REGIONAL NETWORK CENTER RESPONSIBILITIES

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I. INTRODUCTION

This chapter is designed for use by the Regional Network Centers. While the *Type 1 Diabetes Genetic Consortium* (*T1DGC) Manual of Operations* (MOO) is written for the clinics and the Regional Network Centers, this chapter outlines the specific responsibilities of the staff at the Regional Network Center. These include: (1) overseeing the operations of the clinics on a day-to-day basis; (2) assisting clinics with regulatory issues and T1DGC requirements as well as supplying necessary documentation from the clinics to the Coordinating Center; (3) ensuring that family recruitment and subsequent data collection are occurring at the clinics; (4) supporting the clinics throughout the exam period; and (5) entering and transmitting data to the Coordinating Center.

Problems and questions that arise that cannot be resolved at the clinic level are brought to the attention of the Regional Network Center. Likewise, the Regional Network Center will request assistance from the Coordinating Center for unresolved issues.

II. RECRUITMENT

A. Recruitment Goals

Each Network has a recruitment goal as outlined in **Chapter III**, *Recruitment.* The Regional Network Center is responsible for aiding the clinics in their efforts to reach the overall T1DGC goal of 2,800 affected sibling pair (ASP) families as well as trios, cases, and controls.

Real-time recruitment reports are provided on the T1DGC web site to aid in recruitment monitoring and for quarterly reporting to the NIH. Participants are not counted as completed in recruitment reports until all necessary exam forms have been data entered and cell line samples have been received and data entered at the Network DNA Repository.

The Regional Network Center is responsible for working with each network clinic to set an overall recruitment goal, as well goals for specific time periods. The Regional Network Center monitors the number of recruited participants in each individual clinic. If particular clinics are having difficulty in recruiting participants or meeting their goal, it may be necessary for staff from the Regional Network Center to visit the particular clinic in order to assess the problem and develop reasonable solutions or provide suggestions for recruitment.

B. Recruitment Materials

The Regional Network Center is responsible for suggesting recruitment strategies and materials to their clinics (*e.g.*, flyers, brochures, and/or referrals from physicians). Templates for a recruitment brochure and flyer are available on the T1DGC web site and in the appendices of **Chapter III**, *Recruitment*. These may be used by the clinics with appropriate site-specific information inserted. The clinics must submit all recruitment materials to their local Institutional Review Board (IRB) or Ethics Committee (EC) for approval. The Regional Network Center may require submission of proof of approval.

III. ELIGIBILITY

The Regional Network Center answers any questions from the clinics about a family's/participant's eligibility status. In ASP families, both the proband **and** the affected sibling must be eligible and participate in order for a family to be included in the study. For trios, the proband must be eligible and participate **and** both biological parents must be available and participate in order for a family to be included. In the case-control collection, only individuals participate.

An Eligibility Committee has been established for affected participants who do not meet all of the study criteria (diagnosis before 35 years old, insulin use within 6 months of diagnosis without stopping for 6 months or more), but have other evidence of Type 1 diabetes. The clinic confirms the evidence, completes the appropriate *T1DGC Application to Eligibility Committee* and forwards it to the Regional Network Center. The

staff at the Regional Network Center completes their designated portion of the form and forwards it to the Coordinating Center. Staff at the Coordinating Center will communicate with the Eligibility Committee to determine if the participant can be recruited for the T1DGC. Once a decision is made, the Coordinating Center informs the Regional Network Center, who informs the clinic of the decision. The application is data entered at the Coordinating Center. (See **Chapter IV**, *Eligibility,* for more information on the Eligibility Committee.)

Up to three additional affected siblings may participate in an ASP family. However, a *T1DGC ASP Application for Additional Affected Sibling* must be completed for approval of inclusion for each additional sibling. This form is completed at the clinic and forwarded to the Regional Network Center. Staff at the Regional Network Center is responsible for approving inclusion of each sibling. Upon approval, the Coordinating Center is notified and labels for each additional affected sibling are generated and sent to the Regional Network Center. (Alternatively, the Regional Network Center may supply each clinic with a number of label sets for families with additional affected siblings in order to decrease the amount of time between application approval and receipt of label set(s). The application is sent with the entire family form set to the Regional Network Center for data entry.)

IV. DATA COLLECTION AND ENTRY

The Regional Network Center is responsible for monitoring the accuracy and completeness of data collected at clinical sites. They are also responsible for data entry of the forms submitted from the clinics.

A. Label Sets

Label sets are sent from the Coordinating Center to the Regional Network Centers for distribution to the clinics. Label sets are scanned at the Coordinating Center prior to dispersing to the Regional Network Centers. Likewise, when the Regional Network Center receives the label sets they are scanned prior to shipment to

the clinics. (See **Chapter XI**, *Data Entry System*, for detailed instructions on scanning label sets received from the Coordinating Center.)

