



Type 1 Diabetes TrialNet Protocol Development Guidelines

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The application process is described and a sample application form is provided in these guidelines.

Applications and questions should be submitted to the TrialNet Coordinating Center
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TrialNet Protocol Development Guidelines

I. INFORMATION ABOUT THE PROTOCOL DEVELOPMENT PROCESS

Type 1 Diabetes TrialNet is a NIH-sponsored clinical trials network which conducts studies designed to evaluate new approaches to prevent or ameliorate T1D specifically by interdicting the T1D disease process. These include interventions designed to decrease β -cell destruction and/or enhance β -cell survival. Studies are conducted in nondiabetic persons at risk of T1D in an effort to delay the development of T1D as a clinical disease; or (if initiated prior to appearance of autoimmunity) in an effort to delay the appearance of autoimmunity; or in individuals with T1D who are either newly diagnosed or have evidence of sustained beta cell function. Studies may include long term follow-up of subjects developing T1D. The TrialNet network will also support natural history and genetics studies in populations screened for or enrolled in studies conducted by the TrialNet study group. In addition, TrialNet will evaluate methodologies that enhance the conduct of clinical trials interdicting the T1D disease process.

Proposals for protocols may be submitted by any investigator or group of investigators, from within TrialNet or not previously involved with TrialNet. Protocols are reviewed by several TrialNet committees. There are four initial review committees – [1] the Scientific Review Committee, [2] the Clinical Feasibility Committee, [3] the Ethics Committee, and [4] the Safety Review Committee. The reports of these committees, together with the submitted protocol, then are reviewed by the Intervention Strategies and Prioritization Committee, which makes its recommendation to the TrialNet Steering Committee, the governing body of TrialNet. Prior to Steering Committee action, the Executive Committee and NIDDK provide input, particularly as related to the availability of resources. Following Steering Committee approval of any protocol, a Protocol Committee is appointed, generally chaired by the submitting investigator(s), which works together with the standing Protocol Development Team to expedite protocol development. NIDDK executes a Clinical Trial Agreement (CTA) or a Cooperative Research and Development Agreement (CRADA) with any commercial sponsors or sources of drugs or materials needed for conduct of the protocol.

The Scientific Review Committee reviews and scores proposals. Investigators who have unscored proposals will have an opportunity to submit an amended protocol, unless the Committee indicates that an amended protocol will not be considered.

The Clinical Feasibility Committee reviews the feasibility of the proposal. The Committee will review and evaluate the recruitment plan, implementation, and subject retention, and the estimate of the number of sites and subjects for the study. The Committee will identify procedural or safety issues that will limit feasibility.

The Ethics Committee evaluates the protocol for any ethics/human subject protections concerns. The Committee evaluates participant burden, appropriateness of including participants under 18 years of age (if applicable) related to the expected risks and prospect of benefit. The Committee also reviews and evaluates any apparent conflict of interest. The Committee will identify any ethical issues related to the proposal.

The Safety Committee evaluates special safety concerns that an intervention may raise, particularly those related to increased risk of infections or other potential side effects of

interventions. It includes members with special expertise in immunotherapy and infectious diseases.

The reports and comments of these four initial review committees will be forwarded to the Intervention Strategies and Prioritization Committee for consideration. The Intervention Strategies and Prioritization Committee receives the input from the review of the four initial review committees for consideration. The Committee determines: *“Is this study the next one for TrialNet to do?”* in the context of studies under development or implemented by TrialNet (or other groups, e.g. ITN). The Committee will make a recommendation and provide comments to the Executive Committee and NIH for review.

The Executive Committee and NIH will determine if there are any issues and/or concerns regarding support and implementation of the proposed study to include the timeline for implementation. The scoring information and comments from the scientific review, clinical feasibility review, ethics review, safety committee, and intervention strategies and prioritization review will be presented to the Steering Committee for consideration and vote for approval and implementation.

The Steering Committee will conduct two votes. The first vote will include all Steering Committee members on the scientific and ethical merit of the study (2/3 majority is required for approval). The second vote will be taken and each Clinical Center will have only 1 vote. Centers will vote “yes” only if they are willing to participate in the study. The “yes” votes must be as or more numerous than the number of TrialNet sites needed to implement the study.

The Protocol Development Team (PDT) will assume the primary responsibility for the protocol development in conjunction with the Protocol Committee and its Chairman. The PDT is assigned responsibility for the development and coordination of the scientific and operational aspects of the protocol to include mechanistic studies, repositing of samples, participant materials and for coordination of regulatory and budgetary activities.

