Guidance for Complying with the NIAID Clinical Terms of Award

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I. Overview

The National Institute of Allergy and Infectious Diseases (NIAID) supports clinical trials and studies involving human subjects and must ensure compliance with human subjects regulations.

The Clinical Terms of Award requirements are in addition to:

- Instructions in the PHS 398 Grant Application for paper application.
- Supplemental Instructions for Preparing the Human Subjects Section of the Research Plan in the Grant Application Guide for electronic application.
- PHS 2590 Non-Competing Grant Progress Report.
- NIAID Clinical Trial Implementation (U01) Cooperative Agreement program announcement.
- NIAID requests for proposals, requests for applications, program announcements.
- Other U.S. state and local regulations.
- For studies conducted outside the U.S., regulations of a host country. If regulations differ, the more restrictive regulation applies.

To enable NIAID to properly monitor studies, additional information is required beyond that normally submitted with a competitive application, contract proposal, or annual grant progress report. These Clinical Terms of Award define the awardee's responsibilities for

submitting required documentation to NIAID and other NIH offices if applicable. They apply to all NIAID-supported clinical research and to each study supported by an award.

Clinical investigators must include the following in an application or proposal:

1) Research plan, including protocol (if required by the division).

2) Data and safety monitoring plan for clinical trials.

   Independent monitoring is essential for all clinical trials involving investigational drugs, devices, or biologics and other clinical research, including research of licensed products, perceived to involve more than a minimal risk. Data and safety monitoring is intended to provide an independent objective review of the conduct of the research, interim safety and efficacy data, and progress towards achieving the goals of the study.

   NIH policies require:

   - Applications and proposals that propose studies with more than minimal risk to human participants include a plan for data and safety monitoring.
   - Protocols for clinical trials include detailed plans for monitoring.
   - Phase III trials have an independent data and safety monitoring board (DSMB).

As soon as an award is decided, an NIAID program or project officer will advise the awardee to submit the items described above. Forward all submissions electronically or by mail to the responsible program or project officer according to the processes of the awarding division.

The terms will be summarized and attached to the Notice of Grant Award or addressed in the terms of the contract.

II. Submission Requirements Before Enrolling Patients

Before enrolling patients, the awardee will submit the following (as applicable) to the responsible NIAID program or project officer for review and approval according to the review mechanisms applicable to the awarding division.

A. Clinical Protocol

The awardee will submit the IRB- or IEC-approved protocol identified by version number, date, or both, including details of study design, proposed interventions, patient eligibility, and exclusion criteria. Unless otherwise directed, NIAID requires the clinical protocol before enrollment begins.

A protocol for a clinical trial must adhere to International Conference on Harmonisation E6: Good Clinical Practices, Section 6, and must address the following issues related to safety:

- Plans for managing side effects.
- Procedures for assessing and reporting adverse events.
- Plans for data and safety monitoring and monitoring of the clinical study site, pharmacy, and laboratory.

B. Institutional Review Board or Independent Ethics Committee Approval

The awardee is responsible for submitting all IRB or IEC notifications of protocol approval to the responsible NIAID program or project officer, including the name of the IRB or IEC, its Office of Human Research Protection (OHRP) registration number, and OHRP federalwide assurance number.

Where other institutions are involved in the research, e.g., a multicenter study, each institution's IRB or IEC should review and approve the protocol. Provide written documentation of approval from each institution to NIAID. Include a copy of the IRB- or IEC-approved informed consent document identified by version number, date, or both, and dates it is valid.

Some countries have a national IRB or IEC that require protocol and informed consent approval in addition to or in lieu of local IRB or IEC approval. For countries with multiple levels of IRB review, provide NIAID written documentation of protocol approval from each IRB along with a copy of the IRB or IEC approved informed consent document, identified by version number, date, or both and dates it is valid.

