is the principal governing body of the BCBC and actively guides the development of the BCBC. The EC is chaired by the leader of the Coordinating Center. An agenda is distributed in advance of every meeting, and minutes/action items are posted on the Web site. The EC meets regularly by teleconference to exchange information and build consensus in order to quickly and effectively resolve operational issues. In addition to the EC, a Steering Committee (SC) composed of all BCBC investigators and NIDDK program staff meets twice a year during the semiannual BCBC retreats. During this formal discussion, operational issues of potential interest to everyone are discussed. This provides a time during which strategic visions can be presented and discussed, and for any concerns that may have arisen to be openly discussed. An External Evaluation Committee (EEC), composed of 10 highly-regarded scientists, contributes to the scientific review of various projects (CBPs, P&F Program, and SCRBCB Program) and is often asked for input and advice on ongoing BCBC activities and future directions.

In addition, the BCBC has been evaluated by external panels of scientific and lay experts at *ad hoc* evaluation meetings convened by NIDDK in January 2005 and June 2009. These meetings were an opportunity for external experts to evaluate progress and provide input on future research directions (for more information, see the Executive Summary and Appendix B). Through *ad hoc* evaluation meetings and regular meetings of the EEC,

NIDDK continually seeks external input to inform current and future directions for the BCBC.

Program Enhancements

Because of the evolving nature of science, consortia supported by the *Special Diabetes Program* have evolved over time and have undergone enhancements to take advantage of new technologies and research findings, and to accelerate progress. Some enhancements have been made in response to external input and others have been initiated by the consortium members. Examples of program enhancements for the BCBC include:

- During the first funding cycle, the BCBC received critical scientific feedback, via a formal review process that involved the SC, the EEC, and a committee convened at the *ad hoc* planning and evaluation meeting in January 2005, that there was insufficient synergy among BCBC scientists. As a result, the CBP Program was created to support collaboration among various BCBC members and between the BCBC and other scientists. This highly flexible program has supported 21 different short-term (1-3 years) collaborative projects to date.
- Data sharing is critical to the success of the BCBC, however significant issues to protect the confidentiality of unpublished results and to avoid conflict of interest issues generated a barrier to this activity. Two actions were taken to ensure confidentiality to promote the sharing of preliminary research information and reagents. First, the Sharing Agreement that all BCBC members are required to sign was revised to make it more explicit and easier to

understand. Second, access to resource information on the BCBC Web site was restructured to enable a high degree of access control. This assures that BCBC investigators can access all information that they have privileges to see, while maintaining confidentiality of unpublished results and avoiding conflict of interest issues.

- To increase the number of resources described on the BCBC Web site and assure that they become readily and publicly accessible, the BCBC took a multifaceted approach. First, the data collection process was simplified and, when possible, data standards were minimized. Second, descriptions of new reagents were sent to the Coordinating Center by NIDDK staff so that they could be correlated with database entries and released more quickly to the public. Third, the Coordinating Center hired scientists with experience in the fields of genetics, cell and development biology, and molecular biology to help oversee data entry and curation efforts. Finally, incentives were developed to stimulate students and post-doctoral fellows in member laboratories to enter this information into the databases.

Coordination with Other Research Efforts

The BCBC coordinates its efforts with multiple other type 1 diabetes research consortia and networks supported by the *Special Diabetes Program*. Collaboration, coordination, and resource sharing serve to synergize research efforts and accelerate research progress. Examples of coordination with other consortia are given below. For a summary of ongoing collaborative efforts, please see Appendix D.

Sharing Samples, Data, and Resources with the Research Community:

- The BCBC developed a comprehensive Web site (www.betacell.org) with information on mouse models, antibodies, microarrays, and data available to the scientific community.
- Collections of data and bioinformatics analytical tools developed by the BCBC are made available through the EPConDB database (<http://genomics.betacell.org>). This database has been linked to other relevant databases, such as the NIDDK-supported Diabetes Genome Anatomy Project database and the JDRF-sponsored T1Dbase.

Coordinating Research Efforts on Human Islets:

- BCBC investigators obtain human islets through the Islet Cell Resource Centers (ICR) for use in basic science research.

- Data collected from BCBC investigators using ICR samples are collected within the informatics coordination center of the ICR Consortium.

Collaboration Among Mouse Resources:

- Mouse strains developed by BCBC investigators are available through mouse repositories (Type 1 Diabetes Mouse Resource [T1DR] and Mutant Mouse Regional Resource Centers [MMRRC]), which provide greater access to the scientific community to these resources.
- The BCBC mouse database was designed to directly interface with T1DR and MMRRC to foster data sharing.

BCBC Administrative History

Date Initiative Started	2001
Date <i>Special Diabetes Program</i> Funding Started	2001
Participating Components	NIDDK
Web site	www.betacell.org

The BCBC is comprised of a diverse group of 29 laboratories in the United States, Europe, and Israel. The BCBC Coordinating Center at Vanderbilt University oversees all collaborative scientific endeavors of the BCBC, including scientific cores, reagent databases, Steering Committee meetings, investigator retreats, the P&F Program, the SCRBCB Program, and the CBPs.

NON-HUMAN PRIMATE TRANSPLANTATION TOLERANCE COOPERATIVE STUDY GROUP (NHPCSG)

The NHPCSG is a multi-institution Consortium collaboratively developing and evaluating the safety and efficacy of novel therapies to induce immune tolerance in non-human primate (NHP) models of islet, kidney, heart, and lung transplantation. The program also supports fundamental research into the molecular mechanisms of immune tolerance and graft rejection; the identification of surrogate markers for graft rejection; and the induction, maintenance, and loss of tolerance. Two NIAID-funded specific pathogen-free NHP breeding colonies provide high-quality NHPs for these research studies. An Opportunities Pool supports innovative pilot projects, emerging research opportunities, and sharing of resources to further the goals of the NHPCSG. Pre-clinical research conducted by the NHPCSG provides critical information required to move promising therapeutic agents from the laboratory into clinical trials.

HIGHLIGHTS OF PROGRESS

- *Demonstrating long-term and sustained pancreatic islet beta cell function without continuous immunosuppressive therapy following islet transplantation in a drug-induced diabetic NHP model:* The researchers discontinued immunosuppressive treatments 14 days after the transplant. The 14-day tolerance induction protocol, which consisted of anti-CD3 conjugated with immunotoxin (to deplete T cells) and 15-deoxyspergualin (to arrest pro-inflammatory cytokine production and maturation of dendritic cells), was sufficient to protect the transplanted islets from immune rejection and loss of functional islet mass. More than half of the NHPs treated with this regimen remained insulin-free for more than 6 years without the need for pharmacologic immune suppression. Toxicity of immunosuppressive drugs is a major barrier in human islet transplantation. Therefore, if follow-on studies in humans achieve similar outcomes, then islet transplantation may be an option for more individuals with type 1 diabetes.
- *Demonstrating, in a steroid-free immunosuppressive protocol, an immune cell costimulatory blocking protein known as belatacept (LEA29Y) prolonged islet survival in a primate model:* This promising study provided the basis for a phase II kidney transplantation clinical trial. The trial has demonstrated promising results and has led to the development of a pilot study currently being conducted by the NIH Clinical Islet Transplantation (CIT) Consortium. An additional kidney transplantation clinical trial using LEA29Y in a steroid-free protocol is being conducted by the Immune Tolerance Network (ITN) (see Goal II).
- *Prolonging transplanted islet cell survival using a combination of IL-2/IL-15 fusion proteins with a steroid-free protocol:* A clinical trial in patients with new-onset type 1 diabetes is approved for development by the ITN once good manufacturing practice (GMP) grade reagents are available. The Type 1 Diabetes-Rapid Access to Intervention Development (see Goal II) program is undertaking production of reagents for pharmacokinetic and toxicology studies before initiating a clinical trial.

- *Providing basis for a new ITN clinical trial for patients with new-onset type 1 diabetes:* The results of NHPCSG islet transplantation studies of an anti-inflammatory, alpha 1 anti-trypsin molecule provided support for an ITN clinical trial.
- *Demonstrating that a fusion protein, alefacept (lymphocyte function-associated antigen-3-Ig; LFA-3-Ig), selectively eliminated memory T cells and, when combined with abatacept (CTLA-4-Ig), prevented renal allograft rejection and alloantibody formation in NHPs:* These results are promising for the development of future clinical trials in islet transplantation.
- *Demonstrating that elevation of cytotoxic lymphocyte (CL) gene expression preceded the rejection of transplanted islets in NHPs:* These findings also extended to clinical studies in humans in which increased CL gene expression preceded clinical evidence of graft rejection. These results may help identify early stages of islet graft rejection and lead to clinically useful biomarkers that signal the need for early graft-saving interventions.
- Evaluating over 15 different protocols to establish immune tolerance and/or islet graft acceptance.
- Establishing two specific pathogen-free NHP breeding colonies to provide high-quality primates for type 1 diabetes research studies.
- *Performing pedigree analysis and histocompatibility gene typing of key primate colony breeders and offspring to enable establishment of selective breeding groups:* Understanding the degree of Major Histocompatibility Complex (MHC) disparity between the transplant donor and recipient is crucial for interpretation of transplant outcomes. This gene typing program will greatly enhance the value of the colony for future transplantation studies.

Anticipated Outcomes

Model systems in which to study autoimmune disorders and organ transplantation are essential for translation of basic research into clinical practice. The NHPCSG uses primate models for the study of islet, kidney, heart, and lung transplantation since the NHP immune system and physiology most closely approximates those of humans. These studies are critical for the design of scientifically sound and ethically acceptable clinical trials to induce transplantation tolerance. However, there are also limitations in the use of NHP models. Because these animals do not spontaneously develop islet autoimmunity and type 1 diabetes, they lack the

complication, seen in humans, of recurrent autoimmunity following transplantation. The latter is a major barrier to success of islet transplantation efforts in humans. Nonetheless, NHPCSG studies have led to clinically relevant discoveries. Most notably, researchers have demonstrated the ability of transplanted islets to survive in NHPs without the requirement for long-term immunosuppression. Through consortium building, sharing reagents, developing novel protocols, and directing the primate colony breeding program, researchers have made significant contributions to the field of islet transplantation; many of these advances are already being translated to clinical trials. In particular,

two agents, a modified costimulatory blocking protein known as LEA29Y and a combination of IL-2/IL-15 fusion proteins, tested in NHPCSG studies demonstrated the safety and feasibility necessary to progress to human clinical trials. Future NHP studies using novel therapeutic agents may enable control of the immune response in humans, resulting in long-term islet cell graft survival, with limited requirements for short-term immunosuppressive therapy. These primate models serve the crucial role of bridging the gap between basic research and clinical advances in type 1 diabetes research.

Ongoing Evaluation

The NHPCSG Steering Committee (SC) serves as the governing body and is composed of the Principal Investigators (PIs) for each grant and an additional PI from multi-project grants. Program Directors of NIAID and NIDDK serve as non-voting members of the SC. Investigators report on progress and issues that arise in their research at annual meetings. In addition, research agendas, collaborations, and plans for resource development/sharing are established and implemented by the SC. The NHPCSG SC also directs the program's efforts to coordinate research agendas with NIAID and NIDDK clinical trial networks. The NIAID Program Officer coordinates activities of several subcommittees of the SC that maximize resources and promote group collaborations. The NIAID and NIDDK program officers also conduct annual evaluations of individual grants to ensure that appropriate progress has been made prior to the release of funds. The SC establishes guidelines for the identification of appropriate research milestones, and conducts peer review of proposals for support from the NHPCSG Opportunities Pool. Finally, the SC provides recommendations and guidance for the development and content of a secure NHPCSG Web site.

The NHPCSG chair of the SC provided an update of progress to the NIAID Advisory Council (NIAID Division of Allergy, Immunology, and Transplantation Subcommittee) during the open session of the January 30, 2006, meeting. Council members concurred that the NHPCSG has made excellent progress and has made many valuable contributions to transplantation immune tolerance research.

