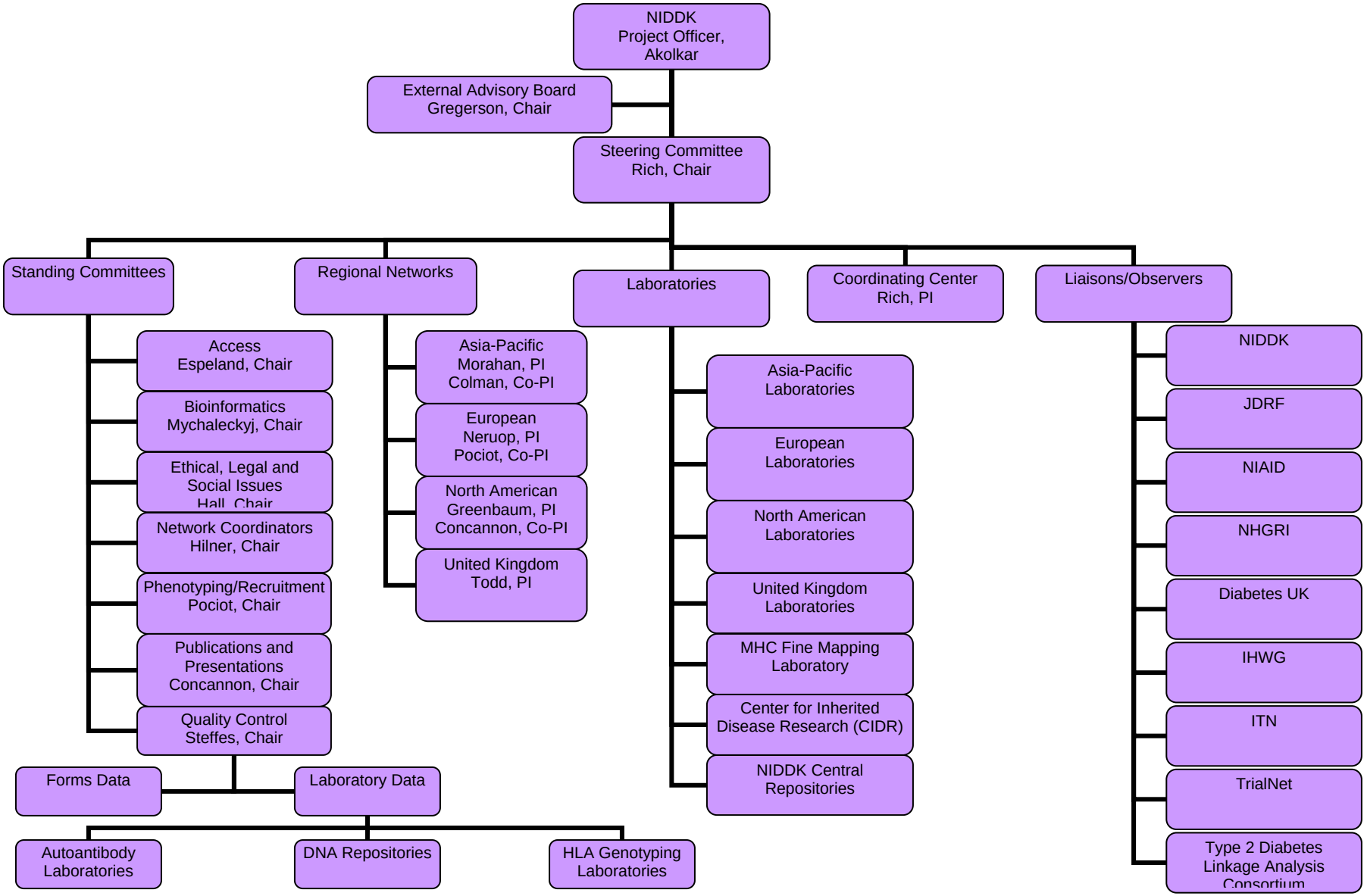
I. Introduction

The Type 1 Diabetes Genetic Consortium (T1DGC) study is an international effort to identify the genes that affect the risk of Type 1 diabetes, and is funded by the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK) in the National Institutes of Health (NIH), U.S. Department of Health and Human Services. Additional sponsors of this international effort include: the Juvenile Diabetes Research Foundation (JDRF); National Institute of Allergy and Infectious Diseases; and National Human Genome Research Institute.

