



## **Type 1 Diabetes TrialNet Sub-Study and Ancillary Studies Policies for ACCESS TO SUBJECTS**

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**Applications and questions should be submitted to the TrialNet Coordinating Center to:**

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### **TrialNet Sub-study and Ancillary Study Policies**

TrialNet recognizes the importance of ancillary studies in the overall mission to better understand the natural history of type 1 diabetes, to devise means to prolong the honeymoon phase in subjects with new onset disease, and to prevent diabetes altogether. Ancillary studies that complement the objectives and thereby enhance the value of TrialNet studies are strongly encouraged. Ancillary studies will be evaluated with careful consideration for their potential impact on the objectives and performance of TrialNet studies. Further, ancillary studies must not interfere with the continued interest and participation of the study subjects and investigators. To protect the interests of TrialNet, each ancillary study must be reviewed and approved by the Ancillary Studies Committee before its initiation. If an ancillary study is considered highly worthy by the Ancillary Studies Committee, but may cause a significant deviation in the study protocol, or may significantly interfere with the subjects' interest or participation in TrialNet, then the study must be additionally reviewed and approved by the affected TrialNet Protocol and/or Steering Committee before formal approval is granted. All approved ancillary studies will be reviewed yearly to evaluate their progress, and impact on TrialNet as a whole. This policy is intended for Ancillary Studies that request access to TrialNet subjects either at a single center or at multiple sites. For Ancillary Studies that request access to archived samples, please see ANCILLARY STUDIES USING ARCHIVED SAMPLES POLICY.

### **Sub-study and Ancillary Study Definitions**

**Ancillary study** is defined as research or data collection involving TrialNet subjects using any technique, medication, procedure, questionnaire, or observation other than those set forth in the primary study protocol. The investigator for the conduct of the ancillary study is a partner in TrialNet, and is therefore obliged to follow the rules and regulations governing the trial as defined in the study protocol and by the Steering Committee, and in accordance with all TrialNet policies.

**Sub-study** is essentially an add-on study like an ancillary study, but one directly related to the goals and objectives of TrialNet, and which is conducted under the auspices of TrialNet and with funding from Trialnet.

### **Reasons for Required Approval of Add-On Studies**

Investigators and subjects are entitled to prior assurance that all ancillary studies are of scientific merit and that no ancillary study will:

1. Cause a deviation from the defined study protocol.
2. Complicate the interpretation of the study results.
3. Potentially affect subject cooperation or interest in the study.
4. Jeopardize the public image of the study.
5. Create a significant diversion of study resources locally or at the coordinating center or any other unit.
6. In any way negatively influence the cooperative spirit of the collaborating investigators.
7. Otherwise compromise the scientific integrity of the study.

### **The Levels of Approval Required for Ancillary Studies**

There are two levels of approval for ancillary studies:

Level 1: Approval by the Ancillary Studies Committee

Level 2: Further approval by the Protocol and/or Steering Committee

In general, Level 1 approval by the Ancillary Studies Committee alone will suffice if the study involves the analysis of available data from the primary TrialNet study for questions not addressed in the major study, or additional tests or observations that will be made on subjects or samples that do not interfere with the primary protocol. For study requests that will involve use of stored specimens, which are a unique and limited resource, applicants are to refer to the ANCILLARY STUDIES USING ARCHIVED SAMPLES POLICY. When consistent with the ancillary study's question, we encourage investigators to obtain samples prospectively by access to subjects, rather than going to the archive, but this activity must not compromise recruitment or participation of subjects or physicians in the primary study. The decision regarding the necessary level of approval will be made on the basis of the above criteria by the Chairman of the Ancillary Studies Committee, and where equivocal, in consultation with the Executive Committee.

Some proposals for additional studies or add-ons to an existing TrialNet study may be considered to be directly related to the goals and objectives of TrialNet and may be considered to merit full funding and support by TrialNet. Such add-ons will be classified as TrialNet Sub-studies rather than as ancillary studies. All proposals for additional studies will be submitted to the TrialNet Coordinating Center and will be reviewed by the Chair of the Ancillary Studies Committee and the Vice Chair for Protocol Development. They will then make a preliminary classification as either a sub-study or an ancillary. A proposal is classified as a sub-study when it directly addresses a primary or secondary aim or objective of



the study, and merits full TrialNet support in its implementation, including complete funding for its conduct and support from TrialNet facilities including the Coordinating Center and central laboratories.

