Immune Tolerance Network

GUIDELINES FOR SUBMISSION

Concept Proposals

The Immune Tolerance Network is sponsored by the National Institute of Allergy and Infection Diseases

Immune Tolerance Network
7500 Old Georgetown Road, Suite 800
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www.immunetolerance.org

IMPORTANT NOTICE:

Please consult the ITN website to ensure you have the latest version of this document as it will be frequently updated with the latest information on ITN policy and procedures.

www.immunetolerance.org

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1. INTRODUCTION

1.1 OVERVIEW OF THE APPLICATION PROCESS

The Immune Tolerance Network's (ITN) application process is a two-stage process designed to expedite applications from proposal to protocol development. The application process is highly interactive and collaborative, designed to assist potential investigators in the preparation of highly focused, relevant scientific proposals. ITN resources will be available to applicants in helping develop proposals.

The two-stage application process includes:

1. ***Concept Proposal*** (instructions for online submission at http://www.immunetolerance.org/professionals/proposals/submit-proposal)

2. ***Full Application*** (by invitation only after approval of Concept Proposal)

Concept Proposals are abbreviated applications (approximately 5 pages) containing a basic outline and justification of the proposed research. Concept Proposals are intended to provide reviewers with a general overview of the clinical strategy or tolerance assay, the study rationale, relevance to tolerance and the requirements of the proposed studies. The review process for Concept Proposals is targeted toward the identification of novel and important ideas rather than detailed scientific treatments of precise methodologies, which will be addressed at the Full Application stage.

Applicants must download, complete and submit the appropriate Concept Proposal template form available on the ITN website (http://www.immunetolerance.org/professionals/proposals/submit-proposal). Instructions for completing and submitting these forms to the ITN's submission and review system are described in this document.

Concept Proposals will be evaluated by well-defined criteria that include: 1) scientific basis and rationale, 2) clinical implications, 3) feasibility, 4) mechanistic studies and tolerance assays, and 5) the reputation and capabilities of the investigator (details in **Section 4.2**). Applicants submitting Concept Proposals will typically be notified of the results of the review process within 4-6 weeks following the application cut-off.

Successful applicants will be invited to submit a more comprehensive proposal (a Full Application) to the ITN. Note that this document addresses Concept Proposal submissions only and information on Full Applications will be provided to invited applicants. Assistance with statistical/sampling considerations, as well as resources for budget development, will be available from the ITN for the preparation of Full Applications. Authors of Full Applications will be invited to present a summary of their proposals to the ITN's scientific advisory board, the Network Steering Committee (NSC), for final review at one of the NSC's bi-annual meetings. Authors of approved Full Applications will be notified and teamed with the ITN's Clinical Trials Group for protocol development.

The ITN emphasizes collaboration during both steps of the application process, and encourages applicants to contact the ITN with any questions regarding development of Concept Proposals.

1.2 CONTACT INFORMATION

All questions regarding this document, the application process or the submission of Concept Proposals should be directed to:

Philip Bernstein, Ph.D.
Executive Director, Strategic Review, Planning and Communications
Immune Tolerance Network
7500 Old Georgetown Road, Suite 800
Bethesda, MD 20814

Phone: (240) 235-6132
Facsimile: (240) 235-6197
E-mail: *pbernstein@immunetolerance.org*

Please be sure to reference the tracking number of your proposal (assigned upon creation of the on-line submission) in all communications with the ITN.

2. CRITERIA FOR CONCEPT PROPOSAL SUBMISSIONS

2.1 GENERAL RESEARCH GUIDELINES

The ITN accepts Concept Proposals for clinical trials and tolerance assays applied to transplantation, autoimmune diseases, (including but not limited to) type 1 diabetes, and asthma & allergic diseases. Concept Proposals for clinical trials should represent novel therapies which have a strong biological basis for inducing tolerance (***requisite pre-clinical investigation must be complete, with encouraging results***). Concept Proposals for clinical trials should include plans for integrated mechanistic studies of biomarkers of disease activity and tolerance assessment. Concept Proposals for studies of individual biomarkers and tolerance assays alone will also be considered, provided appropriate consideration has been given to clinical indications.

