

NIAID Policy: Investigator-Initiated Clinical Trials

Notice Number: NOT-AI-16-084

Key Dates

Release Date: September 28, 2016

Related Announcements

[PAR-16-272](#)

[PAR-16-269](#)

[PAR-16-270](#)

[PAR-16-271](#)

Issued by

National Institute of Allergy and Infectious Diseases ([NIAID](#))

Purpose

This Notice informs potential applicants of changes in NIAID policies and procedures for the acceptance, peer review, and funding of investigator-initiated clinical trials. It supersedes the policies described in NOT-AI-05-021 and NOT-AI-10-024. Detailed information may be found at the NIAID Investigator-Initiated Clinical Trials website (see <https://www.niaid.nih.gov/grants-contracts/investigator-initiated-clinical-trial-resources>), as well as in each of the related Funding Opportunity Announcements (see below).

NIAID will support implementation of investigator-initiated clinical trials through milestone-driven research project grants (R01) and cooperative agreements (U01, U44). Determination of the appropriate instrument is based on the assessment of risk as delineated in the NIAID-specific criteria stated below. Clinical trial planning grants (R34) are not required, but are available as an option to all investigators proposing investigator-initiated clinical trials. If it can be demonstrated that sufficient planning has occurred such that the trial is ready to move forward to implementation, as defined by NIAID-specific criteria, direct submission of the implementation R01, U01 or U44 is permitted. Investigator-initiated clinical trials will only be accepted by NIAID via the Funding Opportunity Announcements (FOAs) and future reissuances of these FOAs listed below unless explicitly stated in the Funding Opportunity Announcement (FOA).

Prior consultation with NIAID is strongly encouraged for submission of an application for the R34 planning grant, the R01 implementation grant, the U01 implementation cooperative agreement or the U44 SBIR Phase II clinical trial implementation cooperative agreement; this consultation applies to both new and resubmission applications. NIAID staff will consider whether the proposed clinical trial meets the goals and mission of the Institute and whether it is appropriate to conduct it as an investigator-initiated clinical trial, but will not evaluate the technical and scientific merit of the proposed trial.

Technical and scientific merit will be determined during peer review. NIAID staff will also advise applicants on whether the proposed trial is considered high risk and should be submitted as an R01 or cooperative agreement. Applicants whose projects do not meet NIAID's programmatic needs or are not appropriate as investigator-initiated clinical trials, will be strongly encouraged to consider other Funding Opportunities

All institutions eligible for NIH support are eligible to submit applications for investigator-initiated planning R34 or implementation U01 and R01 awards. Eligible institutions include, but are not limited to, the following broad categories: foreign and domestic institutions of higher education, for-profit institutions, not-for-profit institutions and governmental entities. For the U44 implementation awards, only US small business concerns are eligible to submit applications.

Each NIAID Clinical Trial Implementation award will support the implementation of a single clinical trial that may include more than one intervention. Applications that include more than one clinical trial will not be supported through the FOAs listed below.

NOTE: Mechanistic studies are supported as part of the application for all clinical trials sponsored by the Division of Allergy Immunology and Transplantation (DAIT), NIAID. DAIT will not support applications without the inclusion of mechanistic studies.

For those trials or studies that are coupled to other projects or research objectives, for example, by inclusion in a multi-project application or inclusion as a mechanistic study associated with a trial, the above considerations apply.

Grant and cooperative agreement applications that propose clinical trials submitted in response to a Request for Applications (RFA) and contract proposals that propose clinical trials submitted in response to a Request for Proposals (RFP) will follow the guidelines and instructions in the RFA or RFP, respectively.