In addition, the NHPCSG was evaluated by external panels of scientific and lay experts at *ad hoc* evaluation meetings convened by NIDDK in January 2005 and June 2009. These meetings were an opportunity for external experts to evaluate progress and provide input on future research directions (for more information, see the Executive Summary and Appendix B). Through these and other meetings described above, NIDDK and NIAID continually seek external input to inform current and future directions for the NHPCSG.

Program Enhancements

Because of the evolving nature of science, consortia supported by the *Special Diabetes Program* have evolved over time and have undergone enhancements to take advantage of new technologies and research findings, and to accelerate progress. Some enhancements have been made in response to external input and others have been initiated by the Consortium members. Examples of program enhancements for the NHPCSG include:

- A longstanding obstacle to NHP transplantation research is the lack of high-quality, specific pathogen-free animals with well characterized histocompatibility genes. NIAID addressed this need by establishing dedicated breeding colonies and selecting progeny based on MHC haplotypes. Other NIAID-sponsored

contract programs support NHP MHC gene/allele discovery and the discovery and development of novel methods to type for these alleles.

- Another major impediment is the lack of reagents that will work, or that work optimally in the NHP model, both for monitoring the immune responses and as immunotherapeutics. NIAID contract support for the NIH NHP Reagent Resource was established to address these needs. This program is producing monoclonal antibodies and other biological reagents when the corresponding biologics licensed, or under investigation, for human use are less than optimally active in NHP.
- To promote and enhance new interactions, training, and collaborations within the NHPCSG, the Consortium holds meetings of the NHPCSG SC 1-2 times per year. The meetings provide a venue for sharing ideas and solutions to specific research problems, evaluating progress, and enhancing ongoing collaborations. Subcommittees of the SC also have periodic conference calls and meetings. For example, a subcommittee for the rhesus macaque colony provides recommendations to NIAID regarding breeding strategies that enhance the utility of the colony.
- The NHPCSG has also engaged the scientific community to develop the highly specialized skills, standardized reagents, assays, and techniques needed for NHP transplantation studies. The NHPCSG has held three NHP Transplantation Techniques Workshops that included NHP transplantation researchers outside of the NHPCSG, and experts on NHP genomics and NHP diseases and disease models. These workshops also engaged many graduate students and fellows to

promote future growth of an experienced cadre of investigators in this highly specialized field. A direct outcome of these workshops is a web-based initiative that shares hundreds of protocols and standard operating procedures both within and outside the Consortium. In addition, Consortium investigators have established collaborations with experts in NHP microarray, genomics, and genetics as a result of these workshops.

- Progress in transplantation biology has been hampered by a lack of resources to validate or exclude immunosuppressive strategies showing promise in rodent models. The establishment of the NHPCSG Opportunities Pool has helped to address this need. An Opportunities Pool funding program within the Consortium provides additional support for collaborations within and outside the NHPCSG with an emphasis on cutting edge research studies. The NHPCSG Opportunities Pool has funded 16 projects, including five that were awarded to non-PI or junior investigators, and at least two outside collaborators were involved in the studies.

Coordination with Other Research Efforts

The NHPCSG coordinates its efforts with multiple other type 1 diabetes research consortia and networks supported by the *Special Diabetes Program*. Collaboration, coordination, and resource sharing provide synergy to research efforts and accelerate research progress. Examples of coordination with other consortia are given below. For a summary of ongoing collaborative efforts, please see Appendix D.

Coordinating Research Studies:

- Cross-representation of investigators between the NHPCSG and the CIT Consortium facilitates collaborative design of pre-clinical testing of novel therapeutics in NHPs.
- ITN priorities for pre-clinical testing of new therapeutics are considered in evaluating NHPCSG Opportunities Pool applications. Several ITN

high-priority strategies are currently funded as pilot projects.

- The CIT Consortium, ITN, and NHPCSG are analyzing similar reagents and approaches for the treatment and prevention of type 1 diabetes or for islet transplantation.
- The NHPCSG and the ITN share information about scientific priorities and interests for research planning.

NHPCSG Administrative History

Date Initiative Started (Islet and Kidney Models)	1999
Date <i>Special Diabetes Program</i> Funding Started	2002
Date NHPCSG Expanded to Include Heart and Lung Transplantation Models	2005
Participating Components	NIAID, NIDDK
The NHPCSG is a multi-institution Consortium consisting of 9 research cooperative agreements, including 3 multi-project awards.	

CLINICAL ISLET TRANSPLANTATION (CIT) CONSORTIUM

The CIT Consortium is a network of clinical centers that conducts clinical and mechanistic studies in islet transplantation, with or without accompanying kidney transplantation, for the treatment of type 1 diabetes. Consortium investigations focus on improving the isolation of islets, determining why donor islets fail, reducing the complications of islet transplantation, and limiting the side effects of immunosuppression.

HIGHLIGHTS OF PROGRESS

- *Launching seven clinical trials, with associated immunologic, metabolic, and mechanistic studies, of islet transplantation in individuals with normal kidney function and type 1 diabetes with severe hypoglycemic events despite intensive medical management:* In collaboration with the U.S. Food and Drug Administration (FDA), CIT investigators are conducting a Phase III multicenter clinical trial that may support future FDA licensure of an islet product. Five pilot trials will test new, innovative islet transplantation approaches. The seven trials will use comparable inclusion criteria and manufacturing specifications to ensure the comparability of study results.
- *Conducting a phase III, multicenter clinical trial that includes Medicare beneficiaries, as mandated by the Medicare Prescription Drug Improvement and Modernization Act of 2003 (Public Law 108-173):* The target population consists of individuals with type 1 diabetes who have previously undergone kidney transplantation for diabetic nephropathy and are thus already receiving immunosuppressive therapy to prevent rejection of the donor kidney. This trial has required close collaboration among NIDDK, NIAID, and the Centers for Medicare & Medicaid Services.
- *Developing an FDA licensure pathway for an islet product based primarily upon the two phase III trials described above:* These trials will use “standard” anti-rejection regimens for both islet-alone and islet-after-kidney transplant protocols. A key FDA requirement for consideration of islet licensure was the development and implementation of a common isolation process with standardized documentation at all sites. The CIT Consortium met these requirements by developing a master production batch record for islet isolation.

Anticipated Outcomes

Islet transplantation is a promising therapy that can yield long-lasting, beneficial results for individuals with difficult-to-manage type 1 diabetes including those with kidney failure. Much has been learned about islet cell biology and the processes leading to rejection of transplanted islets and loss of islet function. In addition, pre-clinical studies are evaluating new approaches to immunomodulation in conjunction with islet transplantation in animal models. Challenges

remain, however, in improving the safety and long-term outcomes of islet transplantation in people with type 1 diabetes. To address these issues, CIT investigators hope to minimize the toxic effects of anti-rejection drugs and identify potential methods to prevent graft rejection without the need for global immunosuppression. Other Consortium research is aimed at abolishing life-threatening hypoglycemic events and achieving long-lasting control of blood glucose with only a single islet transplant. Ultimately, the knowledge gained from these

and other CIT investigations can enable the greater use of islet transplantation in individuals with type 1 diabetes.

Ongoing Evaluation

The CIT Consortium is managed jointly by the NIDDK and the NIAID. NIAID assumes principal leadership for regulatory affairs. The Consortium's clinical protocols are reviewed by the NIDDK Islet Transplantation Data and Safety Monitoring Board, which is composed of outside experts in diabetes, clinical trial design, ethics, transplantation, and biostatistics. The Steering Committee is responsible for the overall Consortium governance and is composed of the chair, the PIs of the six awarded clinical centers and the data coordinating center, the chair of the Mechanistic Studies Subcommittee, and representatives from NIDDK and NIAID.

To inform the CIT Consortium's current and future research directions, NIDDK and NIAID seek external expert review. Through an External Evaluation Committee, input on the design of the CIT Consortium's Islet After Kidney trial was sought. In addition, the Consortium has been evaluated by external panels of scientific and lay experts at *ad hoc* evaluation meetings convened by NIDDK in January 2005 and April 2008. These meetings were an opportunity for external experts to evaluate the progress and provide input on future research directions (for more information, see the Executive Summary and Appendix B).

Program Enhancements

Because of the evolving nature of science, consortia supported by the *Special Diabetes Program* have evolved over time and have undergone enhancements to take advantage of new technologies and research findings, and to accelerate progress. Some

enhancements have been made in response to external input and others have been initiated by the Consortium members. Examples of program enhancements for the CIT Consortium include:

- Establishing a collaboration between the CIT Consortium, the IIDP (Integrated Islet Distribution Program), and Collaborative Islet Transplant Registry (CITR) to harmonize data dictionaries of the three programs, reduce the time involved in data entry, increase data accuracy, and facilitate data sharing.
- Developing and implementing new adverse event reporting, and standard operating and reagent manufacturing procedures to meet FDA requirements for the conduct of a multicenter cellular therapy phase III trial to license an islet product.
- Expanding the Statistical and Data Coordinating Center of the CIT Consortium to increase clinical site monitoring and specimen tracking functions of protocols. In addition, an advisory group to the Coordinating Center has been established.

Coordination with Other Research Efforts

The CIT Consortium coordinates its efforts with multiple other type 1 diabetes research consortia and networks supported by the *Special Diabetes Program*. Collaboration, coordination, and resource sharing serve to synergize research efforts and accelerate research progress. Examples of coordination with other consortia are given below. For a summary of ongoing collaborative efforts, please see Appendix D.

Sharing Data Among Consortia Studying Islet Transplantation:

- Data sharing agreements have been developed among the CIT Consortium, CITR, and the IIDP.

These agreements include use of shared data dictionaries and source verification of data by CIT clinical site monitors, with corrections transmitted to all participants. Monthly teleconferences ensure communication about maintaining up-to-date information. This effort will minimize redundancy in data collection and enhance data dissemination.

- The CITR will list all active islet transplantation protocols on its Web site. The Consortium will use this information as part of its informed consent process for clinical trial participants.

Coordinating Research Studies:

- Cross-representation of investigators between the Non-Human Primate Transplantation Tolerance Cooperative Study Group (NHPCSG) and the CIT

Consortium will facilitate collaborative design of pre-clinical studies and pre-clinical testing of therapeutics in non-human primates.

- The CIT Consortium, ITN, and NHPCSG are interested in analyzing similar reagents to be used as immune modulators for the treatment of type 1 diabetes or for islet transplantation.
- The CIT Consortium and ITN are sharing expertise and coordinating efforts in the planning of immunologic assays in CIT trials. ITN core labs will be used for selected assays in CIT trials.
- The Type 1 Diabetes-Rapid Access to Intervention Development program is supporting the manufacture of reagents for use in CIT trials.

CIT Consortium Administrative History

Date Initiative Started	2004
Date <i>Special Diabetes Program</i> Funding Started	2004
Participating Components	NIDDK, NIAID
Web site	www.citiletstudy.org
The CIT Consortium is composed of 11 clinical centers in the United States, Canada, Sweden and Norway, and one data coordinating center.	

ISLET CELL RESOURCE CENTERS (ICRs)

The notable advances made in understanding human islet function and improving the efficacy and safety of islet transplantation have been facilitated by making human islets available to researchers. Importantly, isolation of human islets from the pancreas is a complex technology mastered by few investigators and facilities. The ICRs were a consortium of the most experienced academic centers that provided human islets for research and helped establish the efficacy and safety of islet transplantation as a treatment for type 1 diabetes. The initial mission of the ICRs was three-fold: (1) to purify clinical-grade pancreatic islets from whole pancreata and distribute them for clinical transplantation; (2) to provide pancreatic islets for basic research studies; and (3) to perform research and development to improve isolation techniques, islet quality, the shipping and storage of islets, and assays for characterizing purified islets.

Islet transplantation research requires multidisciplinary isolation laboratories that meet or exceed FDA guidelines for good manufacturing practice (GMP). The staff must include experts in clinical research and basic science and have specific expertise in the preparation of islets from cadaver pancreata. Over 92 million human islets were produced by the ICRs from 2004-2009. Some clinical-grade human islets were distributed throughout the United States to transplant centers that enrolled patients in approved clinical protocols. Islets were also distributed to approved investigators who used them in basic research protocols. The ICR program was facilitated by a coordinating center at the City of Hope (Duarte, CA) that provided infrastructure support to both the islet production facilities and the research community. The ICR consortium was the first and largest cooperative effort in the world to provide human islet preparations for research while simultaneously addressing the need to improve isolation and transplantation technologies.