The ITN generally looks for Phase I-II trials with a strong rationale for tolerance induction. The ITN also looks for coordinated, comprehensive set of mechanistic studies as a means of evaluating disease-specific efficacy and to permit an objective means of studying patients in future trials.

Note that the ITN will ***NOT*** entertain Concept Proposals for the following:

- Pre-clinical investigations
- Non-human investigations
- Xeno-transplantation

2.1.1 Notes on Concept Proposals for Clinical Study

The ITN evaluates proposals for high-quality, innovative clinical trials in solid organ transplantation, autoimmune diseases (e.g., multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease, SLE, etc.), as well as type I diabetes mellitus, and allergy and asthma. General areas of interest for the ITN include (but are not limited to):

- Developing immune tolerance modifying therapies
- Opportunities to extend current indications of approved therapies into new diseases or conditions with small markets
- Combination studies with known or experimental agents that could lead to novel therapeutic strategies
- Trials where biomarker and mechanistic studies can complement the clinical trial

Additionally, the ITN actively investigates the mechanisms of tolerance induction and maintenance, integrating hypothesis-driven, mechanism-based research into all its clinical trials, and so the ITN looks for proposals for Phase I-II trials which have integrated plans for comprehensive studies of biomarkers of disease activity. Such studies will provide invaluable insight into the disease-specific efficacy of the protocols that could help identify patient phenotypes that best respond to therapy, and further investigate the mechanisms of tolerance.

Major emphasis will be placed on the following criteria when evaluating Concept Proposals:

- Rationale for tolerance induction
- Supporting preclinical or clinical data
- Patient availability
- Laboratory measures of tolerance with clear outcome measures
- Mechanistic plan (genetic and cellular assays of immune function)

2.1.2 Notes on Proposals for Tolerance Assays

In addition to proposals for clinical trials, The ITN accepts applications for the development of novel tolerance assay or mechanistic studies for the purposes of establishing new surrogate markers of immune tolerance and investigating the mechanisms of clinical tolerance. The ITN has a comprehensive set of core laboratories with validated standards of operation and methodologies for controlled collection, storage, shipment, testing, and analysis of assays.

A Tolerance Assay Concept Proposal should highlight the mechanistic hypothesis being tested and describe the novel assays that will be used. In instances where ITN core facilities will be used, the ITN's Biomarker and Discovery Research group will work with investigators to develop a comprehensive program of immunological monitoring of patients. The patient samples can come from ongoing studies from which samples are available to the investigator or from ITN studies under development. Applicants are advised to consider the most appropriate design for the proposed study based on a number of factors: availability of expertise and equipment, volume of samples, ability to ship samples, etc.

Additionally, the ITN makes data and samples from its completed trials accessible to the community at large to expand opportunities for discovery through the ITN's clinical trials research portal, TrialShare (www.ITNTrialShare.org). The goal of ITN TrialShare is to allow study teams and independent investigators to make optimal use of clinical trial data and mechanistic study samples stored within the ITN sample repository. An inventory of available samples and information about submitting a request for specimens are available on TrialShare.

The ITN maintains responsibility for the use of mechanistic samples collected from ITN clinical trials and stored within the ITN repository. The design of mechanistic studies and selection of samples to be used are decided cooperatively by the trial PI (Protocol Chair) and the ITN leadership. The ITN and the trial PI will have exclusive use of all samples for 18 months after the last visit of the last study patient. During this initial time period, sample requests from non-ITN community members must be approved by the PI along with the ITN. After this period, the ITN will evaluate requests for use of samples for studies not previously planned within the protocol.

2.2 INVESTIGATORS

2.2.1 Who May Apply

Applications will be accepted from qualified investigators in academia, industry and private research organizations. Examples would include individuals holding a full-time appointment from a recognized university, research organization or biotech/pharmaceutical company.

If you are unsure whether you qualify under these above guidelines, please contact the Executive Director of the Office of Strategic Review, Planning, and Communications.

In some instances, lead investigators, not themselves involved in clinical studies, may choose to submit a proposal based on the development of a unique reagent or therapeutic opportunity. The ITN welcomes such proposals and encourages the applicant to contact suitable collaborators to assist in development of the clinical strategy.