The Consortium is comprised of four networks (Asia-Pacific, European, North American and the United Kingdom) and a Coordinating Center at Wake Forest University School of Medicine that oversees the operations of the networks. Within each network, there exists an infrastructure consisting of a Regional Network Center and individual clinics. The Regional Network Center is responsible for maintaining and supporting the every day operations of the clinics. The Regional Network Center staff sends label sets to the clinic and data enters the information obtained from the clinics. Clinics are in close contact with the Regional Network Center and are responsible for the recruitment and examination (*i.e.*, questionnaires and blood collection) of families that meet the study criteria. Any problems or questions that arise that cannot be dealt with at the clinic level are brought to the attention of the Regional Network Center. In turn, the Coordinating Center is in close contact with the Regional Network Centers. Any problems or questions that the Regional Network Centers cannot resolve are brought to the attention of the Coordinating Center. Both the Coordinating Center and the Regional Network Centers monitor recruitment and overall operations. See Figure 1 for an overview of the T1DGC study structure. Additional information about the study can be found on its web site, www.t1dgc.org.

Figure 1. TYPE 1 DIABETES GENETICS CONSORTIUM ORGANIZATION CHART



II. Scientific Objectives

The scientific objectives of the Type 1 Diabetes Genetics Consortium are:

1. Ascertain 2800 new families with two or more type 1 diabetic siblings through an established Asia-Pacific Network (340), an European Network (1200), a North American Network (1100), and a United Kingdom Network (160).

2. In order to detect the effects of HLA and other candidate regions/genes on the signals from the genome screen, all samples will be genotyped for HLA class II and class I genes (DRB1, DQB1, DPB1, DPA1, A, B, C), *INS*, and *CTLA4* polymorphisms that have previously been implicated in susceptibility to type 1 diabetes.

3. Refine the localization of the 5 most promising regions identified from linkage and association studies.

4. To aid in the confirmation and identification of diabetes susceptibility genes within linked regions, the Consortium will use existing and planned resources of single case families (trios, including an affected child and both biological parents) to carry out detailed disease association analyses.

The Type 1 Diabetes Genetics Consortium recognizes that much of the work of investigators in the area of genetics of Type 1 diabetes has been limited by insufficient power to map genes, a focus on majority populations under study, and limited resources for the completion of statistical analyses to identify genome areas for further study. In this regard, the Consortium proposes to collect families of many ethnic groups. A key component will be the collection of samples and data under an informed consent that allows sharing of clinical, laboratory and DNA data with all investigators. The Consortium will provide an infrastructure for resource utilization that will enable laboratory and analytic investigations to proceed without the burden of new or additional collections by providing centralized facilities for access to human samples and data.

These new and existing data will create a repository for detailed statistical and molecular genetic analysis. All family members in the new set of 2800 affected sib-pair (ASP) families will be evaluated for clinical and biochemical variables, including age at onset, insulin use, and duration of disease, using standardized protocols. Blood will be collected and lymphoblastoid cell lines (LCLs) established to provide a renewable source of genomic DNA, in order to enable future studies of immune function. DNA will be extracted and sent to a central DNA laboratory. All samples from affected sib-pair families will be genotyped completely for HLA class II and class I genes (DRB1, DQB1, DPB1, DPA1, A, B, C), *INS*, and *CTLA4* polymorphisms. A genome scan for linkage in affected sib-pair families will be performed by the Center for the Inheritance of Disease Research (CIDR), and combined with the existing data for analysis by the T1DGC and its collaborators.

These experiments will reveal the most important linked chromosome regions controlling genetic susceptibility to Type 1 diabetes. These studies will target distinct haplotypes that may

have low population frequencies, thereby facilitating identification of the best candidates for more detailed investigation. To this end, the Consortium will facilitate new collections of diverse families (trios), consisting of the affected child and both biological parents, for fine mapping from Oriental, Mexican-American, and other minority populations.

The ultimate goal of the Consortium is to provide the fundamental clinical and genetic resources to achieve the necessary sample size and sample availability for gene identification. The Consortium will establish a mechanism to ensure that scientists will work together toward a better understanding of the genetic factors that underlies risk for Type 1 diabetes. The Consortium will gain a better understanding of disease mechanisms, with a purpose of altering these mechanisms and pathways in individuals at risk of Type 1 diabetes.

III. Eligibility

An ASP family is eligible if at least two siblings have Type 1 diabetes. The first diagnosed member is referred to as the "proband," and the second is the "affected sibling." Without these two individuals, the family itself is ineligible. The *T1DGC Eligibility Form* can be administered to the proband OR to the parent/guardian of the proband. Once initial eligibility of the family is established, a family ID is assigned and contact with additional family members to determine other potential participants may proceed.