HIGHLIGHTS OF PROGRESS³⁷

- Provided more than 92 million islet equivalents for transplantation in 78 patients.
- Distributed more than 201 million islet equivalents for research to 273 investigators. The number of islet equivalents distributed for basic research grew steadily from 1.3 million in 2004 to 22.3 million in 2008. Similarly, the number of approved institutions and research studies steadily increased from 16 institutions and 19 studies in 2004 to 105 institutions and 156 studies in 2008.
- Of the total 1,076 documented pancreata, 202 (19 percent) were used in clinical islet transplantation and 809 (75 percent) were used for basic research studies. Sixty-five (6 percent) pancreata were not used because consent for research was not obtained or islet quantity or quality did not meet clinical criteria.
- Demonstrated that the oxygen-carrier, perfluorocarbon, stabilizes cadaver pancreata during transportation.
- Optimized the use of shipment materials for transport of purified islets to improve islet viability and quality. An immediate electronic notification mechanism simplified the distribution process and contributed to broadening the availability of pancreatic islets for clinical studies or research.

³⁷ This section includes progress through July 2009 because the ICRs concluded in July 2009 and were replaced, in part, by the Integrated Islet Distribution Program (see this Goal).

- Made progress toward defining clinically practical assays predictive of clinical outcome. The ICR researchers demonstrated the importance of the relationship between total beta cell viability within the islet and successful transplant outcome. Other studies assessed comparative potency analyses and refined shipping methods in order to provide consistency across ICR centers.
- The ICRs supported controlled studies for the assessment of a possible clinical benefit to be derived from the transplantation of purified pancreatic islets into selected eligible patients with type 1 diabetes.

Outcomes

The regional ICRs were successful in the support of national demands for clinical islets and distributed approximately 300 million islet equivalents in 8 years. Using a centrally located, objectively monitored priority list, the centers distributed islets throughout the United States. As a result, institutional access to islets for transplantation and basic research increased since the ICRs were created. This fostered a growing appreciation of the uniqueness of human islet biology as compared to rodent counterparts and accelerated the pace of discovery. Furthermore, the ICRs created a collaborative infrastructure that fostered refinement of preservation and cell culture solutions, optimization of shipping devices for both pancreas and islets, and advances in laboratory technologies to isolate islets. The collaborations helped to meet the challenges inherent in the provision of viable islets with an optimal chance for survival after transplantation. During pancreatic transport and islet purification, preservation, and shipping, the islets are at risk of suffering irreversible damage that reduces their viability and effectiveness as transplanted tissue. ICR research demonstrated that perfluorocarbon stabilized cadaver pancreata during transportation and led to the development of specialized containers for the shipment of purified islets. These achievements improved islet viability, quality, and availability for transplantation and basic research.

Research designed to enable durable islet viability and survival is expected to improve diabetes control after transplant, with a consequent improvement in the recipient's quality of life and health status. However, cadaver islets are foreign tissues for the recipients. Thus, immunosuppressive therapy is required to sustain transplant survival, in addition to optimally prepared donor islets. Further refinements in laboratory assessment of islet potency and viability, purification procedures, and detection of viable islets within the recipient using noninvasive methods are critical. Durable islet survival could lower the number of islets required per patient for successful transplantation, reduce from two to one the number of transplants currently required, reduce the risks and costs associated with transplantation, and extend the availability of islet transplant to a greater number of people with diabetes.

Evaluation

The ICR Steering Committee (SC), composed of the PIs of each ICR, the Administrative and Bioinformatics Coordinating Center (ABCC, City of Hope), NCRR, NIDDK, JDRF, and FDA, as well as a select group of experts and administrators, provided continuous evaluation, oversight, and guidance to the ICRs. In addition, the SC included members of transplantation centers from Canada, the Nordic Network (Sweden), and the Australian Transplant Consortium. Inclusion of non-U.S. experts in islet preparation was intended

to extend the breadth of the group's experience and provide objective, cutting-edge analysis of the ICRs' progress in islet purification, stabilization, and transport. They reviewed procedures and outcomes, adverse events, protocols for scientific studies, and policy matters. The ABCC also received feedback concerning islet quality from users of the pancreatic islets supplied by the ICRs. Finally, the ICRs were evaluated by an external panel of scientific and lay experts at an *ad hoc* evaluation meeting convened by NIDDK in January 2005. This meeting was an opportunity for external experts to evaluate progress and provide input on future research directions.

Program Enhancements

Because of the evolving nature of science, consortia supported by the *Special Diabetes Program* have evolved over time and have undergone enhancements to take advantage of new technologies and research findings, and to accelerate progress. Some enhancements have been made in response to external input and others have been initiated by the consortium members. Examples of program enhancements for the ICRs include:

- To improve further the quality of islets for islet transplantation, the ICRs studied islet shipping procedures and conditions. Efforts were developed to evaluate three islet shipping containers that were designed by ICR scientists and one small business. Two Small Business Innovation Research (SBIR) grants supported applied research in this area and the beta prototypes were tested in conjunction with ICR investigators.
- An *ad hoc* evaluation committee established milestones for ICR participation. Based on their input, three ICR centers failed to demonstrate the

required activity and proficiency in their transplant programs and were discontinued.

- Utilizing islets of the highest-quality possible is critical to conducting research. To foster research targeted towards islet quality improvement, a competitive Opportunities funding program was established in 2006 within the Consortium. This mechanism provided additional opportunities for collaborations within and outside the ICRs and allowed for timely research studies in response to the emergence of promising new technologies. In addition, the ICRs shared new developments with the community through their comprehensive Web site, review of clinical and basic science research proposals, and frequent relevant publications.

Coordination with Other Research Efforts

The ICRs coordinated efforts with multiple other type 1 diabetes research consortia and networks supported by the *Special Diabetes Program*. Collaboration, coordination, and resource sharing served to synergize research efforts and accelerate research progress. Examples of coordination with other consortia are given below. For a summary of ongoing collaborative efforts, please see Appendix D.

Enabling Clinical and Basic Research Studies:

- The ICRs provided clinical grade islets for trials conducted within the Clinical Islet Transplantation (CIT) Consortium.
- The ICRs provided islets for multicenter clinical studies using the "Edmonton protocol" in the Immune Tolerance Network (ITN).
- Type 1 Diabetes–Rapid Access to Intervention Development supported the manufacture of reagents that were tested for their effects on

improving the survival and function of islets in culture.

- Investigators from the following consortia received islets used for clinical assays and for basic research through the ICR basic science human islet distribution program:
 - SEARCH for Diabetes in Youth study;
 - ITN;
 - Autoimmune Disease Prevention Centers;
 - Genetics of Kidneys in Diabetes Study; and
 - Beta Cell Biology Consortium (BCBC).

Sharing Data Across Multiple Research Consortia Studying Islets:

- Investigators who used ICR resources agreed to place their clinical study data in the Collaborative Islet Transplant Registry (CITR).
- The CITR performs on-site data review of transplantation centers and electronically shared the results with the ICRs. The data included

determination of islet quality and collection of transplant outcome information.

- The CIT Consortium, CITR, and ICRs developed data sharing agreements. These agreements included use of shared data dictionaries and source verification of data by CIT clinical site monitors with corrections transmitted to all participants. Monthly teleconferences ensured communication about maintaining up-to-date information. This effort minimized redundancy in data collection and enhanced its dissemination.
- Data from BCBC investigators who used ICR samples were collected within the informatics coordination center of the ICR Consortium.

Improving Characterization of Islet Quality:

- ICR and BCBC investigators shared reagents and expertise to develop improved methods of characterizing islet quality and viability.

ICRs Administrative History

Date ICRs Started	2001
Date ICRs Ended	2009
Date <i>Special Diabetes Program</i> Funding Started	2001
Participating Components	NIDDK, NCRR, JDRF
Web site	http://icr.coh.org

A total of 14 different ICRs participated from 2001-2009, with eight ICRs in operation at the close of the program. The ABCC coordinated the activities of the ICRs and the SC, including the administrative, supervisory, and collaborative achievements required to achieve the goals of the program.

INTEGRATED ISLET DISTRIBUTION PROGRAM (IIDP)

The availability of human islets as a resource for research is critical to advancing islet transplantation and other cell-based therapies as treatment for type 1 diabetes. Importantly, human islets differ from rodent models with respect to the regulatory and metabolic milieu affecting their function, susceptibility to injury, and their adaptive responses for replication. Recognition of these differences underscores the need for human islet investigations. The IIDP is a new program, launched in July 2009, to process and distribute high-quality human cadaveric islets to the diabetes research community for basic research. This new program builds upon the experience of the Islet Cell Resource Centers program that was operative from 2001-2009.

Anticipated Outcomes

The IIDP consists of a single coordinating center (City of Hope, Duarte, CA) that subcontracts with 11 carefully selected islet isolation facilities to process and distribute human cadaveric islets. The coordinating center responsibilities include:

- Maintenance of investigator database
- Monitoring islet production centers
- Implementation and maintenance of notification algorithm
- Financial management of program
- Shipment and tracking of islet tissues
- Performance site and user satisfaction analyses
- Assessment of human islet resource value
- Interaction with the External Evaluation Committee (EEC)
- Completion of reporting requirements

Because pancreas procurement, processing, and testing procedures are expensive, cost sharing by the investigator is required, but with considerable subsidization from NIDDK through the *Special Diabetes Program*. Therefore, the IIDP fulfills the existing need for affordable human islet resourcing for investigators. The IIDP is fully operative and is distributing these precious

resources that will ultimately advance human islet biology and assure the clinical relevance of basic research.

Ongoing Evaluation

The IIDP consists of project officers from NIDDK and JDRF, an EEC, and the Coordinating Center at City of Hope. The EEC currently has five non-Federal members and convenes through regular teleconferences and an annual meeting. The EEC is charged with providing guidance to and assessment of the performance of the Coordinating Center. EEC functions include, but are not limited to:

- Development of criteria required for competitively derived subcontract awards.
- Development of equitable compensation fee schedules for islet production facilities and cost sharing fee schedules for islet recipient investigators.
- Peer review of new investigator proposals that do not have extramural NIH, JDRF, or ADA funding.
- Development of governance policies concerning equitable systems of islet allocation per investigator and project. Implementing policies that enable ongoing progress reviews and criteria for expanding, curtailing, or discontinuing approved studies.
- Review of subcontract performance with evaluation criteria emphasizing maintenance of certification

- records, lot release data, human islet production and shipment activity, islet quality assessments from users, shipment compliance, compliance for correcting recognized deficiencies, and technological innovation.
- Development of islet viability standards necessary for lot release.
- Monitoring performance of the Coordinating Center with respect to implementation of procedures and policies and providing input on modifications where necessary.

Coordination with Other Research Efforts

The IIDP coordinates its efforts with multiple other type 1 diabetes research consortia and networks supported by the *Special Diabetes Program*. Collaboration, coordination, and resource sharing serve to synergize research efforts and accelerate research progress. Examples of coordination with other consortia are given below. For a summary of ongoing collaborative efforts, please see Appendix D.

Enabling Clinical and Basic Research Studies:

- Investigators from the following consortia receive islets used for clinical assays and for basic research through the IIDP:

- SEARCH for Diabetes in Youth study;
- Immune Tolerance Network;
- Autoimmune Disease Prevention Centers;
- Genetics of Kidneys in Diabetes Study; and
- Beta Cell Biology Consortium (BCBC).

Sharing Data Across Multiple Research Consortia Studying Islets:

- The Clinical Islet Transplantation (CIT) Consortium, Collaborative Islet Transplant Registry, and IIDP developed data sharing agreements. These agreements include use of shared data dictionaries and source verification of data by CIT clinical site monitors with corrections transmitted to all participants.
- Data from BCBC investigators who use IIDP samples are collected within the informatics coordination center of the IIDP.

Improving Characterization of Islet Quality:

- IIDP and BCBC investigators share reagents and expertise to develop improved methods of characterizing islet quality and viability.