2.2.2 Conflict of Interest Policy

The ITN requires all applicants to complete the ITN Conflict of Interest/Disclosure form if their Concept Proposal is accepted for development into a Full Application. Full disclosure of applicants' associations and financial relationships with potential industry partners is required. A select body of individuals will review the disclosure forms to determine if a conflict of interest does exist, and then attempt to manage the conflict in an acceptable manner. The ITN understands that many applicants and collaborators will have conflicts of interest; however, disclosure will not necessarily lead to disqualification. The ITN requires full disclosure both to preserve the integrity of the ITN and its research findings, and to satisfy the requirements outlined for ITN review by its external funding agencies. All disclosures made to the ITN will remain confidential with restricted access and removal of personal identifiers wherever possible. Information will be used only for the purpose of ITN business to the extent permitted by law and will only be maintained in ITN databases as long as is legally required. Also note that the ITN will request periodic

updates of information from funded researchers and personnel. The review of disclosure forms and management of conflicts will be an ongoing process for the tenure of all ITN sponsored trials.

2.3 Human Subjects

All ITN investigators must comply with the many safeguards in place to protect research volunteers.

- ITN investigators must follow the ethical guidelines and principles outlined in the Belmont Report (http://ohsr.od.nih.gov/guidelines/belmont.html.), the Declaration of Helsinki drafted by the World Medical Association (http://ohsr.od.nih.gov/guidelines/helsinki.html.) and the guidelines published by the NIH. All ITN clinical trials are to be conducted according to United States and International standards of Good Clinical Practice (FDA 21 part 312) and the International Conference on Harmonization guidelines (http://www.fda.gov/regulatoryinformation/guidances/ucm122049.htm).

- All human subject research sponsored by the ITN is governed by Federal regulations. Federal regulations were established by the HHS and are overseen by the Office of Human Research Protections (OHRP) (http://www.hhs.gov/ohrp/). ITN investigators must satisfy the HHS regulations for the protection of research subjects as they are set forth in the Code of Federal Regulations 45 CFR part 46, referred to informally as the Common Rule (http://www.hhs.gov/ohrp/humansubjects/index.html). When applicable, investigators must satisfy those Subparts of the regulations that provide additional protections for pregnant women, human fetuses, and neonates involved in research (Subpart B); for research involving prisoners as subjects (Subpart C); and for children involved as subjects in research. (Subpart D). Additionally, ITN investigators must comply with Title 45 CFR 160, 164, the Health Insurance Portability and Accountability Act (HIPAA) and Regulations for Standards for Privacy and Individually Identifiable Health Information.

- All human subject research sponsored by the ITN must satisfy the requirements established by the Food and Drug Administration (FDA), an HHS agency that regulates clinical investigations of products such as drugs, biological products, and medical devices. *FDA regulations for the protection of human subjects* are set forth in 21 CFR 50. Additionally, as applicable, ITN investigators are responsible for meeting regulatory criteria established in 21 CFR 312 investigational new device applications; 21 CFR 812, investigational device exemption and 21 CFR 54, financial disclosure by clinical investigator.

- All ITN investigators should comply with the NIH standards for clinical research and the policies and standards established by their home institutions. This includes research involving vulnerable populations including the recruitment and participation of minorities in research (http://grants.nih.gov/grants/policy/hs/hs_policies.htm).

All ITN investigators should utilize protections to minimize risk to study participants. Safeguards should include research proposals based on the Code of Federal Regulations, a sound voluntary informed consent process, institutional review board approval, good clinical practice and when applicable a data and safety monitoring board and certificate of confidentiality.

3. PREPARING & SUBMITTING YOUR CONCEPT PROPOSAL

3.1 GENERAL INSTRUCTIONS

Concept Proposals are intended to provide a general overview of the clinical strategy or tolerance assay, rationale, relevance to tolerance and the requirements for performing the proposed studies. Applicants must complete their Concept Proposal on the appropriate ITN-supplied template. All templates can be found at: http://www.immunetolerance.org/professionals/proposals/submit-proposal.

Three types of forms are available, for clinical trials, tolerance assay projects and revised proposals. Please be sure that you are using the correct set of forms (all available at the above link).

Clinical Trial Concept Proposal Template
Use this template if you are submitting a proposal for a clinical trial.