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. For trio families, the affected child and both biological parents must participate. Eligibility criteria are listed below:

1. Siblings with diagnosis of type 1 diabetes (or for trio families, an affected child and both biological parents)
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)
5. Provide informed consent for blood collection, genetic analysis, and exam (i.e., family history, other autoimmune diseases)

During completion of the *T1DGC Eligibility Form*, it is possible that the clinic will identify a family member whose Type 1 diabetes status is questionable based on information obtained from this questionnaire (e.g., Type 1 diabetes not yet treated with insulin). At this point, eligibility is in question and a clinic staff member will complete the *T1DGC Application to Eligibility Committee* and the committee members will make a decision. The Phenotyping and Recruitment Committee will serve as the Eligibility Committee. Only after the committee approves the application will the clinic continue the eligibility process with this family. The family is considered "pending" until that time. If a family is deemed ineligible, the clinic staff will explain the reasons for ineligibility.

IV. Informed Consent

A model informed consent template has been developed for use by all Networks, but each institution's Internal Review Board (IRB) or Ethics Committee will determine the particular rules for written informed consent at each clinic. Therefore, the following guidelines are general, and while they will be met to the best of each site's ability, there may be some variation among sites and across networks.

The process of consenting individuals to participate in this study begins once potential participants have been asked if they are willing to participate in the T1DGC. For some institutions, this may be required prior to completing the *T1DGC Eligibility Form*, and for some this process begins once the participant is deemed eligible based on the *T1DGC Eligibility Form*. Again, this is determined by the requirements of the local IRB or Ethics Committee.

Once the participant agrees to participate, or to learn more about the study, a copy of the *Informed Consent* is provided to the potential participant or the parent/guardian of the participant. The most current version of the *Informed Consent* approved by the IRB or Ethics Committee must be used. A template for each version of the informed consent (*i.e.*, adult, teenager, and child*)* for the T1DGC is maintained on the web site as a guide for the elements of consent required by the study. However, it is recognized that each clinic will need to modify this template according to the specific requirements of the local IRB or Ethics Committee.

Consent forms must be translated into the participant's native language. All translated forms must be back-translated into English. The most current version of the *Informed Consent* in use at each clinic is stored at the Regional Network Center and the Coordinating Center.

A brief description of the study is written on a cue card and may be used to aid the interviewer in describing the study. However, the participant is required to read or have the *Informed Consent* read to him/her (if he/she is incapable of reading the document). The participant must be adequately informed of the purpose, methods, personal involvement in the study, direct benefit (or lack thereof), potential risks, and his/her rights. All questions that the potential participant/family has regarding the study must be answered thoroughly. Once the *Informed Consent* is provided to and read by the participant and/or parent/guardian, it must be signed. In the case of a minor, the legal guardian signs the form. Once a signature is obtained, a unique individual ID is assigned.

Because this study involves children, special guidelines/considerations may be required at an institution. Each clinic must be familiar with all requirements that the institution has regarding the informed consent process with studies involving children. For example, certain clinics may require that young participants give their assent to participate in the study in addition to consent given by the parent or guardian of the child (ren). Assent is a child's oral or written affirmative agreement to participate in research (*i.e.*, a child says "yes" when asked if he/she would like to participate in the study). In addition, the age requirement for written consent may vary depending on the network, region and/or clinic.

Once informed consent forms have been completed, copies are made. Certain local IRBs may require that the original be kept in the IRB office. A copy must be maintained in the clinic and a copy **must** be provided to the participant. A copy of the page on which the layered consent for various aspects of the exam is obtained is labeled with the participant's ID and sent to the Regional Network Center for entry into a consent database. Regional Network Centers and/or clinics may choose to include an ID label box on this layered portion of the consent form for the participant's ID label. The copy of the informed consent page that is forwarded to the Regional Network Center must be free of personal identifiers and participant signatures. In the event that a participant is re-consented or withdraws their consent, the Regional Network Center is notified and the informed consent database is updated.

The Coordinating Center at Wake Forest University practices strict procedures to maintain privacy and confidentiality of all research participants and the subsequent generated data. Data are released and exchanged only with entities with which a *Data Use Agreement for a Limited Data Set* exists. The Coordinating Center takes every precaution necessary to protect the privacy of all participants who have volunteered their time, and expects that all clinics, regions and networks uphold these same standards. It is expected that individual clinics maintain all participant files in locked cabinets accessible only to the study staff. In addition, information that is considered a personal identifier (*e.g.,* participant name) is kept only by the clinic staff and is never transmitted to the Regional Network Center or Coordinating Center.