C. Data and Safety Monitoring

Include plans for independent safety monitoring in an application or proposal for research involving more than minimal risk. Final decisions regarding the type of monitoring to be used will be made jointly by NIAID and the awardee before enrolling patients. Discussions with the responsible NIAID program or project officer regarding appropriate safety monitoring and approval of the final monitoring plan by NIAID will occur before patient enrollment begins. These discussions may involve the appointment of one of the following.

- **Independent Safety Monitor** – a physician or other appropriate expert who is independent of the study and available in real time to review and recommend appropriate action regarding adverse events and other safety issues.
- **Independent Monitoring Committee (IMC) or Safety Monitoring Committee (SMC)** – a small group of independent investigators and biostatisticians who review data from a particular study.
- **Data and Safety Monitoring Board (DSMB)** – an independent committee charged with reviewing safety and trial progress and providing advice with respect to study continuation, modification, and termination. The awardee may be required to use an established NIAID DSMB or to organize an independent DSMB. A DSMB must review all phase III clinical trials, including those studying licensed products; other trials may require DSMB oversight as well.

After organizing a monitor or monitoring board, submit a description of the monitor or board, its charter or operating procedures, proposed meeting schedule, plan for review of adverse events, and roster, and *curriculum vitae* from all members. NIAID must approve all documents before you enroll patients.

Go to NIAID Principles for Use of a Data and Safety Monitoring Board (DSMB) for Oversight of Clinical Trials Policy.

D. Investigational New Drug or Investigational Device Exemption Requirements

Consistent with federal regulations, clinical research in humans involving the use of investigational therapeutics, vaccines, or other medical interventions (including licensed products or devices used for a purpose other than that for which they were licensed) under a research protocol should be performed under a U.S. Food and Drug Administration (FDA) IND or IDE. Exceptions must be granted in writing by FDA.

If a proposed clinical trial will be performed under an IND or IDE, the awardee must provide NIAID with the name and institution of the IND or IDE sponsor, the date the IND or IDE was filed with the FDA, the FDA IND or IDE number, any written comments from the FDA, and written responses to those comments. In addition, submit risk information (e.g., product development plan, investigator's brochure, or information obtained through published literature review or other venue).

The awardee must wait 30 days from FDA receipt of initial IND or IDE application before enrolling patients. The awardee must notify NIAID if FDA places the study on clinical hold and provide NIAID any written comments from FDA, written responses to the comments, and documentation in writing that the hold has been lifted. The awardee must not use grant or contract funds during a clinical hold.

For all intervention studies, the awardee must obtain regulatory oversight by either FDA (under an IND or IDE) or the regulatory body of the country where the research is to be conducted. In the case of a foreign regulatory body, the awardee must provide NIAID with written documentation from the regulatory body that the awardee is in compliance with local regulatory laws.

E. Recombinant DNA Advisory Committee and Institutional Biosafety Committee

For clinical trials involving the deliberate transfer of recombinant DNA or DNA or RNA derived from recombinant DNA into human research participants (human gene transfer), the awardee must provide NIAID written documentation that the NIH Office of Biotechnology Activities (OBA) Recombinant DNA Advisory Committee (RAC) review process has been completed and that institutional biosafety committee approval (from the clinical trial site) has been obtained. See the NIH Guidelines for Research Involving Recombinant DNA Molecules.

F. Requirements for Training in Human Subjects Protections

The awardee is responsible for submitting written documentation to NIAID that the awardee and all study staff responsible for the design or conduct of the research have received training in the protection of human subjects.

NIAID staff will forward comments to the awardee within three weeks of receipt of the above information. The awardee must address in writing all safety, regulatory, ethical, and conflict of interest concerns raised by NIAID staff to the satisfaction of NIAID before enrolling participants. The IRB or IEC must review and approve any changes to the protocol before participant enrollment.

III. Ongoing Reporting Requirements

Awardees must comply with the Clinical Terms of Award throughout the course of the research. These requirements include the following:

A. Institutional Review Board or Independent Ethics Committee Actions

Unless otherwise directed, the awardee is responsible for submitting to NIAID all IRB or IEC notifications of protocol renewal, amendment, suspension, and termination. When other institutions are involved in the research (e.g., a multicenter study), each institution's IRB or IEC should review and approve the protocol. The IRB for each site will conduct continuing reviews of research at intervals appropriate to the degree of risk, but not less than once per year, as described in 45 CFR 46.109.