### **Sub-Study**

If the add-on proposal is classified as a sub-study, that proposal is also reviewed by the Executive Committee to confirm the classification as a sub-study. A budget will be requested if a sub-study classification is indicated. The proposal will then be reviewed by the ancillary studies committee, augmented by additional ad hoc members as needed to provide expertise in the specific area to be addressed. Such proposals approved by the ancillary studies committee will then be presented to the full Steering Committee for review, the same as a Level 2 Ancillary.

The principal distinction between a sub-study and a Level 2 ancillary is that the former is conducted by and for TrialNet in collaboration with the sub-study investigators, whereas the latter is conducted by the ancillary investigators under the purview of TrialNet but is not conducted by TrialNet.

In general, TrialNet cannot provide funds for ancillary studies, even for additional data analysis for a Level 1 study. If funds are needed, the investigator must explore other avenues, such as submission of a research grant application to federal or private agencies. Approval by the Ancillary Studies Committee should be obtained prior to grant submission. For special funding opportunities, such as time-limited requests for applications, TrialNet may undertake expedited access review before submission, or after scoring of applications, as needed.

### **Preparation of Proposals for Ancillary Studies Committee review**

The proposal submitted to the Ancillary Studies Committee should use the SUBJECTS ACCESS application form. Applicants are encouraged to submit additional information such as grant applications in the National Institutes for Health (NIH) research grant (R01) format, or similar. The applications should be complete and should include all information needed for the Ancillary Studies committee to judge the scientific merit and feasibility of the research. There are no page limits.

The application should indicate whether access is required to subjects study-wide or at a single local center, and if assistance from the TNCC is required to identify subjects for the ancillary study. The proposal should include a description of the objectives, methods, significance and plans for analysis. Detailed descriptions must be provided regarding additional volumes of blood or other specimen types required (with careful consideration that this will not jeopardize obtaining samples already required as part of the primary TrialNet study protocol), procedures to be carried out on subjects, the length of clinic stay, or need for extra clinic visits. In addition, the proposal should discuss the measures to be taken to ensure subject safety and confidentiality, and a statement by the investigator on the potential impact of the ancillary on TrialNet. Human Subjects Committee approval must be obtained prior to ancillary study initiation but is not required for submission to the committee for review. The informed consent form and process will be reviewed by the Ethics and Consent Committee. In addition, the proposal should clearly indicate the resources available for the study and their source. If resources are being sought from granting

agencies then this must be indicated in the application. To facilitate the review of the proposal, the investigator should specifically address each of the following points in a separate section of the proposal:

1. The specific merit of the proposal, and the potential contributions that the proposal will make to the overall mission of TrialNet.
2. The proposed study does not compromise in any way the scientific integrity of the primary TrialNet study. Specifically, the ancillary:
  - a) does not cause a significant diversion or deviation from the primary study protocol.
  - b) does not complicate the interpretation of the results of the TrialNet study.
  - c) does not adversely affect subject cooperation and participation.
  - d) does not affect the cooperative spirit of the collaborating investigators.
  - e) does not exceed safe or prudent limits for the volume of whole blood or sera taken from subjects.
  - f) can request that new kinds of collections can be made, involving additional visits.
  - g) can include safe and brief interventions with mechanistic endpoints.
  - h) does not divert or expend resources from TrialNet, either locally, at the coordinating center, chairman's office, or other TrialNet entities (e.g. core laboratories, etc.).
  - i) must satisfy biostatistical considerations, such that it has adequate power to answer the hypothesis. The initial statistical considerations for an ancillary will be performed by the investigator's statistician. The study will be reviewed by the TNCC to ensure that the power is adequate to answer the study questions. Pilot and exploratory studies are encouraged if well-justified and feasible.
3. Demonstration that adequate resources are available to complete the proposed study, or are being requested from an appropriate granting agency.
4. Techniques and assays essential to the proposed study are well established in the investigator's laboratory. Showing data relevant to the characterization and performance of the assay is usually required.
5. Results of ancillary studies will not be revealed to either TrialNet participants or their clinical team without specific approval from the Ancillary Studies Committee, and in general such information will not be revealed until after the protocol closes. All publications require approval of the Publications Committee.
6. The proposed study must include a member of TrialNet as an investigator or co-investigator. If one is not available locally, a TN investigator will be appointed to the Ancillary Study.