Regional Network Centers must notify the Coordinating Center at least two weeks in advance when additional label sets are needed. Network staff should e-mail the appropriate project manager when label sets and/or additional labels for specific participants are needed.

B. Data Form Review and Entry

As families and individuals are recruited and examined, the Regional Network Center receives completed form sets from the clinics for data entry. It is the responsibility of the Regional Network Center to review the forms as they arrive to check for discrepancies and/or missing data fields, and to ensure that form sets are complete and meet the minimal acceptable standards (*i.e.,* proband and affected sibling prior to data entry for ASP families).

In ASP families, forms sets for **at least** the proband and affected sibling must be completed prior to data entry. In trio families, form sets for the affected child and both biological parents must be completed prior to data entry. Without the following forms on these essential family members who meet eligibility criteria, data cannot be entered and clinics will not be reimbursed: (1) *T1DGC Consent Summary Form; (2)* Layered Portion of the *Informed Consent* (one for each); *(3) T1DGC Eligibility Form*; (4) *T1DGC Exam Form* (one for each); and (5) *T1DGC Blood Collection Form* (one for each).

For the case, the forms required for the individual include: (1) Layered Portion of the *Informed* Consent; (2) *T1DGC Consent Record Form (Addendum to the Layered Consent);* (3) *T1DGC Eligibility Form*; (4) *T1DGC Case Exam Form*; (4) *T1DGC Blood Collection Form*. For the control, the forms required for the individual include: (1) Layered Portion of the *Informed* Consent; (2) *T1DGC Consent Record Form (Addendum to the Layered Consent)*; (3) *T1DGC Eligibility Form*; and (4) *T1DGC Blood Collection Form*.

The Regional Network Center staff is responsible for contacting clinics to resolve errors or discrepancies and/or missing data fields. A *Data Editing Log* was developed and is available on the web site to aid the Regional Network Center staff in tracking these errors.

C. T1DGC Reports and Query System

The Coordinating Center has created numerous dynamic reports available on the T1DGC data entry web site for use by the Regional Network Centers in order to assist in determining the status of a particular family (or family member) and to identify any irregularities that must be corrected. The Regional Network Center and Coordinating Center monitor these reports closely in order to identify and resolve problem areas with a particular network or clinic as quickly as possible.

The T1DGC Query System was created as a dynamic system listing all edits that need to be resolved. The Query System allows the user to sort by network, country, clinic, and family ID. Queries that are not data entry errors originating at the Regional Network Center **must** be sent to the clinic for verification or editing. (See **Chapter XI**, *Data Entry System*, for detailed instructions on the T1DGC Query System.)

D. Data Entry of *T1DGC Shipping Forms*

In addition to tracking errors on the forms sent from the clinic, Regional Network Center staff is responsible for reviewing and tracking errors on shipping forms that are data entered by laboratory staff. The Regional Network Center receives two copies of each T1DGC Shipping Form. The first copy, sent by the clinic, is a copy of the shipping form that the clinic sent to the laboratory (without receipt of sample included); the second copy, sent by the laboratory, is the completed **original** (with receipt of sample included). The Regional Network is responsible for ensuring receipt of both copies of the form and complete and accurate entry of the form. The Regional Network Center contacts the clinic and/or the laboratory regarding missing forms, data entry errors, or discrepancies in the number of samples sent and received.

E. Requests from Contributing Investigators

The Regional Network Center is responsible for receiving requests from Contributing Investigators for quarterly data freeze data and/or samples and genotyping data sets. The Regional Network Center submits these requests to the Coordinating Center via the data entry web site. The Regional Network Center is responsible for reviewing the requests and ensuring that they are completed correctly and entered in a timely fashion. Requests for samples must be received in January-February or July-August. (See **Chapter XI**, *Data Entry System*, for detailed instructions on submitting requests from Contributing Investigators.)

V. REGULATORY ISSUES

A. Informed Consent Forms

The Regional Network Center is responsible for ensuring that the clinics are compliant with all regulatory issues related to data collection for the T1DGC. It is understood that the clinics will follow the regulations set forth by their respective Internal Review Board (IRB) or Ethics Committee (EC), but a current signed *Informed Consent* approved by the local IRB or EC is required by the T1DGC for each participant. In addition, for sites within the United States, the T1DGC requires a signed *Written Authorization* to use and disclose protected health information conforming to United States privacy law (HIPAA regulations), or a combined informed consent/written authorization document on each participant.