Tolerance Assay Concept Proposal Template
Use this template if you are proposing a tolerance assay study, mechanistic study, the addition of specific assays to an existing clinical trial, or to establish a core facility.

Revised Concept Proposal Template
Use this template only if you are responding to an ITN request for a revised Concept Proposal.

TrialShare Concept Proposal Template
Use this template if you are requesting the use of ITN samples. To view available samples, visit www.ITNTrialShare.org.

Template forms may be completed offline and submitted at the applicant's convenience through the ITN website.

3.2 COMPLETING THE CLINICAL CONCEPT PROPOSAL

3.2.1 Cover Page

Title: Enter the title of your proposal in the space provided. A maximum of 120 characters is allowed.

1-2. Principal Investigator/Address: Complete the sections identifying yourself as the Principal Investigator (PI) and your contact information. Be sure to double-check your email address for accuracy, as this will be the primary mode of communication regarding your proposal.

3. Collaborators/Co-investigators: If you have identified other investigators who will collaborate on the proposed trial, list them here and provide a brief description of their responsibilities. List only those collaborators or co-investigators who would play (or have played) an integral part in the conceptual framework and planning of the clinical or assay portions of the study – *do not* provide a list of investigators from all anticipated clinical sites; inclusion of a mechanistic study co-PI is recommended.

4. Additional Information: If this proposal is based upon a proposal previously submitted to the ITN that was not funded or was judged too preliminary, enter the tracking number here. ***Note: If you have been asked to provide the ITN with a "Revised Concept Proposal," you should complete the "Revised Concept Proposal" template form***.

3.2.2 Section 2: Research Information

2A. Clinical Abstract: The abstract must provide ITN reviewers with a clear description of the goals, rationale and proposed methodologies of the study. Note that this section is intended to describe the clinical aspects of the study; associated mechanistic studies are covered in the next section. Use the following headings in preparing your abstract:

Objectives: Provide a clear statement of the research objectives and/or hypotheses for the study.

Basis/Rationale: Provide a short description of the pre-clinical/clinical evidence and/or immunological rationale that underlies your hypothesis and supports conducting this study at this time.

Clinical Protocol Summary: Provide a brief description of the clinical protocol you are proposing. Details should include specific agents to be used, timing of interventions, primary and secondary clinical endpoints, specific patient populations to be studied, number or arms, blinding/masking, duration of the study and follow-up, etc.

Significance: Briefly discuss the significance of the proposed study. Clearly state how the proposed study is relevant to immune tolerance, highlighting innovative aspects of the proposal and the potential for advancing our understanding of clinical tolerance induction.

2B. Proposed Mechanistic Studies: Applicants should note that while each ITN clinical study includes a complementary set of mechanistic assay studies, it is not necessary to provide a detailed list of all assays that will be performed. If fully approved, the ITN Biomarker and Discovery Research Group will collaborate with the PI during protocol development to develop the specific collection of assays that will best address the hypotheses of the study.

Instead, this section should identify the primary scientific questions that complementary mechanistic studies would address and describe the methods that could be used to address them. The specific scientific hypothesis that is being tested should be clearly and succinctly stated. Otherwise, discuss the major mechanistic questions [or proposed immunologic mechanism(s)] that need to be answered with respect to the disease, strategy or particular agent under investigation. Describe the methods that would be used to investigate these questions.

In those cases where the applicant wishes to perform assays that are not currently offered by the ITN, describe where this assay would be performed and provide justification for use of this assay. Describe the requirements of each such assay (i.e., types, volumes of sample required) and if the assay has been validated or not.

3.2.3 Section 3: Additional Study Information

3A. Number of Clinical Sites: Enter the number of clinical sites you anticipate to be required to complete this study. Note that it is not necessary to identify specific sites at this stage.

3B. Reagent/Patient Availability: This section is intended to give reviewers an impression of the feasibility of conducting the proposed trial as described. In particular, reviewers will require an indication that: 1) the proposed patient populations do exist and could be enrolled in sufficient numbers to provide useful information; and 2) key reagents/pharmaceuticals can be obtained to successfully complete the trials.

Describe the patient populations envisioned and discuss the issues which would assist or inhibit sufficient enrolment (i.e. incidence, competition with other trials, existing treatment options).