IIDP Administrative History

Date IIDP Started	2009
Date <i>Special Diabetes Program</i> Funding Started	2009
Participating Components	NIDDK, JDRF
Web site	http://iidp.coh.org
The IIDP consists of a single coordinating center that subcontracts with carefully selected islet isolation facilities to process and distribute human cadaveric islets.	

COLLABORATIVE ISLET TRANSPLANT REGISTRY (CITR)

The CITR expedites progress and promotes safety in islet transplantation through the collection, analysis, and communication of comprehensive and current data on all islet transplants performed in North America. Through additional support from the JDRF, CITR has begun collection of data from selected European and Australian sites. The CITR collects both retrospective and prospective data from participating islet transplant programs. All islet transplants performed since January 1, 1999, are expected to be captured by the CITR, as well as future islet transplants performed through 2013. The CITR prepares an annual report with data on recipient and donor characteristics; pancreas procurement and islet processing; immunosuppressive medications; function of the donated islets; patients' lab results with confidential information removed; and adverse events. This information is widely disseminated throughout the islet transplant and diabetes communities, and also made available to the general public. The data collected and analyzed by the CITR will help to define the overall risks and benefits of islet transplantation as a treatment option for people with type 1 diabetes, and identify the most optimal maintenance therapy. To date, only human-to-human cadaveric islet transplantation has been reported to the CITR.

HIGHLIGHTS OF PROGRESS

- Publication of six annual reports for 2004-2009 with over 200 pieces of data analysis.
- Results from the Annual Report have provided the basis for publications and communications at international transplantation meetings; information for the Islet Investigators Brochure used for recruitment for the Clinical Islet Transplantation (CIT) Consortium; and data to fine-tune eligibility requirements for CIT Consortium trials.
- Determined that episodes of dangerously low blood glucose (hypoglycemia), encountered in most patients prior to transplantation, were nearly absent after islet transplantation. The data were obtained from an analysis of 138 poorly controlled type 1 diabetes patients who had the procedure at 19 medical centers in the United States and Canada.
- Reported that, 1 year after the last islet infusion, 58 percent of recipients no longer had to inject insulin to maintain normal glucose levels, a successful clinical outcome.
- Reported that, for islet-alone recipients, 72 percent achieved insulin independence at least once. Of those who achieved insulin independence, 70 percent retained this status 1 year after achieving it and 55 percent remained insulin independent after 2 years.
- Reported that, 1 year after islet infusion, those individuals still requiring insulin injections had a 69 percent reduction in insulin requirements.
- Current North American database includes information on 339 allogeneic islet recipients (80 percent of all those known done in North America), 658 allogeneic infusion procedures, 722 donor pancreata, 213 autograft recipients and their islets, from 28 centers ever active since 1999 (some have closed). Each transplant center in CITR received inspection, training, software integration, and quality assurance visits.

Anticipated Outcomes

Important components of clinical studies are careful monitoring and reporting of findings. The CTR collects data on patients who have undergone islet transplantation procedures and produces reports that document study parameters and clinical outcomes. This monitoring system enables researchers to track the progress of successful patients as well as to follow patients who experienced graft failure. Importantly, long-term data regarding islet transplantation outcomes are collected for analyses. CTR has reported that 72 percent of islet alone recipients achieved insulin independence at least once and identified factors that are associated with the achievement of insulin independence. The Registry also reported that 1 year after islet infusion, individuals still requiring insulin injections had a 69 percent reduction in their insulin requirements. However, some patients require additional islet transplants, and successful outcomes are not uniformly observed. Tracking these patients is essential to determine the factors that contribute not only to graft function and longevity, but to graft failure. These analyses will also provide the comparative basis needed for determining long-term benefits of induction and maintenance therapies that are most successful. Because islet transplantation is a complex, multifaceted process, and because it is conducted at numerous centers with funding from NIH, voluntary organizations, and local institutions, the CTR is needed as a structure for making valuable assessments that will guide continued improvements.

Ongoing Evaluation

To ensure ongoing evaluation of the CTR's data collection process and procedures, the CTR is both peer reviewed and reviewed at least annually by a Scientific Advisory Committee (SAC). The SAC was established

by the Coordinating Center, in consultation with NIDDK. Current voting members include representatives from University of Miami, United Network for Organ Sharing (UNOS), VA Puget Sound Health Care Systems, UCLA Immunogenetics Center, and the Nordic Network (Sweden). *Ad hoc* members include representatives from the U.S. Food and Drug Administration, Centers for Medicare & Medicaid Services, Health Resources and Services Administration, JDRF, NCRR, NIAID, and NIDDK. In addition, yearly investigator meetings are held, including contributors from the international islet transplantation community. These meetings serve to review the annual activities of the registry and provide guidance for the evolving challenges. Finally, monthly teleconferences including the Scientific Advisor, Program Officer, and CTR investigators provide a forum for discussion of time sensitive issues. Participating investigators and transplant coordinators/data managers serve on the following CTR Committees that review its functions, procedures, and status on a minimum quarterly basis:

- The Compliance Committee monitors participant and islet transplant program compliance, identifies barriers to consistent compliance with participant registration and follow-up, and suggests mechanisms to improve compliance. The Committee also reviews the results of each onsite data audit and recommends appropriate action based on the results of the audit.
- The Data Elements Committee is responsible for monitoring changes in the standard practice of islet transplantation (which includes islet isolation, purification, transplant technique, immunosuppression medications, and metabolic tests) and recommending appropriate modifications to the CTR data definitions and collection tools.

- The Transplant Coordinators/Data Managers Committee provides logistical information to the SAC regarding the working of the CTR from the Coordinators' perspective.
- The Publications and Presentations Committee is responsible for reviewing all proposals, manuscripts, abstracts, and presentations for primary and secondary analysis of the data and dissemination of results.

In addition, the CTR has been evaluated by external panels of scientific and lay experts at *ad hoc* evaluation meetings convened by NIDDK in January 2005 and April 2008. These meetings were an opportunity for external experts to evaluate progress and provide input on future research directions (for more information, see the Executive Summary and Appendix B). Through *ad hoc* evaluation meetings and regular meetings of the SAC, NIDDK continually seeks external input to inform current and future directions for the CTR.

Program Enhancements

Because of the evolving nature of science, consortia supported by the *Special Diabetes Program* have evolved over time and have undergone enhancements to take advantage of new technologies and research findings, and to accelerate progress. Some enhancements have been made in response to external input and others have been initiated by the consortium members. Examples of program enhancements for the CTR include:

- An active collaboration between the CIT Consortium, the Islet Cell Resource Centers (ICR), and CTR was established. One important accomplishment of this collaboration was the successful harmonization of the data dictionaries for

the databases of the three programs to reduce the time involved in data entry at the participating sites, and to facilitate data sharing.

- To respond to general data reporting and storage needs, CTR developed a unified islet module designed to capture detailed procurement, processing, and performance characteristics information on all islet preparations whether used for clinical transplantation or not. The preparations used for clinical transplantation are linked to the recipient and donor information for full analysis.
- To attain and maintain currency in islet transplantation, CTR has recruited all but two centers within North America who have conducted islet transplants since 1999, and is collecting current and historical islet transplant data from these centers. CTR has also launched new electronic data forms for pancreatic islet autograft patients and is collecting these data as well for 1999-2013.

Coordination with Other Research Efforts

The CTR coordinates its efforts with multiple other type 1 diabetes research consortia and networks supported by the *Special Diabetes Program*. Collaboration, coordination, and resource sharing serve to synergize research efforts and accelerate research progress. Examples of coordination with other consortia are given below. For a summary of ongoing collaborative efforts, please see Appendix D.

Sharing Data Across Multiple Consortia Studying Islets:

- The CTR provides all data collection forms, data dictionaries, and code lists to all type 1 diabetes consortia and networks studying islets and islet transplantation.

- Data sharing agreements have been developed among the CIT Consortium, CTR, the UNOS, and the ICRs. These agreements include use of shared data dictionaries and source verification of data by CIT clinical site monitors, with corrections transmitted to all participants. Monthly teleconferences ensure communication about maintaining up-to-date information. This effort will minimize redundancy in data collection and will enhance its dissemination. The CTR is implementing separate data sharing agreements with each of the islet processing centers (former ICR sites) to continue collecting the islet data for transplanted islets.
- Investigators who use CIT resources must agree to place their clinical study data in the CTR, with recipients' consent.
- On-site data review of transplantation centers is performed by the CTR and is provided to the CIT Consortium. Data include determination of islet quality and collection of transplant outcome information.
- Meeting minutes of special interest committees such as the CTR Metabolic Monitoring Committee and the Health Related Quality of Life Committee are shared with all type 1 diabetes consortia and networks studying islets. Members from these groups are invited to participate on these committees.
- The CTR is planning to list all active islet transplantation protocols on their Web site. The CIT Consortium will be using this information as part of its informed consent process for enrollees.
- The CTR archives data from the Immune Tolerance Network islet transplantation trials.

CITR Administrative History

Date Initiative Started	2001
Date <i>Special Diabetes Program</i> Funding Started	2001
Participating Components	NIDDK, JDRF
Web site	www.citregistry.org

The CTR currently consists of one Coordinating Center (The EMMES Corporation, Rockville, MD) and 28 CTR North American centers. Three European and two Australian CTR sites are supported by the JDRF.

Goal IV: Prevent or Reduce Hypoglycemia in Type 1 Diabetes

DIABETES RESEARCH IN CHILDREN NETWORK (DIRECNET)

DirecNet is a multicenter clinical research network investigating the use of technology advances in the management of type 1 diabetes in children and adolescents. DirecNet is also developing a better understanding of hypoglycemia, the dangerous drop in blood glucose that can lead to seizures, loss of consciousness and, in extreme cases, coma or death. Specific goals for DirecNet have been to: (1) assess the accuracy, efficacy, and effectiveness of devices that continuously monitor blood glucose levels in children with type 1 diabetes, the population of patients at highest risk for consequences of hypoglycemia; (2) determine the optimal utilization of continuous glucose monitors (CGMs) in the management of diabetes in children; (3) determine the extent to which exercise contributes to the risk of hypoglycemia; (4) assess the impact of continuous glucose monitoring on quality of life for the child and family; (5) develop tools to incorporate CGMs into diabetes self-management; (6) evaluate and develop distinct, age-appropriate treatment approaches to type 1 diabetes in children; (7) characterize the daily blood sugar profile of nondiabetic children with continuous monitoring; and (8) develop statistical methods for the analysis of continuous glucose monitoring data.

After the completion of the first phase of DirecNet, and in response to a competitive renewal process, DirecNet continued into a second phase in 2007. The goals of DirecNet were to continue trials related to continuous glucose monitoring technologies in children utilizing the information obtained during the first phase of DirecNet. In addition, new specific goals were added to include: (1) evaluating interventions to reduce hypoglycemia in children and young adults with diabetes; (2) studying the pathophysiology of protection against and recognition of hypoglycemia in children; (3) determining the effects of hypoglycemia on brain structure and function using state-of-the-art neuroimaging methodologies and neurocognitive evaluations; (4) determining whether intensive therapy including initial closed loop control followed by pump and continuous glucose monitoring therapy can preserve islet cell function; and (5) expanding the understanding of the effects of exercise on blood glucose control, especially the risk of hypoglycemia.

HIGHLIGHTS OF PROGRESS

- Successful completion of nine protocols on children with or without type 1 diabetes, with five more in progress.
- Showed that the risk of nocturnal hypoglycemia increased nearly two-fold on nights following exercise.
- Showed that the risk of hypoglycemia can be markedly reduced in patients treated with insulin pumps by suspending the basal insulin infusion during exercise.
- Demonstrated that counterregulatory hormone responses to spontaneous nocturnal hypoglycemia are blunted throughout the nighttime period with or without antecedent exercise.