All T1DGC informed consent forms are sent to the NIDDK Central Repositories and CIDR for review, prior to the laboratories shipping samples to these locations. Staff at the Regional Network Center and Coordinating Center also will review each clinic's informed consent forms in order to determine that collections are in agreement with the goals of the T1DGC. Any requests for changes to the *Informed Consent* made by the NIDDK Central Repositories, CIDR, the Coordinating Center and/or the Regional Network Center **must** be implemented, and if necessary, participants will be re-consented to permit distribution of samples. In order to minimize the number of clinics who have to modify their informed consent forms, it is strongly suggested that the clinics

forward their forms to the Regional Network Center so review of the documents can be completed prior to starting recruitment.

The clinic staff is responsible for sending a copy of the layered portion of the informed consent (with signature covered by a participant ID label) to the Regional Network Center for data entry. Staff at each clinic maintains the **original** signed informed consent forms, written authorizations (as required in the United States) and **original** copies of data forms.

For ASP and trio families, the Regional Network Center also must recognize that data entry of forms for a particular family cannot be initiated without an appropriately completed *T1DGC Consent Summary Form*. Additionally, for clinics within the United States, the written authorization to use and disclose protected health information must be signed if it is not part of the informed consent document. The clinics can send the *T1DGC ASP Consent Summary Form* when the proband and the affected sibling are consented. For trios, the *T1DGC Trio Consent Summary Form* must be fully complete. Although cases and controls do not require the *T1DGC Consent Summary Form*, the *Layered Consent Form* must also include the *T1DGC Consent Record Form (Addendum to the Layered Consent).*

B. Ethics Committee and Internal Review Board Approval Letters

In addition to informed consent forms, the Regional Network Center and Coordinating Center must have a **current** copy of each clinic's EC or IRB approval letter. The Regional Network Center and Coordinating Center also must have on file the date the EC or IRB approval was received and the date the EC or IRB approval will expire. This information will be forwarded to the NIDDK Central Repositories and CIDR by the Coordinating Center. The Coordinating Center and Regional Network Center are responsible for monitoring each clinic's EC or IRB expiration date and obtaining a new letter of approval before the current one has expired.

C. Office for Human Research Protections (OHRP) and Federalwide Assurances (FWA)

Each T1DGC clinic must register their IRB and receive a FWA number from OHRP in order to verify compliance with the Department of Health and Human Services (DHHS) regulations for the protection of human subjects. The Regional Network Center and Coordinating Center are responsible for assisting clinics obtain this approval by either: (1) determining if the clinic's IRB is already registered and the institution has a FWA number; (2) helping the clinic to register their IRB and receive a FWA number; or (3) helping the clinic locate another institution and sign an Unaffiliated Investigator Agreement stating that the institution with the approved IRB and FWA number is responsible for the clinic without a FWA number. Each clinic's FWA number is kept on file at the Regional Network Center and the Coordinating Center.

VI. CLINIC OPERATIONS

A. Training and Certification

The Regional Network Center staff is responsible for attending the training sessions conducted by the Coordinating Center staff. During this training, all aspects of the T1DGC study (*e.g.,* recruitment strategies, eligibility criteria, exam form administration, blood collection and shipping, and data entry) are reviewed and discussed.

The Regional Network Centers then are responsible for training the staff at each clinic. Training models are network-specific; training may be completed at a Regional Network Center centralized training session or members of the Regional Network Center may visit each site to train clinic staff. Training should include review of data collection schema, recruitment goals and strategies, eligibility requirements, interviewing instructions and practice, blood collection and processing, sample storage and processing, quality control and a review of the T1DGC forms. Clinic IDs and staff ID numbers, assigned by the Regional Network Center, are provided to all clinic staff and are kept on file at the Regional Network Center and the Coordinating Center.

The Regional Network Centers and the Coordinating Center are responsible for certifying readiness of clinic staff to initiate T1DGC data collection. Certification consists of successful completion of a pilot study that includes administering data forms, collecting blood samples (including a quality control sample for plasma) and preparing and shipping samples to the laboratories. The pilot study is intended to assess the readiness of the clinic to begin data collection for the T1DGC; as such, poor performance during the pilot signals a need to re-train prior to initiating data collection. However, after successful completion of the pilot study, recruitment of T1DGC participants cannot commence until the Regional Network Center and Coordinating Center have the following documentation: (1) FWA Number; (2) EC/IRB Approval Letter; (3) EC/IRB Approval Date (if not apparent from the letter); (4) EC/IRB Expiration Date (if not apparent from the letter); and (5) Blank Copies of the Informed Consent Forms.

Training of new clinic staff should be performed by existing clinic staff with varying degrees of consultation with the Regional Network Center, if desired or needed. Staff turnover at the Regional Network Center will also require training and certification of new personnel by other staff members at the Regional Network Center.