The protocol implementation and operations are carried out by the TrialNet Coordinating Center in conjunction with the Clinical Centers and TrialNet Chairman’s Office.

II. DESCRIPTION OF STUDIES/TRIALS FOR CONSIDERATION BY TRIALNET AND CRITERIA FOR DEVELOPMENT OF NEW STUDY PROPOSALS

A. Preclinical Studies

TrialNet will not be directly supporting preclinical studies, however, if it is believed that clinical trial proposals are missing critical pieces of preclinical data, TrialNet will work with the investigator/company to facilitate this using other resources. This should be done with expert advice from FDA representatives.

B. Phase I Clinical Trials

The purpose of Phase I studies is twofold: 1) to assess safety in humans based on short-term standard toxicity levels and measures of the immune and metabolic systems; and 2) to collect, if possible, preliminary data regarding a biological effect and/or efficacy of the treatment based on immune/mechanistic measures, β -cell function and insulin sensitivity.

TrialNet should support Phase I (a) studies only under extremely unusual circumstances. TrialNet should only support Phase I (b) studies (first time administration of drug to patients with diabetes), if the goal is to obtain data for Phase II study.

Phase I (b) studies have specific issues which must be addressed in the design of the study:

- 1) Subject Age: Phase I (b) studies should be performed using subjects older than 18 years of age. A second Phase I (b) study addressing safety issues in children could be considered if safety is first demonstrated in the over 18 years of age population.
- 2) Duration of Onset of Type 1 Diabetes: Phase I (b) studies generally include subjects with type 1 diabetes of any duration. Although subjects with new onset type 1 diabetes may be needed to obtain efficacy data, this would be considered a Phase II pilot trial.

In order for TrialNet to consider supporting a Phase I (b) study, several criteria must be met:

- (1) The study must have a scientifically plausible hypothesis regarding the treatment's mechanism. It should be noted that a limited amount of information in humans supporting mechanisms exists due to a limitation in assays. TrialNet should not allow ambiguity in animal models regarding the mechanism delay or prevent the consideration of an agent in humans, particularly if the agent has already been demonstrated to be efficacious in clinical trials in other autoimmune diseases.
- (2) If adequate human data is not available, preclinical data showing safety in two animal models when possible under advice from FDA will be acceptable for consideration by TrialNet.
- (3) When possible, at least two studies with preclinical data showing efficacy in *either* prevention or post-diabetes in at least *one* animal model (NOD, BBrat, transgenic models, strep induced) must be presented. Note that additional emphasis may be given if the therapy was demonstrated to be effective when given to NOD after development of diabetes or in an islet rejection model. In the event that at least two studies with preclinical data showing efficacy in *either* prevention or post-diabetes in at least *one* animal model is not presented, the agent's efficacy in other immune-mediated diseases (including transplantation) must be demonstrated. This may include data from Phase II trials.
- (4) If ethically sound, a prior Phase I (a) study must have been completed.

TrialNet will not accept applications for preclinical or Phase I (a) studies except under unusual circumstances to be evaluated by study chair or appointees. TrialNet will, however, accept applications for Phase I (b) studies that are planned to continue development towards Phase II and Phase III studies.

C. Phase II Clinical Trials

The purposes for conducting Phase II studies are to examine the safety and efficacy of agents in humans. Safety is determined through measures of standard toxicity levels, specific immune/mechanistic levels and glucose homeostasis levels. Clinical efficacy in humans is tested based on β -cell function measures. Biological efficacy in humans is measured from immune/mechanistic levels. Lastly, Phase II studies may also obtain safety and efficacy information for use in designing Phase II trials in at-risk subjects. Templates are provided for protocol development for prevention and new onset studies at the end of this section.

1. Phase II Trials in Subjects with Type 1 Diabetes

Several criteria should be considered when determining the whether to support Phase II trial proposals in newly diagnosed subjects with type 1 diabetes.

a. Mechanism. A scientifically plausible hypothesis regarding the mechanism must be shown. It should be noted that a limited amount of information in humans supporting mechanisms exists due to a limitation in assays. TrialNet should not allow ambiguity in animal models regarding the mechanism delay or prevent the consideration of an agent in humans, particularly if the agent has already been demonstrated to be efficacious in clinical trials in other autoimmune diseases.

b. Safety. If adequate human safety data is not available, preclinical data showing safety in two animal models should be presented, if possible, under advice from FDA. Phase I (b) safety data in patients with diabetes should be presented OR demonstrated safety from use in other immune-mediated disease (including transplantation) must be presented. This may include data from Phase II trials. It should be noted that safety may be different in patients with diabetes and that the study design should include an early review for diabetes related safety issues.