Applicants should also describe the source of the key reagents/pharmaceuticals for this study (e.g. does the study use FDA approved pharmaceuticals? Does it involve use of unapproved products or off-label use of approved products?) List any possible industrial collaborators and briefly describe any preliminary discussions you have had indicating their potential interest in collaborating.

[Note: in cases where the reagents/equipment of interest are proprietary in nature and not generally available for research use, the ITN may provide assistance in gaining license for their use. In such cases, applicants are advised to contact the Office of Strategic Review, Planning, and Communications prior to submitting their proposal.]

3C. Ethical Considerations: This section should briefly discuss compliance with Human Subject Guidelines and summarize any potentially troubling ethical questions raised by the proposed research. The ITN Ethics Review Committee, when considering any such ethical problems, will take into account the likelihood of finding an acceptable resolution for such issues. Questions which should be addressed are:

- Have human subjects been used before? If so, why do they need to be used again? If not, why is it appropriate to use human subjects now?
- What are the risks and benefits involved in the proposed research protocol and will these benefits be directly realized by the subjects involved?
- Are there adequate means to ensure the participation of women, minorities and children? If not, what are the justifications for exclusion?
- Does the proposal raise new or troubling ethical questions for the investigators? If so, please describe in detail.

3D. Conflict of Interest Disclosure: The principal investigator and listed collaborators must disclose any personal or professional involvement with industrial concerns that are related to, or would benefit from the proposed research. Likewise, any personal commercial interests that relate directly to the proposed research should be listed in this section. Please supply information about any potential conflicts of interest you foresee in your research and how you will resolve them. *[Note: if accepted for further review, all applicants and collaborators will be required to submit a signed conflict of interest form and a non-disclosure agreement with their Full Application]*

3E. Supporting Publications: List up to five (5) publications that have direct relevance to this proposal. Note that these publications are not necessarily required to be authored by the Principal Investigator. Include those publications which support and/or clarify the current proposal. Provide complete references listing all authors, title, publication, issue and year. *[Note: depending upon availability of electronic reprints, you may be contacted prior to review to supply these to the ITN for use in the review process]*

If you have supporting preclinical or clinical data available you may include that as an attachment to the Concept Proposal. This information will be important when evaluating Concept Proposals.

3.3 COMPLETING THE TOLERANCE ASSAY CONCEPT PROPOSAL

3.3.1 Cover Page

Title: Enter the title of your proposal in the space provided. A maximum of 120 characters is allowed.

1-2. Principal Investigator/Address: Complete the sections identifying yourself as the Principal Investigator and your contact information. Be sure to double-check your email address for accuracy, as this will be the primary mode of communication regarding your proposal.

3. Collaborators/Co-investigators: If you have identified other investigators who will collaborate on the proposed trial, list them here and provide a brief description of their responsibilities. List only those collaborators or co-investigators who would play (or have played) an integral part in the conceptual framework and planning of the clinical or assay portions of the study – *do not* provide a list of investigators from all anticipated clinical sites.

4. Additional Information: If this proposal is based upon a proposal previously submitted to the ITN that was not funded or was judged too preliminary, enter the tracking number here. Note: If you have been asked to provide the ITN with a "Revised Concept Proposal," you should complete the "Revised Concept Proposal" template form.

3.3.2 Section 2: Study Details

2A. Abstract: The abstract must provide ITN reviewers with a clear description of the goals, rationale, proposed methodologies and significance of the study. Use the following headings in preparing your abstract:

Objectives: Provide a clear statement of the research objectives and/or hypotheses for the study.

Basis/Rationale: Provide a short description of the rationale for the study, providing evidence that underlies your hypothesis and supports conducting this study at this time.

Methods: Provide a description of the proposed study, clearly describing the methods to be used, the study endpoints and patient populations required. Note which methods are currently offered by ITN core facilities and which techniques are intended to be performed outside of ITN facilities.

Significance: Briefly discuss the significance of the proposed study. Clearly state how the proposed study is relevant to immune tolerance, highlighting innovative aspects of the proposal and the potential for advancing our understanding of clinical tolerance induction.

2B. Study Requirements: This section provides reviewers with an overview of the feasibility and the implementation plan for the proposed study and research. Describe the clinical specimen requirements for the study, indicating the types, numbers, volumes and required timing of acquisition. Briefly describe any special equipment or expertise that will be needed to carry out the project.

