

IMMUNE TOLERANCE NETWORK

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# **GUIDELINES FOR SUBMISSION**

## **Concept Proposals**

Information on the ITN submission and review process  
and instructions for online submission of Concept Proposals

Rev 2.0  
March 2005



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 Network policy & procedures.*

[www.immunetolerance.org/proposals](http://www.immunetolerance.org/proposals)

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# 1. Introduction

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## 1.1 Overview of the Application Process

The ITN application process is a two-stage process designed to expedite applications from proposal to protocol development. The two stages of the application process are:

1. **Concept Proposal** (submitted on-line)
2. **Full Application** (by invitation only after approval of Concept Proposal)

Applicants submit a short 5-page Concept Proposal to the ITN that provides reviewers with basic conceptual information and justification. Applicants whose proposals are of interest to the ITN will then be asked to submit a more complete Full Application for review.

Applicants should note that the ITN peer review and study development mechanism is a highly interactive, *iterative* process whereby applicants continually refine their proposed research to develop the most appropriate means for addressing their clinical and mechanistic hypotheses. The process allows investigators to take advantage of the significant knowledge and experience of ITN members and staff when designing their study. For instance, during the Full Application review, investigators meet with the ITN reviewers in a Q&A session designed to answer any outstanding questions concerning the applicants proposal. Unlike a traditional R01 application, in this more flexible, collaborative mechanism, the ITN process can result in significant modifications in the design of studies as they progress through Concept Proposal review, Full Application preparation and review and protocol development.

## 1.2 Concept Proposal Submissions

Concept Proposals are abbreviated applications 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. Applicants must download, complete and submit the appropriate Concept Proposal template form available on the ITN website. Instructions for completing and uploading these forms are described in this document.

Applicants submitting Concept Proposals will typically be notified of the results of the review process within 6-8 weeks. Successful applicants will be invited to submit a more comprehensive Full Application prior to a predetermined deadline.

## 1.3 Concept Proposal Deadlines

There is no deadline for submission of Concept Proposals - they are accepted throughout the year, with review cycles taking place several times per year.

## 1.4 Contact Information

Questions regarding the content of Concept Proposals or the ITN peer-review process should be directed to:

**Anita Corman Weinblatt, Ph.D.**  
Executive *Director of Scientific Review*  
Immune Tolerance Network  
4800 Montgomery Lane  
Suite 300  
Bethesda, MD 20814

Phone: 240.235.6132  
Facsimile: 240.497.0351  
E-mail: [osr@immunetolerance.org](mailto:osr@immunetolerance.org)

Technical support for online submission of Concept Proposals should be directed to [websupport@immunetolerance.org](mailto:websupport@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

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### 2.1 General Research Guidelines

The Immune Tolerance Network accepts Concept Proposals for clinical trials and tolerance assays applied to islet, liver & kidney transplantation, autoimmune diseases 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 must 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 are also entertained.

Although the ITN will accept Concept Proposals for all protocols meeting these requirements, priority may be given to those proposals for Phase I-II trials with a 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.

*Key areas of interest to the Network Steering Committee are:*

- Antigen *non-specific* approaches that work through the TCR, including anti-CD3 and anti-CD4 monoclonal antibodies (mAbs).
- Antigen *specific* approaches that work through the TCR, including altered peptide ligands and MHC/peptide complexes
- Combinations of established drugs and/or experimental therapies
- Costimulatory blockade using approaches with demonstrated safety and potential efficacy in pre-clinical model systems
- Soluble mediator directed immunomodulation (e.g. cytokines, chemokines and their receptors)
- Combinations of approved therapeutic agents

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

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

### 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. Intramural government researchers are also encouraged to apply for ITN support.

If you are unsure whether you qualify under these above guidelines, please contact the [Office of Scientific Review](#).

In some instances, principal investigators may choose to submit a proposal for a clinical study in which they themselves will not participate as a clinical investigator (i.e. Clinical site leader). The ITN welcomes such proposals and encourages the applicant to contact one or two suitable collaborators to assist in development of the clinical strategy. In addition, the ITN can also assist in identifying clinical collaborators.