Clinical Trial Implementation (R01, U01, U44)

NIAID will accept, peer review, and consider for funding R01, U01, and U44 applications for implementation of investigator-initiated clinical trials. However, consultation with NIAID is highly recommended before submission. Eligible applicants are reminded that the budget should reflect sufficient funds to support independent study monitoring, regulatory submissions, quality management, safety oversight activities and Clinical Trial insurance, as appropriate. All clinical trial implementation R01, U01 and U44 applications in the below FOAs will undergo peer review by special emphasis panels convened by NIAID. All clinical trial implementation applications must include both NIAID-determined general milestones and investigator-determined, protocol-specific milestones in a milestone plan, which will be incorporated into the terms of award; successful attainment of milestones will be considered during assessment of progress under the R01, U01 or U44 award. In the case of U01 and U44 implementation awards, review of milestone attainment will be conducted upon receipt of each interim progress report, the frequency of which will be determined for each trial and incorporated into the corresponding terms of award. In the case of R01 implementation awards, review of milestone

attainment will coincide with the annual progress review. At the discretion of NIAID, external reviewers may be called upon to assist with periodic review of progress.

Cooperative Agreements (U01)

If the application proposes a clinical trial determined to be high-risk, it must be submitted, peer reviewed, and awarded as a cooperative agreement. For the purposes of this policy, NIAID defines high-risk clinical trials as those that have one or more of the following attributes:

- involves a non-routine intervention, that is, an intervention or non-routine use of an intervention that would not otherwise be provided for the condition under study in the local facility where the study is being conducted;
- involves administration of an unlicensed product; or
- involves administration of a licensed product for an unapproved indication.

If planning activities related to the trial have been completed, the investigator is encouraged to consult with NIAID if they should submit a U01 application. The following documents, which will indicate that planning is completed, should be available at the time of consultation:

- the complete clinical protocol;
- informed consent and, if applicable, assent forms;
- a statistical analysis plan;
- a plan for acquisition and administration of study agent(s);
- the Investigator's Brochure or equivalent for study products;
- documentation of adequate co-funding, if applicable and necessary for completion of the trial;
- a plan for submission of regulatory documents to appropriate regulatory authorities, for example, IND and IRB submissions;
- a listing that includes identification and qualifications of clinical trial sites, pharmacies and laboratories;
- a Table of Contents for the Manual of Operations;
- a comprehensive laboratory plan;
- a data and safety monitoring plan; and
- a site quality management plan.

If the materials listed above will not be available at the consultation phase, the investigator should consider submitting an application for a subsequent due date or for the R34 planning grant.

Research Project Grants (R01)

Clinical trials that are not deemed high-risk as defined above may be submitted as milestone-driven R01 research project grant applications.

If planning activities related to the trial have been completed, the investigator is encouraged to consult with NIAID to see if they are ready to submit an R01 application.

The following documents, which will indicate that planning is completed, must be available at the time of consultation:

- the complete clinical protocol;
- informed consent and, if applicable, assent forms;
- a statistical analysis plan;
- a listing that includes identification and qualifications of clinical trial sites, pharmacies and laboratories;
- a Table of Contents for the Manual of Operations;
- a comprehensive laboratory plan;
- a data safety monitoring plan; and
- a site quality management plan.

If the materials listed above will not be available at the consultation phase, the investigator should consider submitting an application for a subsequent due date or for the R34 planning grant.

Small Business Innovation Research Cooperative Agreement (U44)

If the application proposes a clinical trial from a United States small business concern (SBC), it must be submitted, peer reviewed, and awarded as a cooperative agreement.

If planning activities related to the trial have been completed, the investigator is encouraged to consult with NIAID if they should submit a U44 application. The following documents, which will indicate that planning is completed, should be available at the time of consultation:

- the complete clinical protocol;
- informed consent and, if applicable, assent forms;
- a statistical analysis plan;

- a plan for acquisition and administration of study agent(s);
- the Investigator's Brochure or equivalent for study products;
- documentation of adequate co-funding, if applicable and necessary for completion of the trial;
- a plan for submission of regulatory documents to appropriate regulatory authorities, for example, IND and IRB submissions;
- a listing that includes identification and qualifications of clinical trial sites, pharmacies and laboratories;
- a Table of Contents for the Manual of Operations;
- a comprehensive laboratory plan;
- a data safety monitoring plan; and
- a site quality management plan.