c. Efficacy. 1) When possible, at least two studies with preclinical data showing efficacy in *either* prevention or post-diabetes in at least *one* animal model (NOD, BBrat, transgenic models, strep induced) should be presented. Note that additional emphasis may be given if the therapy is demonstrated to be effective when given to NOD after development of diabetes or in an islet rejection model. If the previously mentioned two study criteria cannot be met, the option exists to present demonstrated efficacy from use in other immune-mediated disease (including transplantation) data instead. This may include data from Phase II trials. 2) Last, if any subjects are <18 years of age, the studies need to be designed in concert with current OHRP, FDA, and local IRB regulations. If available, it would be desirable to be presented with data regarding Phase I (b) or II efficacy in adult patients with diabetes AND/OR efficacy data from Phase II trials in children of similar age range with other immune-mediated diseases.

2. Phase II Trials in Subjects At Risk for Type 1 Diabetes

The relationship between the subject's risk of disease and risk/benefit of therapy should be considered when determining whether or not to support a Phase II trial in *at risk* subjects. As in the case of Phase II trials in subjects with type 1 diabetes, criteria for consideration are the mechanism, safety and efficacy of the therapy or intervention.

a. Mechanism. A scientifically plausible hypothesis regarding the mechanism must be shown.

b. Safety. Whenever possible, Phase II safety data in patients with diabetes is needed. However, therapy may also be considered using safety data from a Phase I trial depending upon the nature of drug. In addition, if the rationale for the study is uniquely appropriate for *at risk* group, protocols may still be considered without previous testing in patients with diabetes. There will, however, be enhanced scrutiny of safety issues.

c. Efficacy. Phase II efficacy data in patients with diabetes is required unless a very high safety profile and some degree of efficacy is demonstrated from Phase I (b) trials in

patients with diabetes. If data is not available, the use of the agent in subjects with other immune-mediated diseases may be presented instead. This may include data from Phase II trials. Lastly, if the rationale for the study is uniquely appropriate for an *at risk* group, protocols may still be considered without efficacy data, although a much greater degree of safety is required.

D. Protocol Templates for Prevention and New Onset Type 1 Diabetes Studies**A. PROTOCOL TEMPLATE FOR TRIALNET PREVENTION STUDIES****I. Introduction****II. Background****III. Study Design**

- **The following categories constitute individuals with varying degrees of risk for development of diabetes. These categories should be considered relevant to the perceived risk/benefit ratio of the prevention therapy to be tested.**
 - 1) Non-diabetic OGTT
 - 2) At least 2 antibodies (GAD65, mIAA, ICA512) present
or
 - 3) 1 antibody with impaired GTT
or
 - 4) 1 antibody with IVGTT < 1st percentile
or
 - 5) 1 antibody with DQ8/DQ2 genotype
- **Exclusion Criteria**
 - 1) Consideration should be given to HLA protective alleles
- **Primary Outcome**

Development of type 1 diabetes by ADA criteria

IV. Patient Enrollment**V. Patient Management**

- **Baseline and Follow-up Assessments**

VI. Statistical Considerations

- **For example, primary outcome is onset of type 1 diabetes with estimated hazard rate of 0.163 per year among high risk subjects in the control group.**

VII. Study Administration**VIII. Timeline**

B. PROTOCOL TEMPLATE FOR TRIALNET NEW ONSET STUDIES

I. Introduction

II. Background

III. Study Design

▪ Entry Criteria

- 1) Within 3-months of diagnosis of type 1 diabetes based on ADA criteria
- 2) Between the ages of 12 and 35 (or 8 and 35) years of age (age range may vary according to agent used, the requirement for blood sampling, and the study design)
- 3) Have stimulated C-peptide levels ≥ 0.2 pmol/ml
- 4) Have either detectable anti-GAD, anti-ICA512/IA-2, insulin autoantibodies (unless received insulin therapy for 7 days or more), or islet cell autoantibodies.
- 5) Willing to comply with intensive diabetes management. The goal of therapy will be an HbA1c within the currently recommended American Diabetes Association age-specific target range.

▪ Primary Outcome

The primary outcome of each patient is the area under the curve of the stimulated C-peptide from the first 2 hours of a 4-hour MMTT conducted at the 2-year visit.