- Demonstrated that most pediatric patients with well-controlled type 1 diabetes fail to release epinephrine, a specific counterregulatory hormone, until blood glucose levels are approaching values that indicate a shortage of glucose in the brain.
- Showed that levels of adiponectin, a protein secreted by fat cells, are stable from day to day, not affected by acute exercise or metabolic control, and vary inversely with obesity in children with type 1 diabetes. Increased levels of adiponectin appear to be associated with a decrease in hypoglycemia risk.
- Showed that both low-fat and high-fat bedtime snacks provide equal protection against nocturnal hypoglycemia. This study also highlighted the feasibility of web-based research in the patients' home environment.
- Demonstrated that continuous glucose monitoring is a better method compared with 8-point glucose profiles as an outcome measure to assess glucose variability in diabetes clinical trials.
- Developed and tested new treatment satisfaction and adherence measures for use in clinical trials of continuous monitoring systems.
- Developed standard algorithms for patients and clinicians to use to adjust basal and bolus insulin doses based on continuous glucose monitoring data.
- Determined sensor accuracy, sensitivity, specificity, and reliability of first generation continuous glucose monitors in detecting hypoglycemia.
- Developed and implemented pilot studies to assess two bedtime interventions (terbutaline and glutamine) in the prevention or reduction of nocturnal hypoglycemia. One of these (terbutaline) proved difficult to recruit for and the other (glutamine) appeared ineffective. Neither was pursued by the study group for a long-term clinical trial.
- Developed and implemented a randomized, controlled trial of continuous glucose monitoring in children 4 to less than 10 years old. This trial is currently under way with 100 patients enrolled and is due for completion in late summer 2011.
- Developed and implemented a pilot and feasibility study of CGM use in children with type 1 diabetes less than 4 years old. This study is ongoing with 28 patients enrolled and is due for completion in early 2011.
- Developed and implemented a protocol designed to assess the relationship of beta cell reserve and glucagon (and epinephrine) response to hypoglycemia in children and adolescents with recent-onset (less than 1 year) type 1 diabetes. Mixed meal tolerance tests and hypoglycemic clamp tests have been performed in 20 patients.
- Developed and implemented a randomized trial, in collaboration with Type 1 Diabetes TrialNet, evaluating whether intensive glycemic control from the time of diagnosis of type 1 diabetes with initial closed loop therapy followed by pump-CGM therapy can preserve islet cell function.

- Developed a protocol to assess the relationship between hypoglycemia and brain structure and function using state-of-the-art magnetic resonance imaging technology and neurocognitive testing in young children with type 1 diabetes. Recruitment for this study will start in summer 2010.
- Developed a pilot protocol to inform the design of a clinical trial to develop and evaluate algorithms to minimize hypoglycemia during and after exercise in active adolescents with type 1 diabetes.

Anticipated Outcomes

In the absence of a functioning endocrine pancreas, people with diabetes are unable to respond to changes in blood glucose levels with insulin release. Over the past 80 years, improvements in technology have allowed patients to measure glucose levels and calculate the amount and variant of insulin to inject. These technological advances have saved many lives, but are far from perfect. The static measurement of glucose levels does not account for changes in diet or activity; there is a lag time between injecting insulin and its effect on the body; and too much injected insulin or inappropriately timed insulin action can lead to dangerous hypoglycemic episodes. The fear and danger of hypoglycemic episodes impede patients from achieving optimal control of blood glucose levels despite definitive evidence from the Diabetes Control and Complications Trial and the Epidemiology of Diabetes Interventions and Complications study that rigorous control can prevent diabetes complications. To address these issues, DirecNet has been testing the next generation of technologies: sensors that continuously monitor glucose levels and sound an alarm if levels cross certain thresholds; measurements that are sensitive to the rate of glucose change, not just the absolute amount of glucose; and insulin pumps that control insulin delivery under the skin. The ultimate goal of the network is to “close the loop” between automatic glucose level measurements and appropriate insulin delivery

responses. The ideal artificial pancreas would relieve the patient of the burden of constantly testing glucose levels and adjusting insulin doses and dietary intake. The role of DirecNet is to determine if the new technologies are safe and effective, particularly for use in children.

DirecNet is a prime example of the interface between industry, academia, health care, and government-sponsored research. DirecNet has carried out independent and scientifically rigorous studies to determine the true benefit of new monitoring technologies. Without the commitment of DirecNet to perform these studies, it could have been many years before the manufacturers of these devices were willing to conduct studies in the pediatric population. The DirecNet group is well positioned to assess new devices for their accuracy, as well as their clinical usefulness in the home environment.

Ongoing Evaluation

The overall decision making body of DirecNet is the Steering Committee (SC) which consists of the principal investigator, one co-investigator, and one coordinator from each clinical center; representatives of the Coordinating Center; and representatives from NICHD and NIDDK. For each protocol being considered, a Protocol Development Group is formed. This group develops a concept document outlining the planned protocol for discussion and approval by the SC and then the Protocol Review Committee, an NIH-appointed,

external review committee. Once the Protocol Review Committee approves the concept document, the Protocol Development Group develops a complete protocol which requires approval by the SC, the Protocol Review Committee, and the Data Safety and Monitoring Board (DSMB).

The DirecNet DSMB is an independent group of experts who meet at least 2 times each year or more frequently if needed to review clinical research protocols in the Network. The primary responsibilities of the DSMB are to: (1) periodically review and evaluate the accumulated study data for participant safety, study conduct and progress, and, when appropriate, efficacy; and (2) make recommendations to the SC concerning the continuation, modification, or termination of the trial. The DSMB considers study-specific data, as well as relevant background knowledge about the disease, technology, or patient population under study. Open session meetings involve DSMB members as well as DirecNet investigators who are chairpersons for specific protocols, the DirecNet SC Chair, Coordinating Center staff, and NIH representatives. The open sessions are followed by closed sessions involving only DSMB members and NIH representatives.

In addition, DirecNet has been evaluated by external panels of scientific and lay experts at *ad hoc* evaluation meetings convened by NIH in January 2005 and April 2008. These meetings were an opportunity for external experts to evaluate progress and provide input on future research directions (for more information, see the Executive Summary and Appendix B). Through *ad hoc* evaluation meetings and other meetings described above, NICHD continually seeks external input to inform current and future directions for DirecNet.

Program Enhancements

Because of the evolving nature of science, consortia supported by the *Special Diabetes Program* have evolved over time and have undergone enhancements to take advantage of new technologies and research findings, and to accelerate progress. Some enhancements have been made in response to external input and others have been initiated by the consortium members. Examples of program enhancements for DirecNet include:

- In order to continually advance progress, DirecNet worked to maintain a steady stream of protocols in the development phase while one or more studies were being implemented. This allowed new studies to be implemented rapidly once resources were available.
- The scope of DirecNet was broadened in 2007 by soliciting competitive proposals in response to a new Request for Applications (RFA). In addition, NIH convened a panel of scientists with hypoglycemia expertise to obtain input on the 2007 research solicitation and to encourage the participation of such experts.
- As DirecNet adds neuroscience and neuroimaging measures to studies of hypoglycemia, NIDDK and NICHD sought the participation of NINDS to further assist in the effort.

Coordination with Other Research Efforts

The DirecNet coordinates its efforts with other type 1 diabetes research consortia and networks supported by the *Special Diabetes Program*. Collaboration, coordination, and resource sharing serve to synergize research efforts and accelerate research progress. Examples of coordination with other consortia are given

below. For a summary of ongoing collaborative efforts, please see Appendix D.

Coordinating Research Studies:

- Coordination with TrialNet on Effect of Metabolic Control at Onset of Diabetes on Progression of Type 1 Diabetes Trial: This trial is testing the impact

of intensive metabolic control from the onset of diabetes on the preservation of beta cell function. The therapy consists of a short inpatient course of sub-cutaneous closed-loop diabetic control at the onset of diabetes followed by real-time continuous glucose monitoring associated with continuous subcutaneous insulin infusion.

DirecNet Administrative History

Date Initiative Started	2001
Date <i>Special Diabetes Program</i> Funding Started	2001
Participating Components	NICHD, NIDDK
Web site	http://public.direc.net
DirecNet consists of a Coordinating Center, five pediatric diabetes centers, and a central laboratory.	

Goal V: Prevent or Reduce the Complications of Type 1 Diabetes

EPIDEMIOLOGY OF DIABETES INTERVENTIONS AND COMPLICATIONS (EDIC)

The aim of EDIC is to study the clinical course and risk factors associated with the long-term complications of type 1 diabetes, using the cohort of 1,441 patients who participated in the landmark Diabetes Control and Complications Trial (DCCT). Completed in 1993, the DCCT revolutionized diabetes management by demonstrating the benefit of intensively controlling blood glucose levels with frequent monitoring and insulin injection for preventing or delaying the early complications of the disease. Both the “conventional” and “intensive” treatment groups from DCCT are being followed observationally, but all participants are now recommended to follow the intensive therapy guidelines. DCCT/EDIC is a prospective study: one of its major strengths is the well-studied cohort of patients in which disease progression has been followed for over 25 years before most complications developed. The *Special Diabetes Program’s* support has been pivotal to the success of EDIC. Major findings highlighted below derive from studies to measure the onset and progression of cardiovascular disease (CVD), diseases of the urinary tract (uropathy), and diseases of the nerves that communicate with the internal organs such as the bladder, bowel, and sexual organs (autonomic neuropathy) and with the hands and feet (peripheral neuropathy). A separate genetics component is described in the section entitled “Genetics of Diabetic Complications.”

HIGHLIGHTS OF PROGRESS

- Results show that after 30 years of diabetes, DCCT participants randomly assigned to intensive glucose control had lower rates of eye damage, kidney damage, and cardiovascular events than the conventional group. The phenomenon of long-lasting effects of a period of intensive or nonintensive glucose control has been termed “metabolic memory,” and suggests that implementing intensive glucose control as early in the course of diabetes as possible could help people avoid life-threatening complications.
- Metabolic memory may wane over time, based on reduction in risk of retinopathy in participants assigned to intensive glucose control.
- Results show that intensive control of blood glucose levels cut the number of CVD events (heart attacks, strokes, or death) in half relative to the control group in the DCCT. This is the first demonstration of the long-term beneficial effects of intensive diabetes therapy on macrovascular complications in type 1 diabetes patients.
- Evaluation of DCCT patients 12 years after the conclusion of the study, using the same neuropsychological tests administered during the DCCT trial, revealed no link between multiple severe hypoglycemic reactions and impaired cognitive function in people with type 1 diabetes in the study. This result means that people with type 1 diabetes do not have to worry that acute episodes of hypoglycemia will damage their mental abilities and impair their long-term abilities to perceive, reason, and remember.

- Results of carotid ultrasonography show significant thickening in arteries of EDIC diabetes patients relative to non-diabetic controls and significantly less progression in the DCCT intensively treated group compared to the conventionally-treated group.
- Results also show that the DCCT intensively treated group has reduced coronary calcification (a subclinical progression of CVD).
- Occurrence of cardiac autonomic neuropathy was significantly lower in the former DCCT intensively treated EDIC cohort compared to the conventionally treated.
- Prevalence of urinary incontinence (urge and stress incontinence) was found to be significantly higher in women in the EDIC cohort than in women in the general U.S. population. Urinary tract infections, however, were not more prevalent in EDIC women, compared to the general population.
- Sexual dysfunction in both men and women in the EDIC cohort were common.
- DDCT/EDIC data and biosamples have been made available to the scientific community through multiple means, including the NIDDK Central Repositories.

Anticipated Outcomes

The dramatic results of the DCCT/EDIC demonstrate the benefits of a long-term prospective study. The DCCT proved conclusively that intensive diabetes therapy reduces the risk and progression of eye disease (retinopathy) by 47 to 76 percent, of kidney damage (nephropathy) by 39 to 54 percent, and of nerve damage (neuropathy) by 60 percent. The EDIC study continues to follow participants in the DCCT study to determine the long-term benefit of intensive blood glucose control and recently reported additional striking results. After 30 years of diabetes, DCCT participants randomly assigned to intensive glucose control had about half the rate of eye damage compared to those assigned to conventional glucose control (21 percent versus 50 percent). They also had lower rates of kidney damage (9 percent versus 25 percent) and cardiovascular events (9 percent versus 14 percent) compared to those receiving conventional glucose control.