1) Continuing review and approval

The awardee is required to submit to the responsible NIAID program or project officer (and contracting officer, if applicable) documentation of the continuing IRB or IEC review and approval annually, at a minimum. The submission must include the following:

- A copy of the IRB or IEC letter of renewal.
- A copy of the current IRB or IEC approved protocol, identified by version number, date, or both (unless otherwise directed).
- A copy of the current IRB or IEC approved informed consent document, identified by version number, date, or both, and dates it is valid.

For countries with multiple levels of IRB review, written documentation of protocol review and approval from each IRB should be provided to NIAID, along with a copy of the IRB- or IEC-approved informed consent document, identified by version number, date, or both, and dates it is valid.

2) Amendment, suspension, termination

The awardee is required to submit to the responsible NIAID program officer (and contracting officer, if applicable) written documentation of any changes in IRB or IEC approval status, including the following:

- All amendments or changes to the protocol, identified by version number, date, or both. (Except in the case of imminent danger to participants, the IRB or IEC must approve changes to the protocol before they are implemented clinically.)
- All changes in informed consent documents, identified by version number, date, or both. The IRB or IEC must approve changes to the protocol before they are implemented clinically.
- Termination or temporary suspension of patient accrual.
- Termination or temporary suspension of the protocol.
- Any change in IRB or IEC approval status.
- Any other problems or issues that could affect the participants of the study.

Notification of any of the above changes must be made within three working days by email or fax, followed by a letter signed by the institutional business official, detailing the change of status notification to the IRB or IEC, and a copy of IRB or IEC responses.

B. Data and Safety Monitoring Reviews

When a monitor or monitoring board is organized, the awardee will submit written summaries of all reviews conducted by the monitoring group to the responsible NIAID program officer within 30 days of reviews or meetings. When reviews are frequent, semiannual or quarterly reports are sufficient.

C. Safety Reporting Requirements

1) IND or IDE reporting

The awardee must notify the responsible NIAID program or project officer in writing if the FDA places the study on clinical hold at any time during the conduct of the clinical trial.

2) IND or IDE safety reporting

Under the IND or IDE, the sponsor is required to provide the FDA with safety reports of serious adverse events. Under the Clinical Terms of Award, the awardee must submit copies to the responsible NIAID program officer as follows.

- *Expedited safety report of unexpected or life-threatening experience or death:* A copy of any report of unexpected or life-threatening experience or death associated with the use of an IND drug, which must be reported to FDA by telephone or fax as soon as possible but no later than seven days after the IND sponsor's receipt of the information, must be submitted to the NIAID program or project officer within 24 hours of FDA notification.
- *Expedited safety reports of serious and unexpected adverse experiences:* A copy of any report of unexpected and serious adverse experience associated with use of an IND drug or any finding from tests in laboratory animals that suggests a significant risk for human subjects, which must be reported in writing to FDA as soon as possible but no later than 15 days after the IND sponsor's receipt of the information, must be submitted to the NIAID program or project officer within 24 hours of FDA notification.
- *IDE reports of unanticipated adverse device effect:* A copy of any reports of unanticipated adverse device effect submitted to FDA must be submitted to the NIAID program or project officer within 24 hours of FDA notification; and
- *Expedited safety reports:* should be reported to the NIH Office of Biotechnology Activities concurrently with the report to FDA.
- Other adverse events documented during the course of the trial should be included in the annual IND or IDE report and reported to NIAID annually.

In case of problems or issues, the NIAID program officer will contact the awardee within 10 working days (by email or fax), followed within 30 calendar days by an official letter to the principal investigator, with a copy to the institution's office of sponsored programs, stating issues and actions to be discussed.