In those cases where the applicant wishes to perform assays that are not currently offered by the ITN, describe where this assay would be performed and provide justification for use of this assay. Describe the requirements of each such assay (i.e. types, volumes of sample required) and if the assay has been validated or not.

3.3.3 Section 3: Additional Study Information

3A. Reagent/Equipment Availability: This section is intended to provide preliminary information on the feasibility of conducting the proposed research. Reviewers will require a plan as to how key reagents and equipment can be obtained to successfully complete the proposed work. Applicants should describe the source of the key reagents/equipment for this study and any considerations for their use (e.g. regulatory compliance for diagnostics, etc.). List any possible industrial collaborators and briefly describe any preliminary discussions you have had indicating their potential interest in collaborating. *[Note: in cases where the reagents/equipment of interest are proprietary in nature and not generally available for research use, the ITN may provide assistance in gaining license for their use. In such cases, applicants are advised to contact the Office of Strategic Review, Planning, and Communications prior to submitting their proposal.]*

3B. Ethical Considerations: In this section, briefly summarize any potentially troubling ethical questions raised by the proposed research, including issues of informed consent for the use of biologic materials. The ITN Ethics Review Committee, when considering any such ethical problems, will take into account the likelihood of finding an acceptable resolution for such issues. Questions which should be addressed include:

- Can appropriate informed consent be obtained for the collection of clinical samples to be used in this project?
- What are the risks and benefits involved in the proposed research protocol and will these benefits be directly realized by the subjects involved?
- Does the proposal raise new or troubling ethical questions for the investigators? If so, please describe in detail.

3C. Conflict of Interest Disclosure: The principal investigator and listed collaborators must disclose any personal or professional involvement with industrial concerns that are related to, or would benefit from theproposed research. Likewise, any personal commercial interests that relate directly to the proposed research should be listed in this section. Please supply information about any potential conflicts of interest you foresee in your research and how you will resolve them. *[Note: if accepted for further review, all applicants and collaborators will be required to submit a signed conflict of interest form and a non-disclosure agreement with their Full Application.]*

3D. Supporting Publications: List up to five (5) publications that have direct relevance to this proposal. Note that these publications are not necessarily required to be authored by the Principal Investigator. Include those publications which support and/or clarify the current proposal. Provide complete references listing all authors, title, publication, issue and year. *[Note: depending upon availability of electronic reprints, you may be contacted prior to review to supply these to the ITN for use in the review process.]*

3.4 COMPLETING THE REVISED CONCEPT PROPOSAL

A. Proposal Information: Complete the fields as required, including the tracking number of the original Concept Proposal upon which this revised proposal is based.

B. Revised Abstract: Applicants submitting a Revised Concept Proposal must prepare a revision to the original abstract that incorporates any changes in goals, rationale or methodologies since the original proposal. This abstract should be prepared in accordance with the appropriate abstract guidelines depending on whether it is for a clinical study (see **Section 3.2.2**) or a tolerance assay study (see **Section 3.3.2**).

C. Additional Information Requested: Applicants should use this section to respond to questions/comments provided by ITN reviewers of the original application. Address each issue/question separately, in a fashion that makes it clear what the reviewers' question/comment was. You may use up to 5 pages. If your response requires graphics such as tables, charts or figures, these should be referenced in the text and described below, in Section D.

D. Attachments: If you need to include figures, tables and/or charts in your response to the ITN review comments (if you are submitting a revised Concept Proposal, for example), they may be submitted to the ITN separately, via email. Use this section to identify and provide captions for the figures you are submitting.

For each figure/table, provide the title, figure caption and name of the file that you will send. For example:

```
Figure 1
Comparative production of IL-2 in T cells of patients treated with Agent
X and controls.
File: il2compare.jpg
```

If you wish to include copies of any manuscripts that have been published since the original Concept Proposal, please provide a reference in this section.

3.5 SUBMITTING A NEW CONCEPT PROPOSAL

You can access instructions for submission and all Concept Proposal template forms at http://www.immunetolerance.org/professionals/proposals/submit-proposal. Before submitting your Concept Proposal, carefully review all the information entered into the template form.