Each of the points listed above will be examined in detail. Final approval is contingent upon the Ancillary Studies Committee receiving a letter signed by all investigators participating in the ancillary in which they agree to the rules and regulations put forth by the TrialNet Steering Committee.

In addition, a yearly progress report summarizing the ancillary sub-study results and the impact of the study on TrialNet must be submitted to the Ancillary Studies Committee, and investigators may be invited to present these reports at Steering Committee meetings. If the annual report is not received within 60 days of the deadline, access to subjects may be revoked.

Finally, it is expected that the final results (annotated data) of the approved Ancillary Study be transmitted to the TNCC for incorporation into the final TrialNet dataset. Data transmission should occur within 2 years of completion of the study or when results are accepted for publication, whichever comes first.

The investigator should send her/his ancillary study proposal to the TrialNet Coordinating Center at The University of South Florida. The Committee will have reviews on approximately the first Friday of the month. Studies must be submitted at least 15 business days prior to each meeting in order to be considered at the upcoming meeting. When possible, the investigator may want to consider even earlier submission of the proposal, in the event that the study is deemed a Level 2 study which will also require consideration by the TN protocol and/or Steering Committee. Primary and secondary reviewers will be appointed for each proposal. Although the committee has broad expertise, in some cases the Chairman of the Ancillary Studies Committee may elect to seek outside expert opinion to ensure thorough scientific review in advance of the committee meeting. In addition, proposals may be reviewed by the relevant Protocol Committees or the Executive Committee, but all communications with the applicant will be via the Ancillary Studies Committee. The investigator submitting the proposal may be invited to participate in part of the review meeting, at the discretion of the Ancillary Studies Committee. A 2/3's majority vote constitutes an approval by the Ancillary Studies Committee when a quorum of at least 2/3's of the members is present. The investigator will be notified within 10 days of the meeting. If the study is not approved, then the investigator may re-submit a revised version for further consideration. In the case of a revision, applicants should include a section entitled "Response to Reviewers" and provide a point-by-point response to the prior critiques. If the Ancillary Studies Committee votes unanimously to reject a proposal, then there will be no further consideration of that proposal.

If the ancillary has been reviewed and approved by the Ancillary Studies Committee, but causes a deviation from the study protocol, or has a potential negative impact on the primary TrialNet study, the proposal will require Level 2 approval. The Steering Committee will then review and vote on the proposal, either electronically via the Web, or in person at Steering Committee meetings. The same criteria apply for approval of an ancillary study (2/3's approval by a quorum of 2/3's of members).

The decision of the Steering Committee is then forwarded to the Chairman of the Ancillary Studies for review prior to implementing these changes. In the event that there is equivocation as to whether an ancillary requires Level 2 approval or not, the Chairman of the Ancillary Studies Committee will review the proposal with the Executive Committee to make the final determination.



### **Recusal**

Members of the Ancillary Studies Committee should recuse themselves from review and approval of proposals from their institution or in which they are a collaborator. Members should also recuse themselves from reviews of applications for which they are competing against for funding.

### **Publicity of Approved TrialNet Ancillary Studies**

Publicity announcing the purposes and starting time of the study will be the responsibility of the investigator, and must be approved by Institutional Review Boards at all participating sites. Any publicity regarding results of the ancillary study must be approved by the Publications Committee before such announcements can be made.

### **Publications and Ancillary Studies**

As members of TrialNet, the ancillary studies investigators are subject to the rules and regulations of the TrialNet Publications Agreement. This agreement requires that all reports, manuscripts, or presentations of data derived from the ancillary study must be approved by the Publications Committee, who has the responsibility of overseeing publications, prior to their publication or presentation according to the procedures set forth in the TrialNet Policy on Publications and Presentations.