- *Safety reporting for research not performed under an IND or IDE:* Final decisions regarding ongoing safety reporting requirements for research not performed under an IND or IDE will be made jointly by NIAID and the awardee.

D. Recombinant DNA Advisory Committee and Institutional Biosafety Committee

The awardee submits to the NIAID program officer copies of the adverse event and annual reports required by NIH Office of Biotechnology Activities and by the site IBC, if applicable.

E. Requirements for Training in Human Subjects Protections

The awardee is required to submit documentation in the annual progress report that newly hired study staff responsible for the design or conduct of the research have received training in the protection of human subjects.

F. Inclusion Enrollment Reports

The "Inclusion Enrollment Report" includes cumulative accrual and demographic information for human subjects enrolled in the clinical research protocol. Submit this report annually. The annual submission of the enrollment report will coincide with each noncompeting renewal or annual progress report. For paper applications, see the PHS 398 for more detailed instructions. For electronic applications, see the Grant Application Guide for your Grant Application Package.

IV. NIAID Clinical Terms of Award Checklist

This checklist serves as a reminder of information that an awardee must submit to NIAID. The investigator may complete this checklist and attach it to a submission to the program or project officer following the awarding division's procedures.

Principal Investigator: Date:

Phone:

Fax:

Email:

Grant or Contract Number:

Site Name:

Address:

Protocol Title:

OHRP IRB or IEC Registration Number and Name:

Requirements at Time of Competitive Application and Proposal

☐ The research plan, including protocol, if required by the division.

☐ Data and safety monitoring plan, if applicable.

☐ Targeted/Planned Enrollment Table.

Requirements Before Study Enrollment

☐ IRB or IEC documents and protocol or protocols, identified by version number, date, or both; attach the following for each investigative site or IRB.

- IRB or IEC name.
- Federalwide assurance number for institution or site.
- IRB or IEC OHRP registration number.
- IRB or IEC notification of protocol approval.
- IRB or IEC approved protocol.
- IRB or IEC approved consent forms identified by dates valid.

☐ ISM, SMC, or DSMB information, if applicable (attach charter, operating procedures, proposed roster, and CVs).

☐ Additional information for clinical trials with INDs or IDEs.

- ☐ Name, institution, and address of IND or IDE sponsor.
- ☐ FDA IND or IDE number (attach copy of letter from FDA).
- ☐ FDA correspondence (attach copies of all written communication with FDA).
- ☐ Risk information (e.g., investigator's brochure or information obtained through published literature review or other venue).

☐ Safety reporting for research not performed under an IND or IDE.

☐ Additional information for gene transfer clinical trials.

☐ NIH Recombinant DNA Advisory Committee initial review.

☐ Date of letter from OBA: _____ NA_____

☐ Public RAC review: Yes:____ No:____

Include copy of letter from the Office of Biotechnology Activities either:

1) Stating the protocol has been exempted from public review.

2) Summarizing the RAC suggestions and PI response to the recommendations.

☐ IBC-related documents for human gene transfer protocols.

☐ Name of institution IBC serves.

☐ Copy of written IBC approval of protocol.

☐ Copy of protocol approved by the IBC and IRB.

☐ Documentation of training in human subjects protection for all study staff responsible for design or conduct of the research.

Ongoing Reporting Requirements

☐ Documentation of IRB or IEC continuing reviews – attach the following for each investigative site.

- IRB or IEC OHRP registration number.
- OHRP federalwide assurance number for site.
- IRB or IEC continuing review and approval.
- IRB or IEC approved consent form identified by version number, date, or both and dates it is valid.
- IRB or IEC approved protocol identified by version number, date, or both unless otherwise directed.
- Documents related to protocol amendments, suspensions, or termination.

☐ For the duration of the award, the awardee must notify NIAID of protocol amendments or changes in IRB or IEC approval status within three working days of the IRB's or IEC's decision. Documents related to an amended protocol must be submitted to NIAID before implementing changes unless participants are in imminent danger.

☐ Data and safety monitoring reviews or summaries, if applicable – submit within 30 days of review or meeting.

