V. RECRUITMENT AND ELIGIBILITY

A. ELIGIBILITY

The Type 1 Diabetes Genetics Consortium proposes to newly ascertain and phenotype 2,800 affected sib-pair (ASP) families in order to perform a genome scan to identify type 1 diabetes susceptibility genes.

The desired ASP family structure is two affected siblings, both biological parents, and up to two unaffected siblings. The minimum family structure is two affected siblings. Eligibility criteria include the following:

1. siblings with diagnosis of type 1 diabetes;
2. diagnosis before 35 years of age;
3. use of insulin within 6 months of diagnosis;
4. continuous use of insulin (without stopping for 6 months or more); and
5. provide informed consent for blood collection, genetic analysis, and exam (*i.e.*, family history, other autoimmune diseases).

In addition, trio families will be collected in selected populations with a low prevalence of the disease throughout the Asia-Pacific, European and North American Networks. The required family structure is an affected child and **both** biological parents. Eligibility criteria are the same as listed above.

Cases and controls will be collected throughout the Asia-Pacific, European and North American Networks in selected low-prevalence populations. Cases and controls will be frequency matched (to the extent possible) by primary ethnic group. Eligibility criteria for cases are the same as above. Eligibility criteria for controls include the following:

1. no diagnosis of type 1 diabetes;
2. no first-degree relatives with type 1 diabetes, type 2 diabetes or MODY;
3. no known autoimmune disease; and
4. provide informed consent for blood collection, genetic analysis and exam.

B. STUDY POPULATIONS

Affected sib-pair families will be recruited in four networks (Asia-Pacific, European, North American, and United Kingdom). It is important to note that extensive infrastructure for recruitment of families already exists. Within each recruiting network, individual clinics will participate in the recruitment and phenotyping of participant family members.

Trio families, cases and controls will be recruited in the Asia-Pacific, European and North American Networks in specific low-prevalence populations. These collections are of extreme interest for trans-racial mapping.

1. Asia-Pacific Network

The Asia-Pacific Network is estimated to enroll 340 ASP families as well as trios, cases and controls in ethnic groups other than Caucasian. Participating countries include: Australia; India; Malaysia; New Zealand; Philippines; Singapore; and Thailand.

2. European Network

The European Network is estimated to enroll 1,200 ASP families. As part of the European Network, one clinic in Africa will enroll trio families, cases and controls. This network consists of 83 countries, many of which participated in the European Nicotinamide Diabetes Intervention Trial (ENDIT). Using the established ENDIT network and existing national registries, it is possible to trace new (and existing) type 1 diabetic patients among the subjects originally screened. Participating countries include: Austria; Belgium; Cameroon; Czech Republic; Denmark; Estonia; Finland; Germany; Greece; Hungary; Israel; Italy; Latvia; Lithuania; Netherlands; Poland; Portugal; Romania; Russia; Slovenia; Spain; Sweden; Switzerland; and Turkey.

3. North American Network

The North American Network is estimated to enroll 1,100 ASP families. In addition, trio families, cases and controls will be collected in African-American and Mexican-American populations throughout the network. These families will be derived from a number of sources, primarily through ongoing clinical trial (TrialNet) and observational epidemiologic (SEARCH) studies. In addition, several collection centers within the US and Canada will participate in the T1DGC. Participating TrialNet sites include: Florida; Texas; San Francisco, Los Angeles, Stanford, Miami, Minnesota, Seattle, Toronto, Pittsburgh, Indiana, and New York City. Participating SEARCH sites include: South Carolina, Ohio, California, and Washington. Other designated clinics are located in Augusta, Baltimore, Billings, Boise, Boston, Bronx, Buffalo, Chicago, Columbus, Denver, Edmonton, Grand Rapids, Greenville, Houston, Iowa City, Little Rock, Milwaukee, Montreal, Morristown, Nashville, New Hyde Park, Oakland, Ogden, Omaha, Orange, Philadelphia, Richmond, Rochester, Salt Lake City, San Antonio, Seattle, Spokane, St. Petersburg, Syracuse, Vancouver, Winnipeg, Worcester and Wynwood.

4. United Kingdom Network

The United Kingdom Network is estimated to enroll 160 ASP families. The UK GRID network of type 1 diabetes centers provides the infrastructure for the United Kingdom Network. Forty-eight of the clinics that participated in the UK GRID will recruit ASP families for the T1DGC.