When you are certain that all the information you have supplied is correct, send your proposal to conceptproposals@immunetolerance.org.

3.6 SUBMITTING A REVISED CONCEPT PROPOSAL

The ITN may request a revised Concept Proposal if additional information/clarification or more discussion is needed before a final decision. For revised Concept Proposals, use the Revised Proposal Template Form which can be found at http://www.immunetolerance.org/professionals/proposals/submit-proposal. Before submitting your revised Concept Proposal, carefully review all the information entered into the template form.

When ready to submit, send the revised proposal to conceptproposals@immunetolerance.org.

4. ITN REVIEW PROCESS

4.1 CONCEPT PROPOSAL REVIEW

4.1.1 Scientific Review

Concept Proposals are reviewed by the Network Steering Committee (NSC), a scientific advisory board comprised of expert clinicians and researchers from leading institutions around the country, the Network Directors,, other ITN members and representatives from the National Institutes of Health, and the Policy and Ethics Committee (PEC). The current membership of the NSC may be found on the ITN website. All Concept Proposals submitted to the ITN will be made available to the NSC for feedback and critical evaluation. On occasion, the NSC may solicit advice from *Ad Hoc* experts, where conflicts exist or sufficient expertise does not exist within the ITN. When necessary, the NSC may elect to contact the applicant for clarification of any information contained within his/her proposal.

Review criteria listed in **Section 4.2** will be used to determine the priority for Concept Proposals. Note that no pre-determined cut-off will be applied – ITN funding, new developments in the field and other factors will affect the number of proposals which are passed to the Full Application stage. Applicants will be notified generally within 4-6 weeks of the submission date, of one of the following three results:

> ***1) APPROVED*** – The proposed study appears to meet ITN criteria and will be considered in greater detail by the ITN. **Applicants are invited to submit a Full Application**.
>
> ***2) DEFERRED*** – The proposed work, while sound and of interest to the ITN, was not ranked at the highest priority at present. Additional information/clarification or more discussion will be needed before a final decision is made. These concepts will be considered again by the NSC. A Revised Concept Proposal may be requested.
>
> ***3) NOT APPROVED*** – The proposed work did not meet ITN criteria or was found to be of low priority. Applicants will be notified that the ITN will take no further action.

Authors of approved proposals will be invited to submit a more detailed Full Application (pending a successful Ethics Review, detailed in **Section 4.1.2**). Details for completing Full Applications will be provided to invited applicants.

4.1.2 Ethics Review

All successful Concept Proposals reviewed by the NSC and approved for Full Applications will be subject to review by the Policy and Ethics Committee (PEC). The PEC will consider the overall ethical soundness of the proposals and address any potential conflicts of interest relating to the proposed research. In particular, the PEC will determine if the proposal raises new or troubling ethical questions**,** including whether potential patient safety issues exist, and examine possible solutions to these problems. In addition, the PEC will examine the extent of any conflicts of interest and recommend appropriate solutions where available.

In cases where the PEC identifies potential ethical issues within a proposed study, the ITN and the PEC will work with the Investigator to resolve the identified issues. The PEC will provide assistance to the applicant in developing alternative strategies to allay the ethical issues identified. In rare cases where the PEC and lead investigator cannot resolve ethical concerns, the NSC will convene a special meeting to address the issues raised by the proposal and hold a binding vote on whether to rescind the invitation for a Full Application.

4.2 CONCEPT PROPOSAL REVIEW CRITERIA

The review process for Concept Proposals is targeted towards the identification of novel and important ***ideas***, rather than detailed scientific treatments of the precise methodologies. As such, the scientific basis for the project, and its implications in terms of clinical benefit and our understanding of tolerance, form a major portion of the review criteria. Projects chosen to be supported by the ITN will be those which hold significant potential to increase our understanding of, and our ability to induce and maintain, a state of clinical tolerance within the ITN's targeted disease areas.

The NSC will consider the criteria listed in the following sections – issues such as resource requirements, availability and selection of clinical sites and detailed protocol design (including statistical/sampling matters) will be considered subsequently during review of Full Applications.