Only in the long-term follow-up EDIC study (average 17 years of follow-up) have the benefits for CVD become apparent as well: intensive diabetes therapy reduces non-fatal CVD events by 57 percent. Heart disease is a chronic condition, developing over decades. It is difficult to prospectively study a population continuously from a young age before the onset of symptoms through CVD events, such as heart attacks and strokes. Yet as shown in EDIC, therapy early in the course of disease has profound consequences decades later. Because pharmaceutical companies and the biotechnology industry have a limited willingness to develop products that require years of testing before their clinical effects can be realized, it is therefore important to develop and validate subclinical biomarkers that the U.S. Food and Drug Administration (FDA) will accept as a basis for approval of new drugs for diabetes complications. For example, the DCCT demonstrated that the level of hemoglobin A1c (HbA1c)—a modified form of hemoglobin that circulates in the blood and correlates to the average blood

glucose levels over a 3-month period—can be used as a surrogate endpoint for therapies that seek to reduce complications of diabetes. This test has subsequently become an important outcome measure for future clinical trials of both type 1 and type 2 diabetes. The use of HbA1c as an outcome measure was the basis for FDA approval of improved forms of insulin, as well as many other new drugs for type 2 diabetes.

Comprehensive and meticulous data collection in the DCCT/EDIC cohort for more than 25 years, with participation rates of about 95 percent, has created an unparalleled resource of individuals with type 1 diabetes that is ideal for future study of the clinical course of diabetes and its complications and for the validation of surrogate endpoints that can facilitate future drug development. These include assessment of subclinical markers such as testing new imaging techniques to measure the clogging, narrowing, and hardening of major arteries (atherosclerosis), heart muscle function, and other signs of CVD. EDIC has pioneered the use of new noninvasive diagnostic tools such as using ultrasound to measure the thickness of the carotid artery, or use of a “heart scan” (electron beam computed tomography) and multi-detector scanning to determine the extent of coronary calcification, and most recently using cardiac magnetic resonance imaging (MRI) to assess the structure and function of the heart allowing detection of silent heart attacks and congestive heart failure. By validating new analytical tools for early detection of CVD complications before events occur, the results of EDIC are paving the way for future trials that are smaller, shorter in duration, and less expensive to conduct.

Longitudinal assessment of the cohort allows analysis of the rate-of-change of complications over time, including the interactions among complications and co-occurrence

of complications, as well as further evaluation of the longer-term effects of original DCCT interventions on advanced complications. This study is also leading to an examination of the longevity of the metabolic memory phenomenon and whether it applies to all diabetic complications, as was mentioned earlier with the waning of metabolic memory found with retinopathy. Important insights will be gained regarding the disease-causing mechanisms that underlie the development and progression of diabetic complications.

Ongoing Evaluation

To ensure ongoing evaluation of the study design and progress of the EDIC, NIDDK has established an External Evaluation Committee (EEC). The EEC is composed of investigators with scientific expertise relevant to research conducted by the EDIC, but who are not members of the Consortium. The EEC meets annually to:

- Review activities that affect the operational and methodological aspects of the study (e.g., quality control procedures and performance of clinical centers, data and clinical coordinating centers, central laboratories, and reading centers);
- Review data to ensure its quality, provide input on procedures for analysis and data display, and provide input on interpretation and implications of results; and
- Review proposed major modifications to the protocol or operations of the study for appropriateness, necessity, and impact on overall study objectives.

In addition, *ad hoc* groups have been assembled to review new initiatives being proposed in EDIC and to review progress once initiatives have been implemented. Examples of these groups have included an *ad hoc* group for genetics studies, review groups for proposals to obtain EDIC nonrenewable biologic samples, and

groups recommending specific measures to be obtained for assessing CVD and autonomic and peripheral neuropathy.

Finally, EDIC has been evaluated by an external panel of scientific and lay experts at an *ad hoc* evaluation meeting convened by NIDDK in January 2005. This meeting was an opportunity for external experts to evaluate progress and provide input on future research directions (for more information, see the Executive Summary and Appendix B). Through *ad hoc* evaluation meetings and regular meetings of the EEC, NIDDK continually seeks external input to inform current and future directions for the EDIC.

Program Enhancements

Because of the evolving nature of science, consortia supported by the *Special Diabetes Program* have evolved over time and have undergone enhancements to take advantage of new technologies and research findings, and to accelerate progress. Some enhancements have been made in response to external input and others have been initiated by the consortium members. Examples of program enhancements for EDIC include:

- To capitalize on the long-term investment in resources in this select cohort of patients and because this cohort provided a good opportunity to examine subclinical CVD markers (e.g., carotid intima-medial thickness, coronary calcification, myocardial function), EDIC developed additional cardiovascular studies. A total of three

measurements of carotid intima-medial thickness have been taken so that changes in atherosclerosis can be measured over time. The cohort is currently undergoing a cardiac MRI procedure to assess the structure and function of the heart, allowing detection of silent heart attacks and congestive heart failure.

Coordination with Other Research Efforts

EDIC coordinates its efforts with multiple other type 1 diabetes research consortia and networks supported by the *Special Diabetes Program*. Collaboration, coordination, and resource sharing serve to synergize research efforts and accelerate research progress. Examples of coordination with other consortia are given below. For a summary of ongoing collaborative efforts, please see Appendix D.

Enhancing Data Comparison Among Studies:

- The National Glycohemoglobin Standardization Program certifies clinical laboratories to use the standard set by DCCT/EDIC for measurements of HbA1c. Nearly all commercial laboratories providing this clinical test in the United States are now certified through this program supported by the *Special Diabetes Program*. This has allowed the National Diabetes Education Program to promulgate a nationwide public health campaign to achieve targeted HbA1c values based on the DCCT/EDIC and led the American Diabetes Association to recently recommend HbA1c as a more convenient approach to diagnose type 2 diabetes.

EDIC Administrative History

Date Initiative Started	1994
Date <i>Special Diabetes Program</i> Funding Started	1998
Participating Component	NIDDK
Web site	http://www2.bsc.gwu.edu/bsc/oneproj.php?pkey=10

EDIC is a long-term follow-up study to the DCCT of 1,441 patients with type 1 diabetes conducted between 1983 and 1993.

ANIMAL MODELS OF DIABETIC COMPLICATIONS CONSORTIUM (AMDCC)

The AMDCC is an interdisciplinary Consortium designed to develop animal models that closely mimic the human complications of diabetes for the purpose of studying disease pathogenesis, prevention, and treatment. In addition to creating animal models, the goals of the AMDCC include defining standards to validate each diabetic complication for its similarity to the human disease, testing the role of candidate genes or chromosomal regions that emerge from genetic studies of human diabetic complications, and facilitating the sharing of animals, reagents, and expertise between members of the Consortium and the greater scientific community via its bioinformatics and data coordinating center. In its second funding cycle, the AMDCC formed a close partnership with the Type 1 Diabetes Mouse Resource (T1DR, described earlier in this Appendix) and the Mouse Metabolic Phenotyping Centers (MMPCs).

HIGHLIGHTS OF PROGRESS

- Generated about 40 animal models of type 1 diabetes that closely mimic various aspects of the human complications of diabetes.
- Published over 180 scientific publications in highly respected peer-reviewed journals.
- Published about 60 laboratory protocols on the AMDCC public Web site (www.amdcc.org) for use by the research community.

Anticipated Outcomes

Animal models are an important scientific resource because they enable researchers to investigate underlying disease processes that cannot be studied in humans. For example, the demonstration of the key role of immune cells in the destruction of beta cells in type 1 diabetes would not have been possible without animal models. These models also permit assessment of novel therapeutic interventions before they are tested in people. The creation of the non-obese diabetic (NOD) mouse provided investigators with a critical tool for pre-clinical testing of new drugs for type 1 diabetes. Just like people with type 1 diabetes, the NOD mouse has genetic susceptibility due to molecules regulating the immune response; the disease is influenced by environmental encounters; the animal produces autoantibodies against beta cell proteins; and the white blood cells infiltrate the pancreatic islets. In the animal model, beta cell

destruction can be attenuated through application of agents capable of influencing the immune response. Following this successful approach, the AMDCC is creating better animal models of diabetes complications. Because the Consortium has invested in infrastructure to share its resources with the larger scientific community, the impact of its efforts on drug discovery is enormous. Animal models also provide an opportunity to identify surrogate markers for diabetic complications. Diagnosing intermediate stages of disease progression is a major challenge inhibiting clinical translation because disease progression is long-term. With about 40 new animal models and 180 peer-reviewed scientific publications, the AMDCC has played a critical role in propelling research progress by developing, validating, and distributing animal models with greater fidelity to human type 1 diabetes and its complications.

Ongoing Evaluation

The AMDCC is jointly managed by NIDDK and NHLBI, with input from NINDS, NEI, and JDRF staff. NIH staff and AMDCC investigators participate in monthly conference calls to discuss business and science. An External Evaluation Committee (EEC) meets with the AMDCC investigators annually. This meeting usually lasts 2 days and includes an open session where the investigators present their work and a closed session where NIH staff and the EEC evaluate progress and discuss future directions. The EEC prepares a written report of their deliberations, to which the investigators must respond in writing. AMDCC investigators also prepare an annual progress report. This document provides a written summary of yearly progress, an appraisal of the interactions between the ongoing projects at each site, and a description of the existing and planned collaborations with other members of the Consortium. All annual progress reports are available to the public at www.amdcc.org. A representative from the JDRF often participates in the monthly conference calls and always participates in AMDCC face-to-face meetings.

In addition, AMDCC has been evaluated by external panels of scientific and lay experts at *ad hoc* evaluation meetings convened by NIDDK in January 2005 and June 2009. These meetings were an opportunity for external experts to evaluate progress and provide input on future research directions (for more information, see the Executive Summary and Appendix B). Through *ad hoc* evaluation meetings and regular meetings of the EEC, NIDDK continually seeks external input to inform current and future directions for the AMDCC.

Program Enhancements

Because of the evolving nature of science, consortia supported by the *Special Diabetes Program* have

evolved over time and have undergone enhancements to take advantage of new technologies and research findings, and to accelerate progress. Some enhancements have been made in response to external input and others have been initiated by the consortium members. Examples of program enhancements for AMDCC include:

- In its second funding cycle, the AMDCC formed a close partnership with the T1DR and the MMPCs to ensure that all interesting models are screened across multiple complications.
- Recognizing the need to bolster research efforts for both diabetic retinopathy and neuropathy, the AMDCC worked closely with the MMPCs to organize a workshop entitled “Advances Toward Measuring Diabetic Retinopathy and Neuropathy” in April 2007. The meeting provided a forum for identifying needs and research opportunities for the AMDCC and MMPC Pilot & Feasibility (P&F) programs. Two P&F awardees targeted by this workshop presented their exciting work at the AMDCC meeting in June 2008: one discussed a novel technique for measuring intraretinal ion activity and retinal thickness in diabetic mice using manganese-enhanced magnetic resonance imaging and another presented data on the use of “hyperspectral” imaging for diabetic peripheral neuropathy and wound healing.
- The AMDCC has been working with the broader neuropathy community to enhance pre-clinical studies. The AMDCC and JDRF supported a planning meeting in late 2007 to set the agenda for a 2-day meeting in 2008 entitled “Consensus meeting on experimental models of diabetic neuropathy” to establish a definition of diabetic neuropathy in experimental rodent models. A distinguished

group of basic and clinical researchers from around the world produced a definition including assessments of functional, sensory, behavioral, and anatomical measures.

Coordination with Other Research Efforts

The AMDCC coordinates its efforts with other type 1 diabetes research consortia and networks supported by the *Special Diabetes Program*. Collaboration, coordination, and resource sharing serve to synergize research efforts and accelerate research progress. Examples of coordination with other consortia are given below. For a summary of ongoing collaborative efforts, please see Appendix D.

Synergism with Consortia Studying Animal Models:

- The AMDCC collaborates with the T1DR to enhance model development and phenotype characterization under controlled husbandry conditions. One example of this collaborative partnership is an ongoing investigation to examine the significant variation seen in the susceptibility of inbred mouse strains to the development of diabetic nephropathy. Consortial studies have characterized the differential responses of mouse strains to the development of hyperglycemia. They have also delineated mouse strains that are most and least susceptible to development of albuminuria and renal histopathologic changes in response to diabetes. These findings

have been widely disseminated in the research community and have had a profound and fundamental impact on the design of studies of experimental diabetic nephropathy.