IV. Patient Enrollment

V. Patient Management

▪ Baseline and Follow-up Assessments

- Duration of MMTT: 4- hour MMTT at baseline and at 2 years, with additional MMTTs being 2-hour tests
- Baseline MMTT must be no earlier than 3 weeks after diagnosis
- HLA testing will be for DQA, DQB, DRB subtypes for DR4
- IAA testing must be within 7 days of starting insulin therapy

VI. Statistical Considerations

▪ Primary Analysis

Comparison of the mean 2-hour area under the curve for stimulated C-peptide from the 2-year MMTT adjusted for age and the baseline 2-hour area under the curve.

▪ Sample size

Determined to provide adequate power to detect a relative difference of interest.

VII. Study Administration

VIII. Timeline

III. TRIALNET APPLICATION AND EVALUATION PROCESS

A. APPLICATION INSTRUCTIONS

TrialNet is pleased to consider proposals involving prevention of type 1 diabetes or immune intervention in subjects with type 1 diabetes..

Type 1 Diabetes TrialNet is an NIH sponsored network designed to conduct intervention and prevention trials in type 1 diabetes. There are 18 clinical centers, 15 “major affiliates”, as well as multiple other affiliate and satellite investigative groups throughout North America, Canada, Europe and Australia. Type 1 Diabetes TrialNet welcomes applications for clinical trials in these areas from investigators in academia and/or industry.

You also should be aware of The Immune Tolerance Network (ITN), a collaborative research effort that solicits, develops, implements, and assesses clinical strategies and biological assays for the purpose of inducing, maintaining, and monitoring tolerance in humans for kidney, liver, and islet transplantation, autoimmune disease, and allergy and asthma. <http://www.immunetolerance.org/>. TrialNet is co-sponsoring several studies with ITN, and ITN’s Tolerance Assay group works with TrialNet on other studies.

B. FORMAT FOR PROPOSAL APPLICATIONS (see the templates above for TrialNet recommended study design components)

Format for Proposal Application - Phase II-III Clinical Trial

(Required elements are underlined)

Title of Study

The title must include the name of the Investigator(s), their institutions, and their contact information. This section must also include a brief statement of the investigator’s qualifications as well as a brief list and description of the qualifications of potential collaborating clinical sites (if any).

A. Statement of Scientific Hypothesis

The statement must include a summary of supporting evidence as well as references.

B. Statement of Proposed Study Design

This statement must include information on the subjects to be recruited including the age range of the subjects and the state of the disease in such subjects. Dosing must also be explained. Specific issues related to this therapy that need to be considered in final study design (i.e. drug causes rash...therefore cannot fully mask study) must also be described.

C. Proposed Mechanistic Studies *(if any)*

Mechanistic assay studies may be proposed to help elucidate the underlying mechanism of the agent or treatment intervention being studied and/or the pathogenesis of the disease pathogenesis or disease process under investigation. TrialNet may collaborate with ITN to provide mechanistic assays for protocols. Briefly describe the rationale and the procedures (and provide references, as appropriate).

D. Preclinical Safety Data *(table format, if possible)*

The proposal must list/describe animal model(s) safety data stating the dose, frequency, and duration of dosing. The safety data must be summarized providing the appropriate references including the investigator's name.

E. Preclinical Efficacy Data *(table format, if possible)*

The proposal must list/describe animal model(s) efficacy data stating the dose, frequency, and duration of dosing. Efficacy outcome data must be summarized providing the appropriate references including the investigator's name.

F. Clinical Safety Data *(table format, if possible)*

The proposal should list/describe clinical safety data noting the sample size, age range and disease studied. In addition, the dose, frequency, and duration of dosing for the study should be included. Clinical safety data should be summarized providing the appropriate references including the investigator's name. It should be clearly stated if no clinical safety data is available.

G. Clinical Efficacy Data *(table format, if possible)*

The proposal should list/describe clinical efficacy data noting the sample size, age range and disease studied. In addition, the dose, frequency, and duration of dosing for the study should be included. Clinical efficacy data should be summarized providing the appropriate references including the investigator's name. It should be clearly stated if no clinical efficacy data is available.

H. Ethical Considerations

Describe the potential risks in addition to that noted under (Section F - Clinical Safety Data). Also describe the potential benefits for each group of subjects participating in the proposed study (n.b. benefits may be different for those in a control group). Lastly, describe alternative treatments (including standard" treatments) and their potential risks and benefits to subjects.

I. Conflict of Interest Disclosure

Disclose any personal or professional involvement with industrial concerns or personal commercial interests held by yourself and your collaborators that are relevant to the current proposal.

J. Additional Pertinent Information