For guidance on using this document, see the Clinical Terms of Award Guidance.

NIAID Clinical Terms of Award

Awardees must comply with the NIAID Clinical Terms of Award that will be incorporated in their Notices of Grant Award or contracts. Potential applicants and offerors are encouraged to contact appropriate NIAID program staff concerning this policy. For additional clinical trial requirements, see the NIAID Clinical Trial Implementation (U01) Cooperative Agreement program announcement.

NIH policy requires certain information regarding research that involves human subjects. The terms outlined here are in addition to and not in lieu of other NIH policies, including instructions in the PHS 398 Grant Application for paper application, the Supplemental Instructions for Preparing the Human Subjects Section of the Research Plan in the Grant Application Guide for electronic application, and the PHS 2590 Non-Competing Grant Progress Report as well as NIAID requests for proposals, requests for applications, program announcements, the Department of Health and Human Services (DHHS) regulations (45 CFR 46), Public Health Service guidelines, DHHS grant administration regulations (45 CFR parts 74 and 92), and Office of Management and Budget administrative guidelines.

Clinical Terms of Award

These Clinical Terms of Award detail an agreement between the NIAID and the awardee; they apply to all grants and contracts that involve clinical research.

A. Safety and Monitoring Issues

Institutional Review Board or Independent Ethics Committee Approval

Before award and then with the annual progress report, the grantee must submit to NIAID a copy of the current IRB-or IEC-approved informed consent document, documentation of continuing review and approval and the OHRP federalwide assurance number for the institution or site.

If other institutions are involved in the research (e.g., a multicenter clinical trial or study), each institution's IRB or IEC must review and approve the protocol. They must also provide NIAID initial and annual documentation of continuing review and approval, including the current approved informed consent document and federalwide number.

The grantee institution must ensure that the application as well as all protocols are reviewed by their IRB or IEC.

To help ensure the safety of participants enrolled in NIAID-funded studies, the awardee must provide NIAID copies of documents related to all major changes in the status of ongoing protocols, including the following:

- All amendments or changes to the protocol, identified by protocol version number, date, or both and dates it is valid.
- All changes in informed consent documents, identified by version number, date, or both and dates it is valid.
- Termination or temporary suspension of patient accrual.

- Termination or temporary suspension of the protocol.
- Any change in IRB approval.
- Any other problems or issues that could affect the participants in the studies.

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

If a clinical protocol has been reviewed by an institutional biosafety committee (IBC) or the NIH Recombinant DNA Advisory Committee (RAC), the awardee must provide information about the initial and ongoing review and approval, if any. See the NIH Guidelines for Research Involving Recombinant DNA Molecules.

Data and Safety Monitoring Requirements

NIAID strongly recommends independent safety monitoring for clinical trials of investigational drugs, devices, or biologics; clinical trials of licensed products; and clinical research of any type involving more than minimal risk to volunteers. Independent monitoring can take a variety of forms. Phase III clinical trials must be reviewed by an independent data and safety monitoring board (DSMB); other trials may require DSMB oversight as well.

A risk is minimal where the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. For example, the risk of drawing a small amount of blood from a healthy individual for research purposes is no greater than the risk of doing so as part of a routine physical examination (45 CFR 46.102I).

- Final decisions regarding the type of monitoring to be used must be made jointly by NIAID and the awardee before enrollment starts. Discussions with the responsible NIAID program officer regarding appropriate safety monitoring and approval of the final monitoring plan by NIAID must occur before patient enrollment begins and may include discussions about 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** – 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. All phase III clinical trials must be reviewed by a DSMB; other trials may require DSMB oversight as well. Go to NIAID Principles for Use of a Data and Safety Monitoring Board (DSMB) For Oversight of Clinical Trials Policy.

When a monitor or monitoring board is organized, a description of it, its charter or operating procedures (including a proposed meeting schedule and plan for review of adverse events), and roster and *curriculum vitae* from all members must be submitted to and approved by NIAID before enrollment starts.

Additionally, the awardee must submit written summaries of all reviews conducted by the monitoring group to the NIAID within 30 days of reviews or meetings.

B. NIAID Review Process Before Patient Enrollment Begins

NIAID has a responsibility to ensure that mechanisms and procedures are in place to protect the safety of participants in NIAID-supported clinical trials. Therefore, before patient accrual or participant enrollment, the awardee must provide the following (as applicable) for review and approval by NIAID.

- IRB- or IEC-approved clinical research protocol identified by version number, date, or both, including details of study design, proposed interventions, patient eligibility, and exclusion criteria.
- Documentation of IRB or IEC approval, including OHRP federalwide number, IRB or IEC registration number, and IRB or IEC name.
- IRB or IEC approved informed consent document, identified by version number, date, or both and dates it is valid.
- Plans for the management of side effects.
- Procedures for assessing and reporting adverse events.
- Plans for data and safety monitoring (see B above) and monitoring of the clinical study site, pharmacy, and laboratory.
- Documentation 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 comments will be forwarded 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 patient accrual or participant enrollment can begin.

C. Investigational New Drug or Investigational Device Exemption Requirements

Consistent with federal regulations, clinical research projects involving the use of investigational therapeutics, vaccines, or other medical interventions (including licensed products and devices for a purpose other than that for which they were licensed) in humans under a research protocol must be performed under a Food and Drug Administration (FDA) investigational new drug (IND) or investigational device exemption (IDE).

Exceptions must be granted in writing by FDA. If the proposed clinical trial will be performed under an IND or IDE, the awardee must provide NIAID the name and institution of the IND or IDE sponsor, the date the IND or IDE was filed with FDA, the FDA IND or IDE number, any written comments from FDA, and the written responses to those comments.

The awardee must wait 30 days from FDA receipt of an initial IND or IDE application before initiating a clinical trial.

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.

Required Time-Sensitive Notification

Under an IND or IDE, the sponsor must provide FDA safety reports of serious adverse events. Under these Clinical Terms of Award, the awardee must submit copies to the responsible NIAID program or project 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.
- *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 the 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, listing issues and appropriate 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 must be made jointly by the NIAID and the awardee.