- The AMDCC also supports the MMPCs to enhance phenotyping of mouse models of diabetic complications. The MMPCs are charged with providing the scientific community with standardized, high-quality metabolic and physiologic phenotyping services for the mouse. The MMPCs provide state-of-the-art technologies to investigators for a fee, and with AMDCC support, the MMPCs have expanded their services to include a wide range of tests for diabetic nephropathy, retinopathy, and cardiovascular disease. The MMPCs also support a P&F program to develop new technologies for phenotyping animal models, and with the input of the AMDCC have provided focused solicitations in the areas of diabetic complications.
- The AMDCC has partnered with the Type 1 Diabetes-Rapid Access to Intervention Development (T1D-RAID) project, in which the T1D-RAID contractor acts as a histology and phenotyping resource for diabetic neuropathy. Tissue specimens received from The Jackson Laboratories as part of ongoing AMDCC projects are processed to blocks, analyzed, and stored. Stored tissues are available to all interested members of the research community.

AMDCC Administrative History

Date Initiative Started	2001
Date <i>Special Diabetes Program</i> Funding Started	2001
Participating Components	NIDDK, NHLBI, NINDS, NEI, and JDRF
Web site	www.amdcc.org

The AMDCC is comprised of thirteen “pathobiology sites” that study complications such as diabetic nephropathy, uropathy, neuropathy, cardiomyopathy, and vascular disease. The Consortium also supports and has formed a close partnership with the T1DR and the MMPCs. All data and resources from the consortium and its partners are freely available through a joint AMDCC-MMPC Coordinating and Bioinformatics Unit.

GENETICS OF DIABETES COMPLICATIONS

The following three consortia were grouped because they all address genetic factors that predispose people with diabetes to, or protect them from, developing complications in various organs. Each has unique attributes that make it highly valuable for genetic studies: the Epidemiology of Diabetes Interventions and Complications' strength is the careful characterization of the cohort over 25 years of follow-up; the Family Investigation of Nephropathy and Diabetes has a very large collection of families in which two or more siblings have diabetes; and the Genetics of Kidneys in Diabetes Study matches people with type 1 diabetes, with and without kidney complications, and collects information from their parents.

Epidemiology of Diabetes Interventions and Complications (EDIC)

The aim of EDIC is to study the clinical course and risk factors associated with the long-term complications of type 1 diabetes, using the cohort of 1,441 patients who participated in the landmark Diabetes Control and Complications Trial (DCCT), which showed that intensive glucose control can prevent or delay microvascular (eye, kidney, and nerve) disease complications. To capitalize on the long-term investment in the select EDIC cohort, the *Special Diabetes Program* supports a study on the genetics underlying diabetes complications in these patients. The study is analyzing expanded data regarding the progression of complications in EDIC participants and their affected and non-affected family members to identify DNA sequence differences that influence susceptibility to diabetic complications.

Family Investigation of Nephropathy and Diabetes (FIND)

The FIND Consortium is carrying out studies to elucidate the genetic susceptibility to kidney disease (nephropathy) in people, especially those with diabetes, as well as genetic susceptibility to eye disease (retinopathy) in people with diabetes. Five to ten percent of the people in FIND have type 1 diabetes. FIND is primarily supported by regularly appropriated NIH funds; however, support from the *Special Diabetes Program* permitted expansion of FIND by initiation of a study of the genetic determinants of diabetic retinopathy in persons enrolled in the FIND family study. This component of the study seeks to identify genes that may influence the development and severity of diabetic eye disease. FIND has also created a resource of genetic samples and data for use by investigators outside the FIND study group, for ancillary or follow-up studies. FIND represents the first large-scale study of the genetic determinants of retinopathy.

Genetics of Kidneys in Diabetes Study (GoKinD)

People with type 1 diabetes have a high risk of developing kidney disease. The fundamental aim of GoKinD was to facilitate investigator-driven research into the genetic basis of diabetic nephropathy by creating a resource of genetic samples from people who have both type 1 diabetes and renal disease, and "control" patients who have type 1 diabetes but no renal disease. With this design, the genes that confer risk for renal disease can be distinguished from those that are primarily risk factors for type 1 diabetes. The GoKinD study was concluded in 2007. Any researcher can apply for access to this collection of samples and data to investigate the role of specific genes.

HIGHLIGHTS OF PROGRESS

- Genome-wide association studies (GWAS) examine genetic variation across the entire human genome to try and identify genetic differences that are associated with a particular disease. GWAS have been completed for cohorts of patients with type 1 diabetes in the GoKinD Study and the EDIC Study. The data are being shared through the NIH's Database of Genotypes and Phenotypes (dbGAP). In 2009, samples from the FIND study were tested using GWAS; analysis of these data is ongoing. The resulting data from DCCT/EDIC and GoKinD have been used by numerous investigators in various genetic analyses to identify genetic regions associated with a disease, to replicate promising findings from other studies, or to refine analytic methods. Some of these studies are highlighted below.
- Using GWAS data from the DCCT/EDIC cohort, researchers identified a gene region, which is near the *SORCS1* gene, associated with hemoglobin A1c (HbA1c) levels. Other genetic regions were also found to be associated with HbA1c levels, and some of the regions were also associated with low blood glucose levels and eye complications of diabetes. The association with the *SORCS1* gene region was replicated in the GoKinD study control group.
- The GoKinD GWAS data was used to identify two genes/genetic regions associated with diabetic nephropathy: *FRMD3* and *CARS*. The results from the genotyping were confirmed by comparison to the GWAS data from the DCCT/EDIC study.
- Using GWAS data from the GoKinD collection, scientists determined that *ELMO1* is associated with diabetic nephropathy, thereby further establishing the gene's role in the susceptibility of this disease.
- Studying three European-American cohorts, including GoKinD participants, researchers identified a gene associated with risk of kidney and eye complications of diabetes. They compared 11 genes in people with type 2 diabetes who either had or did not have proliferative diabetic retinopathy (PDR; a serious form of diabetic eye disease) and end-stage renal disease (ESRD). The researchers found that variation in a region of DNA near the erythropoietin gene was associated with PDR and ESRD. They also analyzed genes of people with type 1 diabetes and found the same result, suggesting even more strongly a link between this genetic variation and diabetic eye and kidney disease in people of European American ancestry.
- *HLA DRB1*04* alleles have been associated with protection from some of the injurious hyperglycemic effects related to diabetic nephropathy in the GoKinD study population.
- A region upstream of the *PLEKHH2* gene on chromosome 2p21 that is exclusively expressed in the glomerulus has been associated with diabetic nephropathy by transmission to trio probands, and as a risk factor for diabetic nephropathy in the independent case/control population of the GoKinD study. This region was found by a GWAS of *human leukocyte antigen*-matched GoKinD case and control samples that minimized the problem of population stratification.

- FIND investigators studied 2,368 people with diabetes from 767 families enrolled in the FIND-Eye study. They determined that the overall prevalence of diabetic retinopathy was high: 33.4 percent had proliferative diabetic retinopathy; 7.5, 22.8, and 9.5 percent had severe, moderate, and mild nonproliferative diabetic retinopathy, respectively; 26.6 percent had no diabetic retinopathy. They also found that the severity of diabetic retinopathy was significantly associated with severity of diabetic kidney disease.
- Using genome-wide scans of samples collected from over 1,200 people with diabetes-related kidney disease and their relatives, FIND researchers identified four regions on chromosomes 7, 10, 14, and 18 where subtle variations correlated with an increased risk of diabetic kidney disease. Similar scans identified three regions on chromosomes 2 and 15 and a different part of chromosome 7 associated with elevated protein in the urine. The strength of the linkages varied with the ethnic background of participants. These findings confirm earlier studies implicating regions of chromosomes 7, 10, and 18 in increased risk of diabetic kidney disease, and identify a new region of interest on chromosome 14.

Anticipated Outcomes

Through these research efforts, many new insights into the genetic underpinnings of diabetes complications have emerged. With more complete knowledge of the genetic factors that contribute to different complications, the patient's doctor may be able to personalize therapy and intervene early to prevent or delay specific complications. For example, a patient genetically predisposed to diabetic nephropathy could employ clinical strategies such as carefully controlling blood pressure and taking angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers, which lower protein in the urine and are thought to directly prevent injury to the kidney's blood vessels. In another example, understanding the genetic factors that contribute to patients' control of HbA1c levels may provide insights as to why people on similar treatment regimens have different HbA1c values and inform personalized therapies to achieve similar levels.

Although these genetic findings are extremely exciting in and of themselves, they represent just the beginning of new knowledge that is expected to emerge as research is

setting the stage for even more scientific breakthroughs.

For example, a newly associated gene may produce a protein that interacts with numerous other proteins. Therefore, discovering the disease association not only implicates that protein in the disease, but also the proteins with which it interacts. This knowledge could illuminate several new therapeutic targets for disease prevention or treatment. Studying genes that were not thought to be involved in a disease can lead to brand new avenues for research that would likely not have been pursued otherwise. Identifying the functions of genes may not only enhance understanding of molecular mechanisms that underlie disease, but may also reveal new targets for therapy.

In addition to the genes and genetic associations with diabetes complications that have been discovered and are still emerging from EDIC, FIND, and GoKinD, each of these consortia also serves as a resource for ongoing and future efforts: tissue, genetic samples, data, and analytic methods from each study are stored in a repository or database. The large and diverse sample and data collections—with families, cases, and controls—

are a widely-used resource for genetic studies of susceptibility to diabetic complications. The availability of immortalized cell lines for each participant provides a renewable source of DNA, allowing investigators to explore novel hypotheses or analytical approaches.

Ongoing Evaluation

To ensure ongoing evaluation of the study design and the progress of FIND and EDIC, NIH has established External Evaluation Committees (EEC). Each EEC is composed of investigators with scientific expertise relevant to research conducted by the Consortium, but who are not members of the Consortium. Please see a description of the EDIC EEC in the EDIC section of this Appendix. The FIND EEC meets periodically to review the progress of the study. The experts comment specifically on activities that affect the operational and methodological aspects of the study (e.g., quality control procedures and performance of clinical centers, data and clinical coordinating centers, and central laboratories and reading centers), review data to ensure its quality, provide input on procedures for analysis, and review proposed significant modifications to the protocol or operations of the study for appropriateness, necessity, and impact on overall study objectives. The GoKinD Executive Committee oversaw the day-to-day operation of the study and consisted of representatives from academia, government, and voluntary organizations. An external Steering Committee consisting of scientific and lay reviewers met once a year to review the study and make recommendations. The GoKinD study was concluded in 2007.

In addition, these programs were evaluated by an external panel of scientific and lay experts at an *ad hoc* evaluation meeting convened by NIDDK in January 2005. This meeting was an opportunity for external experts to evaluate progress and provide input on future research

directions (for more information, see the Executive Summary and Appendix B). Through *ad hoc* evaluation meetings and regular meetings of the EECs, NIDDK and CDC continually seek external input to inform current and future directions for these research programs.

Program Enhancements

Because of the evolving nature of science, consortia supported by the *Special Diabetes Program* have evolved over time and have undergone enhancements to take advantage of new technologies and research findings, and to accelerate progress. Some enhancements have been made in response to external input and others have been initiated by the consortium members. Examples of program enhancements for FIND, GoKinD, and EDIC include:

- Since the inception of these research programs, new and emerging genetics technologies have become available. The FIND and GoKinD studies were designed and launched at a time when genetic analyses focused on sibling pairs and only low resolution methods were available for gene hunting. Over time, the two consortia responded to the emergence of novel methodologies by changing their genotyping strategies to use GWAS. The robust design of each consortium's recruitment allowed them this flexibility: both relatives and unrelated individuals were recruited in enough numbers to permit the older and newer analytic methods to be used. The EDIC study also changed its strategies from examining familial clustering of diabetic complications (in siblings and parents of EDIC probands), to examining candidate genes, to using GWAS in conjunction with FIND and GoKinD.
- Resources for sharing samples and data have also changed these projects significantly. The NIDDK

Central Repositories, created in 2001, facilitate rapid and efficient sharing of samples and data. In addition, the NIH's dbGAP database and associated mandated GWAS data sharing policies ensure maximum rapid access to GWAS data. These two changes, external to the consortia, made some of the organizational and administrative functions of the consortia redundant, and they were reduced accordingly.

