



Type 1 Diabetes TrialNet Sub-Study and Ancillary Studies Policies

Revision Date 08/24/09

Applications and questions should be submitted to the TrialNet Coordinating Center to:
Julie Ford, MSN, RN-BC, TrialNet Committees Manager
Email: Julie.ford@epi.usf.edu
Fax (813) 910-5973

TrialNet Sub-study and Ancillary Study Policies

Introduction

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 deviation in the study protocol, or may interfere with the subjects' interest or participation in TrialNet, then the study must be additionally reviewed and approved by the TrialNet 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.

Sub-study and Ancillary Study Definitions

An 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.

A 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.

Reasons for Required Approval of Add-On Studies

Investigators and subjects are entitled to prior assurance that all ancillary studies are of high 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 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 that do not interfere with the primary protocol. Other types of ancillary research will customarily require both Level 1 and Level 2 approval.

We anticipate that many such study requests will involve use of stored specimens, which may constitute a unique and limited resource. As such, these requests will necessitate Level 2 approval. When possible, we encourage investigators for Ancillary Studies to obtain their own samples prospectively, during the course of an active study, 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.

Sub-Study

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/sub-study. 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. A proposal is classified as an ancillary/sub-study when it addresses questions not directly relevant to the primary or secondary TrialNet study objectives and when no TrialNet funding or support is to be provided.

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 (not reviewed for merit). Proposals for sub-studies should include a budget and justification and one would be requested if not originally provided. The proposal will then be reviewed by the ancillary/sub-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/Sub-Study.

The principal distinction between a sub-study and a Level 2 ancillary/sub-study 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/sub-study investigators under the purview of TrialNet but is not conducted by TrialNet.

Funding for Ancillary Studies

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. While existing funding for the proposed study does not have to be identified for study approval, the source and

amount of anticipated funds must be identified in any application to the Ancillary Studies Committee. Approval by the Ancillary Studies Committee should be obtained prior to grant submission.

Preparation of Proposals for Ancillary Studies Committee review

The proposal submitted to the Ancillary Studies Committee should follow the National Institutes for Health (NIH) research grant (RO1) format. The applications should be complete, but brevity is encouraged, particularly ancillary study proposals that will undergo independent peer review (e.g. study section) elsewhere. However, a complete application is required for proposals that will only undergo scientific review by the TrialNet Ancillary Studies Committee, particularly sub-study proposals.

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 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/sub-study on TrialNet. Human Subjects Committee approval must be obtained prior to ancillary/sub-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/sub-study:
 - 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) 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.).

g) must satisfy biostatistical considerations, such that it has adequate power to answer the hypothesis. The initial statistical considerations for an ancillary/sub-study 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.

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.

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.

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/sub-study in which they agree to the rules and regulations put forth by the TrialNet Steering Committee.

Finally, 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 every 12 months, and investigators may be invited to present these reports at Steering Committee meetings. If the annual report is not received within 30 days of the deadline, the investigator will be asked to return to the original application procedure, and re-apply to the Ancillary Studies Committee.

Procedures for Obtaining Approval

The investigator should send her/his ancillary/sub-study to the TrialNet Coordinating Center at The University of South Florida, which will then distribute it to members of the Ancillary Studies Committee, via the web if possible. The Committee will have monthly ancillary/sub-study reviews, with projected meeting dates posted on the TrialNet web site. 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 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. These reviews will be posted to the Ancillary Studies Committee web site prior to the monthly meetings. For the monthly meetings, the Ancillary Studies Committee will discuss the proposal. The investigator submitting the proposal may be invited to participate in this meeting, at the discretion of the Ancillary Studies Committee. The PI of the impacted primary TrialNet study, and if relevant, other committee chairs, will be invited to also review the proposal and participate in this discussion, and later deliberations, but will not be eligible for voting. The committee will vote following a

discussion not involving the investigator. 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 are present. The investigator will be notified within 48 hours of the meeting. If the study is not approved, then the investigator may be invited to re-submit a revised version for further consideration. If the Ancillary Studies Committee votes unanimously to reject a proposal, then there will be no further consideration of that proposal.

If the ancillary/sub-study 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/sub-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/sub-study 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 Section

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.

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/sub-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/sub-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.