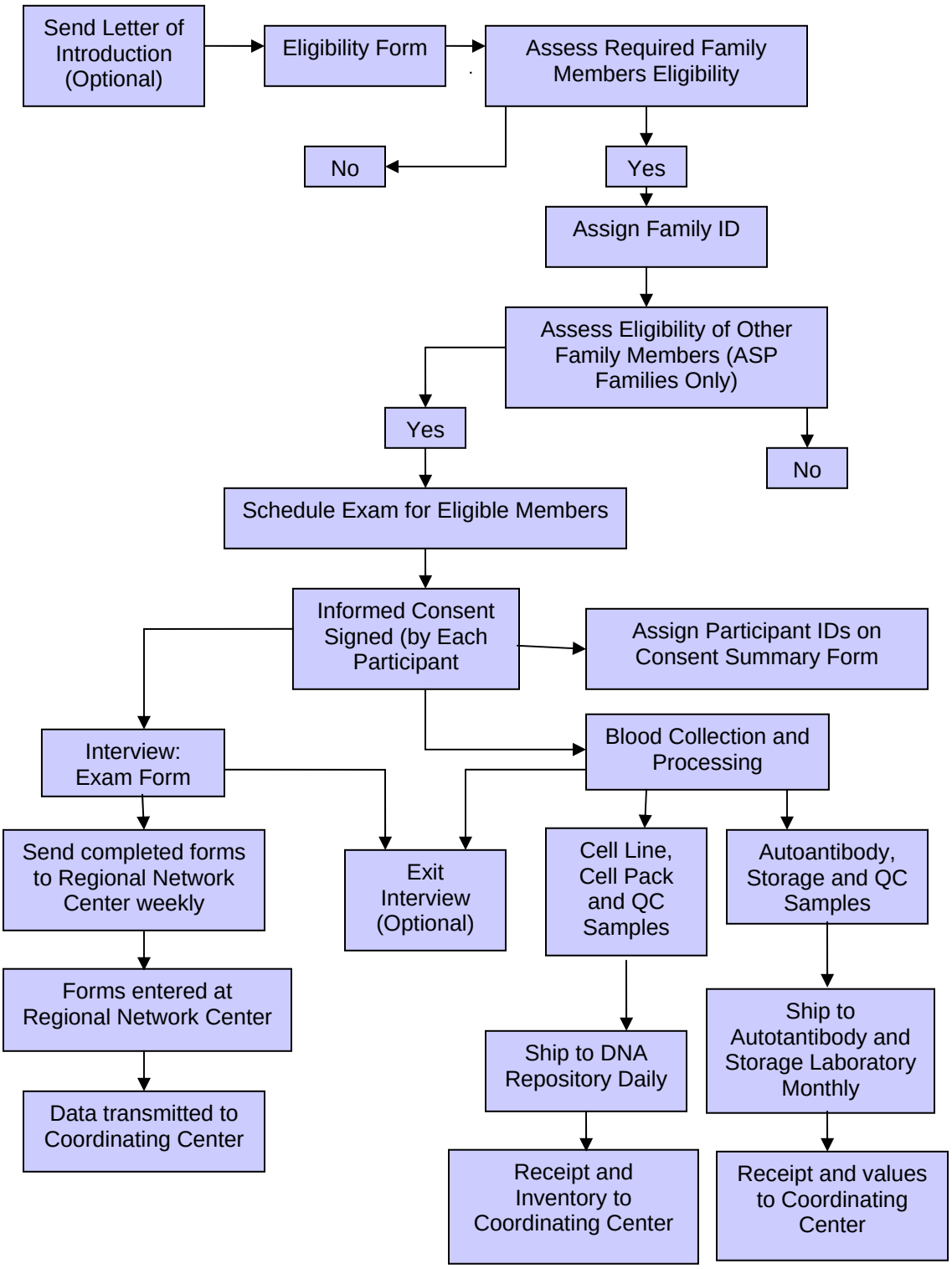
All medical and genetic information will be kept confidential to the extent the law allows. Absolute confidentiality cannot be guaranteed. Information about participants will not be given to insurance companies, employers, or used for any purposes not described in the informed consent. The information from this research will be made widely available to researchers, doctors, scientists, and other people, but participant's identity will not be released. Blood and DNA samples and the information provided by the participant will be stored in different places under a code number, without the participant's name or other identifying information. T1DGC will be able to identify participants if needed for research purposes. In some cases, people from NIDDK may need to see participant's records to verify study information, but they will not be able to identify participants.

V. Exam

The exam consists of two required components, a brief interview and blood collection for each consented family member. Family members may attend the exam during a single visit to the clinic or each member may come on a separate day. Thus, the length of time required to complete examination of an entire family will vary. Clinics will be flexible in scheduling exams and every effort will be made to accommodate participant schedules.