4.2.1 Clinical Trials Concept Proposals

Concept Proposals for *clinical trials* will be evaluated by well-defined criteria, as described in **Table 1**. On completion of the Concept Proposal review process, the applicant will receive a summary of reviewers' comments.

Table 1: Factors considered in the review of *clinical trial* Concept Proposals.

Review Criteria
i) Scientific Basis and Rationale
ii) Clinical Implications
iii) Feasibility
iv) Mechanistic Studies and Tolerance Assays
v) Reputation and Capabilities of Investigators

Further detail on the review criteria are listed below:

i) ***Scientific Basis and Rationale*** – Are the proposed studies relevant to immune tolerance and the mission of the ITN? Is the therapeutic strategy scientifically sound and based on well-established scientific principles? Have pre-clinical studies been completed and to what extent do these pre-clinical studies demonstrate promising results regarding safety and potential efficacy? Are there novel aspects to the study? Do the studies proposed address important questions and do the studies appropriately address the question asked? Are there more effective methods of addressing the questions/hypotheses proposed?

ii) ***Clinical Implications*** – How will the proposed studies impact disease outcome? Will they offer insight for subsequent clinical development of related strategies? If successful, would the strategies have potential for extension to immune-mediated diseases other than those proposed?

iii) ***Feasibility*** – Are the proposed methods plausible? Are study goals realistic? Will a sufficient number of patients be available to accomplish the proposed study and can enrolment numbers be achieved? Are there any obstacles to acquiring the reagents needed for the study and can the ITN assist in overcoming these obstacles (e.g. supply or manufacture problems, intellectual property issues, etc)? How can the trial be incorporated into existing ITN facilities/resources?

iv) ***Mechanistic Studies and Tolerance Assays*** – Are the proposed assays likely to provide insights into the basis of unresponsiveness and possible tolerance induction in the proposed patients populations? Will the proposed studies contribute to our understanding of the tolerant state? Are new and novel assays proposed?

v) ***Reputation and Capabilities of Investigators*** – Do the investigators (applicant and collaborators) have a record of achievement in tolerance research and/or the diseases proposed for study? Do they have experience in performing clinical studies? Are there potential conflicts of interest in pursuing the proposed trials?

4.2.2 Tolerance Assay Concept Proposals

Concept Proposals for *tolerance assay* studies will be evaluated by well-defined criteria, as described in Table 2. On completion of the Concept Proposal review process, the applicant will receive a summary of reviewers' comments.

Table 2: Factors considered in the review of *tolerance assay* Concept Proposals.

Review Criteria
i) Scientific basis
ii) Relevance to Tolerance
iii) Feasibility
iv) Reputation and Capabilities of Investigators

Further detail on the review criteria are listed below:

i) ***Scientific Basis*** – Is the idea scientifically sound? Are the scientific principles of the method well-established? Have appropriate background studies been completed, yielding promising results? Do the studies proposed appropriately address the question asked?

ii) ***Relevance to Tolerance*** – Does the proposed assay offer unique information on the loss or induction of clinical tolerance? Or, does it provide a better or more efficient means of obtaining information already being routinely assessed by the ITN? Does the assay proposed extend the existing capabilities of the ITN? Will the assay offer insight for subsequent clinical development of tolerance strategies? Does the method offer potential as a routine clinical procedure?

iii) ***Feasibility*** – Are the proposed methods plausible? Are study goals realistic? Are there any obstacles to acquiring the reagents/equipment needed for the study and can the ITN assist in overcoming these obstacles (e.g. supply or manufacture problems, intellectual property issues, etc)? Is there expertise either within or outside the ITN to perform the proposed studies? Can the necessary clinical materials be gathered for the proposed work?

iv) ***Reputation and Capabilities of Investigators*** – Do the investigators (applicant and collaborators) have a record of achievement in assay development in the proposed area? Do the investigators have well-founded expertise in tolerance research? Do they have experience in performing mechanistic assays? Are there potential conflicts of interest in pursuing the proposed trials?

5. ADDITIONAL INFORMATION

5.1 TERMS OF ACCEPTANCE

Applicants successfully completing the review process and granted funding to pursue the described project will be assigned to the Clinical Trials Group or the Biomarker and Discovery Research Group. These groups will work with the lead investigator to develop the protocol. In some cases, the trial leader and proposal author may not be the same person.