Coordination with Other Research Efforts

The consortia studying the genetics of complications coordinate their efforts with each other and with multiple other type 1 diabetes research consortia and networks supported by the *Special Diabetes Program*. Collaboration, coordination, and resource sharing serve to synergize research efforts and accelerate research progress. Examples of coordination with other consortia are given below. For a summary of ongoing collaborative efforts, please see Appendix D.

Coordinating Studies of Genetics in Type 1 Diabetes:

- EDIC, FIND, and GoKinD participated in a coordination meeting with the T1DGC.

- Key personnel from the FIND study served in official advisory capacities for GoKinD.

Developing Interoperable Databases for Data Sharing:

- A series of database coordination meetings between FIND, EDIC, and GoKinD helped standardize vocabularies, allowing investigators to search data across databases.
- The NIDDK is supporting the development of tools at the NIDDK Central Repositories to allow searching across the stored data from major clinical studies, which include EDIC, GoKinD, and FIND.
- The uniformity of GWAS data allows results from EDIC, GoKinD, and FIND to be housed in a single location (dbGAP), and still be accessed by investigators through the NIDDK Central Repositories. dbGAP works cooperatively with the NIDDK Central Repositories to provide easy, interoperable access to all three datasets.

EDIC Administrative History

Date Initiative Started	1994
Date <i>Special Diabetes Program</i> Funding Started	1998
Participating Components	NIDDK
Web site	http://www2.bsc.gwu.edu/bsc/oneproj.php?pkey=10

EDIC is a long-term follow-up study to the DCCT of 1,441 people with type 1 diabetes conducted between 1983 and 1993.

FIND Administrative History

Date Initiative Started	1999
Date <i>Special Diabetes Program</i> Funding Started	2001
Participating Components	NIDDK, NEI, NCMHD

Ten percent of the people in the FIND family study have type 1 diabetes. Funds from the *Special Diabetes Program* permitted expansion of FIND to support ancillary studies searching for determinants of diabetic retinopathy.

GoKinD Administrative History

Date Initiative Started	1998
Date <i>Special Diabetes Program</i> Funding Started	1998
Participating Components	CDC, JDRF
Web site	www.jdrf.org/gokind
Concluded	2007

Saved DNA, blood plasma, blood serum, and urine samples as well as data are being stored in the NIDDK Central Repositories for use by any investigators in the diabetes research community based on a review process.

DIABETIC RETINOPATHY CLINICAL RESEARCH NETWORK (DRCR.NET)

The DRCR.net is a collaborative, nationwide network of eye doctors and investigators conducting clinical research of diabetes-induced retinal disorders (diabetic retinopathy, diabetic macular edema, and associated conditions). The DRCR.net supports the identification, design, and implementation of multicenter clinical research while incorporating standardization of multiple study procedures, utilization of novel technology, extensive integration of information technology, and the ability to leverage its resources to bring promising new therapies to evaluation that might otherwise not exist. Principal emphasis is placed on clinical trials, including comparative effectiveness trials, but epidemiology, outcomes, and other research approaches may be supported as well. Diabetic retinopathy is a complication associated with both type 1 and type 2 diabetes; DRCR.net, which is funded in part by the *Special Diabetes Program*, enrolls both type 1 and type 2 diabetes patients. In soliciting site participants, involvement of community-based, as well as academic-oriented partners, has been encouraged.

HIGHLIGHTS OF PROGRESS

- Establishment of a nationwide network that currently includes 112 clinical sites, 1,165 personnel, and spans 36 states. Community-based clinical sites comprise 81 percent of the network, representing about one-third of the U.S. retina specialists; most major research institution-based programs are also involved.
- Rapid implementation of 15 protocols (both large and small) since inception, in response to basic research and applied technological developments in the field of diabetic retinopathy. Four protocols are currently recruiting and four additional protocols are in development.
- Landmark comparative effectiveness trial demonstrating that a new combination therapy of ocular injections of a U.S. Food and Drug Administration (FDA)-approved drug, ranibizumab (Lucentis®), and laser treatment was definitively superior to the standard practice of laser treatment alone. With the potential to slow progression, and in many cases, reverse vision impairment from diabetic retinopathy, this is the biggest advance in diabetic retinopathy in 25 years, since a previous NIH study established the standard laser therapy. Nearly 50 percent of patients who received the combination treatment experienced substantial visual improvement after 1 year, compared to 28 percent who received the standard laser treatment, while fewer than 5 percent experienced substantial visual loss with the combination treatment compared with almost 15 percent who received the standard laser treatment.
- Determined that focal/grid laser photocoagulation for diabetic macular edema can lead to substantial improvement of visual acuity far more often than was previously thought.
- Demonstrated that steroid injections into the eye, although effective in reducing diabetic macular edema, were not superior to focal/grid laser alone, and had considerable side effects.
- Compared the safety of a single panretinal laser treatment, versus multiple treatments, the standard course employed for over 30 years. If preliminary results indicating similar safety profiles are confirmed in a larger trial,

they would have far-reaching implications for the cost and convenience of one of the most common treatments for diabetic retinopathy.

- Completed study measuring variability in retinal thickening throughout the day in patients with diabetic macular edema.
- Distributed electronic visual acuity testing devices to all sites. This FDA-approved test is faster to administer than the standard version, and results are easily incorporated into a database.
- Collaborated with industry on an innovative protocol to create a drug that would not otherwise be commercially pursued (preservative-free intraocular steroid).
- Compared new therapies across multiple industries. This effort included negotiations for clinical site funding costs with these industries, utilizing the Network's industry collaboration guidelines.
- Developed an online system for collecting, reviewing, maintaining, and publicly reporting financial relationships of investigators with industry.
- Publication of 24 manuscripts by various journals, with an additional six manuscripts accepted for publication, three currently under review, and 11 currently in development. DRCR.net investigators also gave 16 poster or platform presentations on behalf of the Network at national and international conferences in 2009 alone. The Network Web site provides free public access to these publications (<http://drcrnet.jaeb.org/Publications.aspx>).

Anticipated Outcomes

Diabetes (type 1 and type 2) is the leading cause of new blindness in people 20-74 years old, and diabetic retinopathy causes 12,000 to 24,000 new cases of blindness each year.³⁸ Laser photocoagulation is an effective technique that uses the heat of a laser beam to seal abnormal leaky blood vessels in the retina. While laser photocoagulation can prevent blindness, the technique itself can lead to impaired vision. Therefore, improved technologies are being developed and tested by DRCR.net. The network provides infrastructure for conducting multiple concurrent and consecutive studies, with the ability to rapidly develop and initiate new protocols. Already, DRCR.net has made several

significant contributions to the treatment of diabetic retinopathy, including results of a landmark combination therapy trial (described above), which are already being implemented in clinical practice to slow progression and in some cases reverse the vision impairment from diabetic retinopathy.

One of the most important DRCR.net priorities is to have a portfolio of ongoing clinical trials that not only encompasses a broad diversity of promising new therapeutic approaches, but also addresses the full spectrum of patients with diabetic eye disease. The Network is actively pursuing identification and design of important clinical trials that complement each other in

³⁸ Centers for Disease Control and Prevention. National diabetes fact sheet: general information and national estimates on diabetes in the United States, 2007. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2008. Accessed from www.cdc.gov/diabetes/pubs/factsheet07.htm

terms of patient eligibility and therapeutic approach. This approach prevents competition between studies for similar patients and expands the opportunities for patients to participate in these investigations. Ultimately, the goal is for any person with diabetes to be potentially eligible for a DRCR.net study protocol. As a large-scale multicenter network, DRCR.net has been successful at leveraging its resources to work with industry in developing therapies that might not have been otherwise pursued. Appreciation of the Network's benefits have prompted numerous inquiries from commercial entities regarding evaluation of new therapies by DRCR.net. These opportunities are being carefully considered to ensure that any such study would assess a need judged timely and critical by DRCR.net and would maintain rigorous scientific and ethical guidelines.

DRCR.net contributes to the training and knowledge of the ophthalmologic community with regard to rigorous clinical trials. This is one of the reasons for including a large number of community-based sites, offering them an opportunity to participate and become experienced in these efforts. Such expansion of quality clinical centers helps not only the Network, but patients throughout the country and the overall education of the ophthalmologic community.

Ongoing Evaluation

The DRCR.net Data and Safety Monitoring Committee (DSMC) has a dual role of external monitoring of the Network's protocols and providing input to NEI on the merits of the protocols proposed by the Network as well as the Network's progress. The Committee meets in person at least twice a year and by conference call as needed throughout the year. Furthermore, new protocols for large randomized trials are presented

to an External Protocol Review Committee, which provides input to NEI on the merits of the concept behind the protocol.

The DRCR.net Executive Committee is involved in policy decisions and oversees the scientific direction of the Network. Executive Committee membership includes broad leadership across the Network including the current and past Network Chairs, the Director and Executive Director of the Coordinating Center, the current and past Principal Investigators of the Reading Center, three rotating clinical site investigators and one clinical site coordinator, as well as representation from the NEI. The Executive Committee has monthly conference calls and meetings in person at least twice per year.

The DRCR.net Operations Group is responsible for the day to day management and monitoring of the Network. The Group consists of the current and past Network Chairs, three Network Vice-Chairs, an NEI representative, and the Coordinating Center Principal Investigator and Executive Director. The Operations Group reviews preliminary protocol ideas and monitors clinical site performance including quality of enrollment, follow-up, adherence to protocol, and timeliness of response to data queries.

Additional committees have developed organizational structure policies: editorial policies, publicity and presentation policies, industry collaboration guidelines, financial disclosure and conflict of interest policies, competing studies policies, ancillary study policies, confidentiality policies, policies on maintenance of activity for a site or investigator, and DSMC standard operating procedures. Each committee enjoys broad representation from Network investigators.

In addition, DRCR.net has been evaluated by external panels of scientific and lay experts at *ad hoc* evaluation meetings convened by NIDDK in January 2005 and April 2008. These meetings were an opportunity for external experts to evaluate progress and provide input on future research directions (for more information, see the Executive Summary and Appendix B). Through *ad hoc* evaluation meetings and other meetings described above, NEI continually seeks external input to inform current and future directions for the DRCR.net.

Program Enhancements

Because of the evolving nature of science, consortia supported by the *Special Diabetes Program* have evolved over time and have undergone enhancements to take advantage of new technologies and research findings, and to accelerate progress. Some enhancements have been made in response to external input and others have been initiated by the consortium members. Examples of program enhancements for DRCR.net include:

- Major randomized clinical trial proposals are reviewed for scientific merit by the External Protocol

Review Committee and the Network’s DSMC. To expedite the review process, mechanisms have been implemented to provide for a 2-week turnaround time by the External Protocol Review Committee.

- Patient retention beyond 1 year had been a challenge for DRCR.net in the past. To address this issue, the Network emphasizes to investigators and coordinators how enrollment and retention are equally important to the success of the Network. Although, most protocols now have at least a 90 percent 1-year retention rate, the Network strives for higher rates.

Coordination with Other Research Efforts

The Network also provides funding for small projects judged critical to the development or implementation of its trials. For example, a phase 2 study on bevacizumab was conducted to provide preliminary evidence of anti-vascular endothelial growth factor (VEGF) effect in macular edema, prior to embarking on a large phase III study.

DRCR.net Administrative History

Date Initiative Started	2002
Date <i>Special Diabetes Program</i> Funding Started	2002
Participating Sites (Offices)	134
Participating Physicians	469
Participating Components	NEI, JDRF, NIDDK
Web site	www.drcr.net

DRCR.net consists of two cooperative agreements including the Coordinating Center and the Operations Center; clinical site participation is open to all qualified investigators/clinicians whose sites have the requisite equipment to conduct a study protocol.