Once the participant has signed an informed consent, the *T1DGC Exam Form* for each consented family member is completed. Once the exam form is completed, the participant will have blood collected and the *T1DGC Blood Collection Form* is completed. See Figure 2 for the flow of data collection in the T1DGC.

Figure 2. T1DGC DATA COLLECTION FLOW



1. Blood Collection

The blood collection protocol is designed to obtain blood samples to establish cell lines as a source of DNA for genotyping, to extract DNA from EDTA cell packs, to establish a plasma and serum storage repository for future assays, and to test for autoantibodies in affected siblings. Blood collection can potentially cause anxiety or injury, but if carefully and professionally done, it provides a positive, safe experience for the participant.

The following procedures are designed to standardize sample collection:

1. Blood will be collected with the participant in a seated position; the reclining position will be used only in extreme circumstances (e.g., history of fainting)
2. Participants will be instructed to drink plenty of water (e.g., at least 8 large glasses of water) prior to the clinic exam; the blood collection will be easier if participants are well hydrated.
3. No restrictions are required for fasting, vigorous activity the day of the exam or smoking.
4. Blood collection will occur after the questionnaires for eligible participants have been completed.

The blood collection will be done by a nurse or technician with documented class time and experience in phlebotomy. Certification will occur during or following a training session and prior to data collection. Gloves will be used at all times while processing blood samples.

2. Blood Volume

If safe and appropriate, all participants under the age of 16 will have 19.9 ml (20.9 ml in the United Kingdom) of blood collected; this is less than 1.5 tablespoons. All participants aged 16 or older will have 27.4 ml (29.4 ml in the United Kingdom) of blood collected; this is less than 2 tablespoons. The tubes to be used are listed as follows:

One 7.5-ml green top (sodium heparin) tube OR one 8.5-ml yellow top (CPDA) tube;
One 7.5-ml red top (serum) tube;
One 4.9-ml lavender top (EDTA plasma) tube;
One additional 7.5-ml green top (sodium heparin) tube OR one 8.5-ml yellow top (CPDA) tubes in participants 16 years or older.

An additional quality control sample of 4.9-ml OR 7.5-ml will be taken randomly only from participants who are at least 16 years old. Thus, a quality control participant will have 5 tubes drawn, totaling 32.3 ml (34.3 ml in United Kingdom) OR 34.9 ml (36.9 ml in United Kingdom).

Any participant who is too young, too small, or whose veins are not healthy enough to give this much blood will not be required to give more blood than is safe or appropriate.

In some cases, it may be necessary to contact participants to return to the clinic for a second blood collection. Reasons for a re-collection include: inability to obtain sample(s) during initial clinic visit (including failure to obtain serum samples on a proband or affected sibling);

loss of sample(s) due to local freezer failures or shipping errors; failure of the green top (sodium heparin) or yellow top (CPDA) sample to produce a viable cell line for future DNA samples; or low DNA yield from the EDTA cell pack when participant refused cell line. Only one attempt at re-collection will be made for any one participant. Quality control will never be done on a participant returning for a re-collection.

VI. Adverse Event Reporting

It is expected that few, if any, adverse events related to the study protocol will occur throughout the exam period. Inserting a needle for blood sampling can be associated with some discomfort and bruising and, although very rarely, with inflammation and infection of the arm veins. These risks are considered to be minimal and are addressed in the protocol and the informed consent forms. There may be other adverse events associated with the clinic visit (e.g., falling or other injury) that also will be reported. If such an event occurs, the incident must be reported.

Any event that is reported to either the Principal Investigator or his/her designated research staff by the participant or medical staff caring for him/her will be evaluated and graded by the Principal Investigator and/or research staff and documented on the *T1DGC Adverse Event Report* that is completed at the data collection clinic. Regardless of the severity, all adverse events reported to the clinic staff or Principal Investigator are documented, and the *T1DGC Adverse Event Report* is completed and submitted to the Internal Review Board (IRB) and/or Ethics Committee at the local data collection site, Regional Network Center and the Coordinating Center. The report includes a description of the event, when and how it was reported, severity grade, and a grade to assess the relation the incident had to the protocol, a summary and description of the outcome, as well as any official chart records or documentation to corroborate the event or the reporting of the event. Any severe and/or unanticipated adverse event is immediately reported. All other adverse events will be reported in a timely fashion within 2 weeks of the date of the event. All adverse events will be summarized annually and submitted to the IRB or Ethics Committee at the local clinic, Regional Network Center and Coordinating Center.