If the materials listed above will not be available at the consultation phase, the investigator should consider submitting an application for the R34 planning grant.

Clinical Trial Planning Grants (R34)

NIAID supports clinical trial planning (R34) grants for complete planning and design of, and preparation of documentation for all investigator-initiated clinical trials. Prior consultation with NIAID is highly encouraged for submission of an R34 application. R34 applications to the FOAs below will undergo peer review by special emphasis panels convened by NIAID. For R34 awardees who, based on the results of the planning effort, propose to implement the trial, the product of the R34 will be all of the information and documents required for submission of an application for a clinical trial implementation research project grant (R01) or cooperative agreement (U01, U44). However, the R34 is not a pre-requisite for submission of either the R01, U01 or U44 implementation application.

The R34 grant will provide support for a number of planning activities, including, but not limited to:

- establishment of the research team;
- identification of collaborators and enrollment sites;
- design of the study;
- development of the complete clinical protocol;
- development of the statistical analysis plan;
- development of the data management plan;

- development of the informed consent(s) and assent form(s) (if applicable);
- development of the Investigator's Brochure or equivalent;
- development of a manual of operations including details, validation, and quality control for any non-standard clinical or laboratory/mechanistic testing that will be performed;
- development of a plan for the acquisition and administration of study agent(s);
- obtaining required Office of Human Research Protections (OHRP) assurances if not already in place;
- development of the milestone plan;
- determination of whether an application for an IND/IDE should be submitted to the FDA (or relevant regulatory agency outside the US), and who will hold the IND/IDE;
- development of a complete set of suitable documents for submission to the appropriate regulatory authorities;
- development of a data and safety monitoring plan (i.e., DSMB, SMC, and/or ISM);
- development of a detailed budget for conduct and completion of the clinical trial including funding for preparation of a final study report; and
- development of training materials and training plans for study staff.

The R34 Clinical Trial Planning Grant is not designed for the collection of preliminary or prospective data or for the conduct of pilot studies to support the rationale for a clinical trial.

NIAID reserves the right to specify whether an application for an IND/IDE should be submitted to the FDA (or relevant regulatory agency outside the US), as well as the right to hold the IND/IDE. NIAID also reserves the right to determine the composition of the DSMB/SMC and who will convene it (see <https://www.niaid.nih.gov/research/data-and-safety-monitoring-boards>)

In most cases, it is expected that receipt of an R34 grant will lead to the timely submission of an application for support to implement the clinical trial, incorporating the elements developed under the planning grant. Nevertheless, prior consultation with NIAID is still encouraged for subsequent submission of a U01 or U44 cooperative agreement application or an R01 research project application.

In reference to this NIH Guide Notice, NIAID has published four related Funding Opportunity Announcements:

[PAR-16-272](#), NIAID Clinical Trial Planning Grants (R34), provides guidance on the submission, peer review, and award of the Clinical Trial Planning Grant.

[PAR-16-269](#), NIAID Clinical Trial Implementation Research Project Grants (R01), provides guidance on the submission, peer review, and award of the Clinical Trial Implementation Research Project Grant.

[PAR-16-270](#), NIAID Clinical Trial Implementation Cooperative Agreements (U01), provides guidance on the submission, peer review, and award of the Clinical Trial Implementation Cooperative Agreement.

[PAR-16-271](#), NIAID SBIR Phase II Clinical Trial Implementation Cooperative Agreement (U44), provides guidance on the submission, peer review, and award of the Small Business Innovation Research (SBIR) Cooperative Agreement – Phase II and Fast Track Only.

Inquiries

Please direct all inquiries to:

Inquiries concerning the overall NIAID policy for investigator-initiated clinical trials should be sent to:

NIAID DEA Policy

Email: DEAPolicyShop@niaid.nih.gov

Inquiries regarding programmatic, peer review and grants management issues should be sent to the staff contacts listed in the appropriate FOAs.