### **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 Network 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 Network business to the extent permitted by law and will only be maintained in Network 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 Network sponsored trials.

### **2.3 Human Subjects**

All studies involving human subjects must conform to the principles of the Declaration of Helsinki of the World Medical Association and must meet all of the requirements governing informed consent of the country in which the study is performed. All research supported by the ITN must conform to the National Institutes of Health's policy that women and members of minority groups and their subpopulations must be included in all NIH-supported biomedical and behavioural research projects involving human subjects, unless a clear and compelling rationale shows that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances may be made based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. This policy applies to research subjects of all ages.

In accordance with NIH policy, children (i.e., individuals under the age of 21) must be included in all human subjects research, unless there are clear and compelling reasons for exclusion. Therefore, proposals for research involving human subjects must include a description of plans for including children. If children will be excluded from the research, the application or proposal must present an acceptable justification for the exclusion.

## 3. Preparing & Submitting Your Concept Proposal

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### 3.1 General Instructions

To submit a Concept Proposal to the ITN, applicants must download and fill out a short, ~5 page proposal on a standard template form. The completed template for is then uploaded through the ITN website submission system. Under normal circumstances, online submission should only take 5-10 minutes

Applicants must complete their Concept Proposal on the appropriate ITN-supplied template, available in either Adobe PDF or Microsoft Word formats through the ITN website. Please be sure that you are using the correct set of forms as three different versions are available: for clinical trials, tolerance assay projects and revised proposals.

Concept Proposal template forms can be downloaded from the ITN website or via the links below. Please use the MS Word template forms whenever possible. A Rich Text format version of the templates are provided as an alternative for users without the ability to edit MS Word files.

#### Clinical Trial Concept Proposal Template

*Use one of the following if you are proposing a clinical trial. For both solicited and unsolicited proposals. For new proposals only.*

- MS Word: [http://www.immunetolerance.org/proposals/downloads/ITN\\_CPForm\\_clinical.doc](http://www.immunetolerance.org/proposals/downloads/ITN_CPForm_clinical.doc)
- Rich Text Format: [http://www.immunetolerance.org/proposals/downloads/ITN\\_CPForm\\_clinical.rtf](http://www.immunetolerance.org/proposals/downloads/ITN_CPForm_clinical.rtf)

#### Tolerance Assay Concept Proposal Template

*Use one of the following 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. For both solicited and unsolicited proposals. For new proposals only.*

- MS Word: [http://www.immunetolerance.org/proposals/downloads/ITN\\_CPForm\\_assay.doc](http://www.immunetolerance.org/proposals/downloads/ITN_CPForm_assay.doc)
- Rich Text Format: [http://www.immunetolerance.org/proposals/downloads/ITN\\_CPForm\\_assay.rtf](http://www.immunetolerance.org/proposals/downloads/ITN_CPForm_assay.rtf)

#### Revised Concept Proposal Template

*Complete and submit this form only if you are responding to an ITN request for a Revised Concept Proposal.*

- MS Word: [http://www.immunetolerance.org/proposals/downloads/ITN\\_CPForm\\_Revised.doc](http://www.immunetolerance.org/proposals/downloads/ITN_CPForm_Revised.doc)
- Rich Text Format: [http://www.immunetolerance.org/proposals/downloads/ITN\\_CPForm\\_Revised.rtf](http://www.immunetolerance.org/proposals/downloads/ITN_CPForm_Revised.rtf)

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

### 3.2 Completing the Clinical Concept Proposal Template

#### 3.2.1 Cover Page

**1A. Title:** Enter the title of your proposal in the space provided. A maximum of 120 characters is allowed.

**1B/1C. Principal Investigator/Address:** Complete the sections identifying yourself as the Principal Investigator (P.I.) 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.

**1D. 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.

**1E. Previous Tracking Number:** 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 not complete this version of the Concept Proposal forms, rather, complete the [“Revised Concept Proposal” template form](#).

### 3.2.2 Section 2: Study Details

**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 Tolerance Assay Group will collaborate with the P.I. 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 generally describe the methods that could be used to address them.

If you intend to investigate a particular scientific hypothesis, it 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, noting potential use of ITN core facilities, where applicable.