B. Manual of Operations and Forms

Staff at the Regional Network Center must be proficient in the use of the *T1DGC Manual of Operations* (*MOO*) and the data forms. Regional Network Centers are notified by the Coordinating Center when updates to the *T1DGC MOO* and/or data forms are made. The *T1DGC MOO* is web-based, and each Regional Network Center must have a printed copy of the most updated version of the manual at their site. Additionally, it is the Regional Network Center's responsibility to ensure that the clinics are using and referring to the most updated version of the *T1DGC MOO* and data forms. For sites without Internet access, the Regional Network Center distributes printed copies of the *MOO* and data forms to the clinics. For sites with Internet access, the Regional Network Center notifies the clinics of such changes via phone call or e-mail and requests that the clinics print the updated chapters.

C. Reimbursement for Completed Examinations

Regional Network Centers invoice the Coordinating Center on a periodic basis (monthly or quarterly). Only examined families with all required data on the proband **and** the affected sibling (or, in trios, the affected child **and** both biological parents) are eligible for reimbursement. Required data includes: *T1DGC Consent Summary Form,* Layered Portion of *Informed Consent* (for all required family members)*, T1DGC Eligibility Form, T1DGC Exam Form* (for required family members), *T1DGC Blood Collection Form* (for required family members) and cell line samples on participating family members. In the case-control collection, examined individuals with all required data are eligible for reimbursement. For the case, required data includes: Layered Portion of *Informed Consent, T1DGC Consent Record Form (An Addendum to the Layered Consent), T1DGC Eligibility Form*, *T1DGC Case Exam Form*, *T1DGC Blood Collection Form* and a cell line sample*.* For the control, required data includes: Layered Portion of *Informed Consent, T1DGC Consent Record Form (An Addendum to the Layered Consent), T1DGC Eligibility Form, T1DGC Blood Collection Form* and a cell line sample*.*

On a monthly basis, the Coordinating Center will supply the Regional Network Centers with a list of all participants who the Coordinating Center confirms as eligible for reimbursement. The Regional Network Center must supply the Coordinating Center with a detailed invoice, listing the participants they believe to be eligible for reimbursement. Funds will be forwarded from the Coordinating Center to the Regional Network Center and the Regional Network Center is responsible for reimbursing each clinic in the network.

D. Contact with Coordinating Center and Clinics

Weekly conference calls are held between a Project Manager located at the Coordinating Center and the Regional Network Center Coordinator and/or other designated staff members to identify problems, resolve issues, and note progress. Additionally, the Coordinating Center Project Manager is available throughout the week via phone, FAX and e-mail. Each year, the Deputy Director of the Coordinating Center

and a Project Manager from the Coordinating Center will site visit each network. The Network Coordinator also is responsible for participating in monthly calls with the Deputy Directory, the Project Managers and the Network Coordinators from all networks (*i.e.,* Network Coordinators' calls).

Regional Network Centers also must be in regular contact with each clinic within their network. The frequency of this contact is established by the staff at the Regional Network Center. Contact can include phone calls and e-mail on a clinic-specific basis, newsletters, network-wide conference calls, web site notifications, and/or Network Meetings. Regional Network Center staff may need to perform site visits to specific clinics throughout the data collection period.

E. Clinic Close-Out

Regional Network Centers are responsible for assisting each of clinics within their network with close-out. The Regional Network Center Coordinators will work with each clinic to: identify all remaining families needing completion, provide regular communication regarding the status of data irregularities and reports, ensure all possible re-collections have occurred, ensure all samples have been received at the network laboratories, and determine procedures for destroying or redistributing T1DGC materials remaining at the clinic after close-out. The Regional Network Center Coordinators will update the Coordinating Center about the status of close-out activities on a regular basis via the *Clinic Close-Out Form* and frequent communications with the Project Managers. Refer to **Chapter XIV**, *Study Close-Out,* for detailed information regarding adverse events.

VII. ADVERSE EVENTS

An adverse event is defined as both an expected side effect that is of a serious nature or an unexpected side effect/event regardless of severity. For the T1DGC, these incidents are anticipated to be infrequent. However, appropriate procedures must be in place if an adverse event occurs. All adverse events reported by the clinics are graded

both by attribution and severity of the incident at the clinic site. (See **Chapter IX**, *Adverse Event Reporting,* for detailed information regarding adverse events.)

The clinic staff completes the *T1DGC Adverse Event Report* and forwards it to the Regional Network Center. The Regional Network Center is responsible for reviewing the incident and signing and dating the form before forwarding to the Coordinating Center for final review. After review at the Coordinating Center, it is sent back to the Regional Network Center where a copy is retained and the Regional Network sends a copy of the form back to the clinic. (See Appendix A of **Chapter IX**, *Adverse Event Reporting*, for instructions for completing the form.)