☐ IND or IDE safety reports.

☐ For 7-day IND telephone or fax reports, send copy to NIAID program or project officer within 24 hours of FDA notification.

☐ For 15-day IND written reports, send copy to NIAID program or project officer within 24 hours of FDA notification.

☐ For IDE reports of unanticipated adverse device effect, send copy to NIAID program or project officer within 24 hours of FDA notification.

☐ Report adverse events not included in expedited reports in the annual IND or IDE report.

- ☐ For safety reports for gene transfer clinical trials, send to OBA concurrently with the report to FDA.

☐ Documentation for Gene Transfer Clinical Trials

- ☐ Annual report and adverse event reports not included in expedited reports to OBA.
- ☐ IBC continuing approval.

☐ Training in human subjects protection for new study staff, if applicable – submit annually to coincide with each noncompeting renewal or annual progress report.

☐ Inclusion enrollment reports – submit annually to coincide with each noncompeting renewal or annual progress report.

☐ Notify NIAID if FDA places the study on clinical hold and provide NIAID any written comments from FDA, written responses, and documentation in writing that the hold has been lifted. Do not use grant or contract funds during a clinical hold.

V. NIAID Points of Contact

General Inquiries

Direct general inquiries related to this notice to:

Office of the Director
Division of Extramural Activities, NIAID
Telephone: 301/496-7291
Fax: 301/402-0369
Email: ac20a@nih.gov

Grant or Contract Inquiries and Document Submission

Direct inquiries about a grant or contract to the appropriate NIAID program or project officer. All information and documentation required by the NIAID Clinical Terms of Award must be forwarded electronically or by mail to the responsible NIAID program or project officer according to the review mechanisms applicable to the awarding division.

VI. Regulations and Guidelines

The NIAID Clinical Terms of Award conform with NIH policy on human subjects research and are consistent with and complementary to requirements stated in the instructions for your application, NIAID request for proposals, request for applications, or program announcement. NIAID-supported clinical research must adhere to applicable clinical research and human subject protection regulations and guidelines, including those listed below.

Policy References

Office for Human Research Protections

All clinical research supported by NIAID must comply with OHRP requirements for human subject protection, informed consent, IRB or IEC registration, assurances and responsibilities, including ongoing review. Go to the OHRP Internet.

Required Education in the Protection of Human Research Participants

All investigators receiving NIAID funds for research involving human subjects are required to receive education on the protection of human subjects. NIH provides an online tutorial, Human Participant Protections Education for Research Teams. Note: Other non-NIH-supported training programs are also available. NIAID provides you a sample form letter to send with your application.

Code of Federal Regulation Title 45 Part 46

All clinical research supported by NIAID must comply with applicable Parts of U.S. Code of Federal Regulations, Title 45, Part 46 "Protection of Human Subjects."

International Conference on Harmonisation Guidelines for Good Clinical Practice

All clinical trials supported by NIAID shall comply with ICH and GCP guidelines. See a complete list at Guidance for Industry.

FDA Guidance Documents

Find guidance documents that represent the FDA's thinking at the Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research guidelines.

For questions, consult the FDA Good Clinical Practice Program.

Find FDA's Information Sheet, Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors (1998), which represents the agency's current guidance on protection of human subjects of research.

Requirements for Research Conducted Under an IND

NIAID-supported clinical trials conducted under an FDA IND application must comply with relevant parts of CFR Title 21.

Title 21, Part 50, "Protection of Human Subjects"

Title 21, Part 54, "Financial Disclosure by Clinical Investigators"

Title 21, Part 56, "Institutional Review Boards"

Title 21, Part 312, "Investigational New Drug Application"

NIH Office of Biotechnology Activities

See the NIH Guidelines for Research Involving Recombinant DNA Molecules.

Help in Preparing a Human Subjects Application

For more help and advice in preparing a human subjects application, see our How to Write a Human Subjects Application tutorial that shows how to plan and write your application, including how to prepare for and follow the policy requirements.