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: i) the proposed patient populations do exist and could be enrolled in sufficient numbers to provide useful information; and ii) 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 Scientific Review](#) 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]*

### 3.3 Completing the Tolerance Assay Concept Proposal Template

#### 3.3.1 Cover Page

**1A. Title:** Enter the title of your proposal in the space provided. A maximum of 120 characters is allowed.

**1B/1C. 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.

**1D. 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.

**1E. Previous Tracking Number:** 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 not complete this version of the Concept Proposal forms, rather, 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 Scientific Review](#) 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 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]*

**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 Template

**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, 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.


\*\*\*Once you have completed the online submission process, you must send copies of the files listed in Section D to the Office of Scientific Review at [osr@immunetolerance.org](mailto:osr@immunetolerance.org). Please be sure to reference your tracking number in all correspondence regarding your proposal.

### 3.5 Online Submission of a New Concept Proposal

Note that you must repeat the online procedures for each Concept Proposal you wish to submit.

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, open your web browser to the following URL: [www.immunetolerance.org/proposals/submit](http://www.immunetolerance.org/proposals/submit).

Click on "Submit a NEW Concept Proposal" in the upper right hand corner of the screen. This will bring up the New Proposal Submission Form.

**[HINT: When completing the online forms, if you have questions about any of the fields, click on the  icon next to the field for additional help.]**


For each Concept Proposal you wish to submit:

1. Complete the "Principal Investigator" section of the online form. The Principal Investigator will receive all information pertaining to the review of your proposal. Be sure to use the email address that you check most frequently.
2. Complete the "Proposal Information" section on the form to the left. If this proposal is being submitted in response to an RFA, enter the number, otherwise, leave that field blank. Your short description should be no longer than 75 words. If your proposal covers more than one Clinical area, select all that apply.
3. Upload your completed off-line proposal forms or RFA response. Except for RFA responses, you must use the appropriate ITN off-line template. Click "Browse," locate and select the file on your computer and continue to the next step.
4. Please read the authorization statement. Indicate your approval by checking the adjacent box. Proposals will not be accepted if this box is left unchecked.
5. When you are ready to proceed with submission, please review all of your information for accuracy and ensure all required fields are complete. When you are satisfied, click the "Submit" button (only click once – there may be a short delay while your form uploads, depending on the speed of your connection and the size of the file). Clicking more than once can result in multiple submissions).
6. Once the upload is complete you will be forwarded to a confirmation page, where you must confirm your entries. Carefully check the information contained on this page, if you are satisfied the information is accurate, click the "Confirm" button to finalize your submission (press only once).
7. Following confirmation, you will be forwarded to a web page containing a record of your submission. You should print this page for your records and make a note of the tracking number. A copy of your tracking number will also be emailed to the address you supplied in the online forms.

### **3.6 Online Submission of a Revised Concept Proposal**

Before submitting your revised 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, open your web browser to the following URL: [www.immunetolerance.org/proposals/submit](http://www.immunetolerance.org/proposals/submit).

Click on "Submit a REVISED Concept Proposal" in the upper right hand corner of the screen. This will bring up the Revised Proposal Submission Form.

**[HINT: When completing the online forms, if you have questions about any of the fields, click on the  icon next to the field for additional help.]**

Complete the following steps to submit your proposal online:

1. In the appropriate fields, enter the tracking number of the original proposal that this revision is based upon and the email address that you used for this proposal and click the "Log-on" button. [Note: If you cannot locate your tracking number, contact the [Office of Scientific Review](#).] This will bring up a page that lists your contact information and a summary of the original proposal.
2. Review the information in section "1: Principal Investigator Information". [Note: For security reasons, this information cannot be changed online. However, if any of this information has changed or is incorrect, please contact the Office of Scientific Review prior to proceeding with your submission.]