C. RECRUITMENT PROCEDURES

Recruitment of study participants will occur at each clinic. It should be noted that specific recruitment approaches must be tailored for each country and be sensitive to the culture of the citizenry. In brief, each participant considered to be eligible for the Consortium will be informed of the opportunity to participate. For prospective ASP families, the participant will then be asked to inquire whether he/she has any siblings with type 1 diabetes; if so, the participant is asked whether his/her siblings would be interested in taking part in the study. At the same time, the availability of biological parents and unaffected siblings is queried. For

prospective trio families, the participant is asked whether his/her biological parents would be interested in taking part in the study. To assist the participant in explaining the study to family members, copies of a brochure describing the goals and procedures of the Consortium will be provided to participants for them to share with relatives. If the other family members agree, they will then be contacted directly to obtain verbal consent. Appointments are scheduled for clinical examinations, at which times written consent is obtained. One of the strengths of this approach is that the population will be recruited using standardized, carefully designed protocols, instead of *de novo* ascertainment and recruitment. We anticipate that family members of participants will respond positively and will be amenable to participating. For cases and controls, no additional family members are recruited.

Although each clinic within each network has a successful recruitment record for other studies, the family recruitment process will be given priority attention by the T1DGC Steering Committee. In addition, the Coordinating Center has a project manager assigned to each of the four networks. The Coordinating Center Project Manager and Regional Network Center Coordinator will conduct weekly conference calls in order to facilitate recruitment. The Phenotyping and Recruitment Committee has been established to assist in problem-solving and strategic planning. The Coordinating Center assists in tracking by providing weekly recruitment reports to each network, the T1DGC Steering Committee, the Phenotyping and Recruitment Committee and the NIDDK representatives. Given the experience of the clinics in weekend and evening clinic hours and coordination of travel to clinics, there are few additional barriers to recruitment of family members. Using the network approach, if another clinic that is performing the same standardized examination protocol is located more conveniently for family members, they will be assisted in scheduling their clinical evaluations at the alternative site. It is anticipated that each network will have one meeting of clinical investigators each year, and the Principal Investigators of each of the four networks will report on progress at each Consortium Steering Committee meeting.

Recruitment of ASP and trio families was initiated in January 2004 and ended in August 2009. Recruitment of cases and controls in low prevalence populations was initiated in December 2007 and ended in January 2010. Final enrollment by participant type and network are provided in Table 1.

Table 1. T1DGC enrollment, by participant type, network and overall.

Network	ASP Families (Individuals)	Trio Families (Individuals)	Cases	Controls
Asia-Pacific	326 (1,341)	290 (870)	23	77
European	1209 (4,786)	10 (30)	5	2
North American	1140 (4,828)	193 (579)	802	889
United Kingdom	161 (671)	N/A	N/A	N/A
Overall	2836 (11,626)	493 (1,479)	830	968

D. PHENOTYPING

The T1DGC procedures and data collection instruments will be standardized across all networks to the extent possible. Table 2 provides the procedures and questions that will be performed or asked of each potential participant.

Table 2. T1DGC data and sample collection items.

	Affected Sibling(s) and Cases	Biological Parent(s)	Unaffected Sibling(s)	Controls
Diagnosis of type 1	**X**	**X**		
Diagnosis of another type of diabetes		**X**		
Age of diagnosis	**X**	**X**		
Insulin use	**X**	**X**		
Date of birth/current age	**X**	**X**	**X**	**X**
Genetic disorders or diseases that caused diabetes	**X**			
Gender	**X**	**X**	**X**	**X**
Race and ethnic origin	**X**	**X**	**X**	**X**
Medical history (autoimmune diseases)	**X**	**X**	**X**	
Body habitus at time of diagnosis	**X**			
Family history (children, siblings, half siblings, parents, grandparents)	**X**			
Cells for DNA, LCL (lymphoblastoid cell lines)	**X**	**X**	**X**	**X**
Serum for autoantibody analysis	**X**			
Serum for storage and future assays	**X**	**X**	**X**	**X**
Plasma for storage and future assays	**X**	**X**	**X**	**X**
Plasma for DNA extraction from cell pack	**X**	**X**	**X**	**X**

E. RISKS VS. BENEFITS

The physical risks to participants of this study are small, principally related to venipuncture. The total amount of blood to be collected is approximately 27.4 ml (29.4 ml in the United Kingdom Network) for participants aged 16 or older. For participants under the age of 16, 19.9 ml (20.9 ml in the United Kingdom Network) of blood is collected.

With research involving family studies and genotyping, there is always the potential risk of breach of confidentiality and stigmatization. Because of the nature and prevalence of the disease process under study (type 1 diabetes), the risk of stigmatization is fairly small. To minimize risks, all data will be kept confidential. Data will be coded and all analyses will be performed using coded data only.

Individuals are unlikely to directly benefit from participation in this study. However, the benefits to be derived by mankind are expected to be substantial and may lead to advances in the prediction, prevention and treatment of type 1 diabetes. The potential benefits are the identification of human gene markers for type 1 diabetes and autoimmunity, with the delineation of genetic heterogeneity, and the development of means to identify those at high risk. All are

essential steps in understanding the pathogenesis and natural history of this disease. They are also essential in the design of future epidemiologic or therapeutic trials. In view of the potential importance of such new information, we feel that the risk-benefit ratio is very favorable and the minimal risks to study subjects are warranted.