3. Review the information in section "2. Proposal Information". If you require changes to any of the information in this section, you may do so in the web form fields.
4. In section 3, "Revised Proposal Upload", you must upload your completed revised proposal template form. Click "Browse," locate and select the file on your computer and continue to the next step.
5. Please read the authorization statement in Section 4. If you have questions, please contact the ITN Office of Scientific Review. Indicate your approval by checking the adjacent box. Proposals will not be submitted if this box is left unchecked.
6. When you are ready to proceed with submission, please review all of your information for accuracy and ensure all required fields are complete. When you are satisfied, click the "Submit" button. Following confirmation, you will be forwarded to a web page containing a record of your submission. You should print this page for your records and make a note of the tracking number. A copy of your tracking number will also be emailed to the address you supplied in the online forms..
7. If you indicated on the Revised template form that you are submitting figures or tables as attachments, these should be emailed to the Office of Scientific Review at [osr@immunetolerance.org](mailto:osr@immunetolerance.org)

## 4. Network Review Process

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### 4.1 How Proposals are Reviewed

#### 4.1.1 Scientific Review

The Immune Tolerance Network submission and review process has been designed to expedite the funding of new research projects by the ITN. The two-stage application process has an associated two-stage review mechanism. The Concept Proposal review serves to minimize the work load on the ITN review panel by extending invitations for Full Applications only to authors of well-planned, well developed ideas and/or strategies that fall squarely within the ITN's mandate. This "triage" process ensures rapid and judicious consideration of all submitted Full Applications.

Concept Proposals are reviewed several times per year by the Network Steering Committee (NSC), a 29 member panel comprised of the ITN Director, Clinical and Tolerance Assay Scientific Advisors 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 Network Steering Committee (NSC) for feedback and critical evaluation. On occasion, the NSC may solicit advice from *Ad Hoc* experts, where conflicts exist or appropriate 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 rank Concept Proposals in order of priority. Note that no pre-determined cut-off will be applied – Network 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 following the initiation of a review cycle, of one of the following three results:

- 1) APPROVED** – The proposed work appears to meet network 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 Network Steering Committee. A Revised Concept Proposal may be requested..
- 3) NOT APPROVED** – The proposed work did not meet Network 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 of this application and the criteria for review are available on the ITN website and in the ITN's "Guidelines for Submission – Full Applications" document. After submission, applicants will also be required to present a short summary presentation of their proposal at the subsequent Network Steering Committee meeting, prior to the final decisions.

The ITN will make available a number of resources to assist the applicant in the preparation of Full Applications. Guidance on statistical and sample size considerations will be provided at the applicant's request. Further assistance in matters of study design, complementary mechanistic and tolerance assay studies, and ethical considerations will be provided by the Clinical Advisory Committee, the Tolerance Assay Group and the Policy and Ethics Committee, respectively. In addition, an ITN advisor will work closely with the Principal Investigator to guide him/her through the process.

Formal review of the Full Applications will be performed by the ITN Steering Committee (NSC),. The Network Steering Committee will rank all applications according to priority, and identify those protocols to be implemented by the ITN. NSC decisions will be subject to budgetary approval by the Network Executive Committee. Authors of Full Applications will generally be notified of the results of the review process within 8 weeks of the submission deadline. Successful applicants will work with the ITN Clinical Trials Group to begin protocol development.

#### **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). Note that applicants will be notified of the request for a Full Application prior to the completion of the ethics review, in order to allow applicants sufficient time to prepare their Full Applications. The PEC will complete its review and forward a summary report to applicants within two weeks subsequent to notification.

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 problem. 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, a report detailing the issues will be forwarded to the applicant, with a request to address the specific issues in an addendum to their Full Application. The PEC will provide assistance to the applicant in preparing this addendum and in developing alternative strategies to allay the ethical issues identified. In rare cases where the PEC and lead investigator can not resolve ethical concerns, the Network Executive Committee 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 Network Steering Committee will consider only those 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 and after the 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.

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#### Judgment Criteria

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- i) Scientific Basis and Rationale
  - ii) Clinical Implications
  - iii) Feasibility
  - iv) Mechanistic Studies & 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 Immune Tolerance Network? 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 Network facilities/resources?
- iv) **Mechanistic Studies & 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? Is there thoughtful use of assays provided by network? 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.

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#### Judgment Criteria

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- i) Scientific basis
  - ii) Relevance to Tolerance
  - iii) Feasibility
  - iv) Reputation & 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 & 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?