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

Clinical Terms of Award

Awardees must comply with the Clinical Terms of Award that will be incorporated in their Notices of Grant Award or contracts. Potential applicants are encouraged to contact appropriate National Institute of Allergy and Infectious Diseases (NIAID) program staff concerning this policy.

NIAID's Clinical Terms of Award are presented below. They delineate awardee responsibilities including submission of the required documentation to NIAID. These terms apply to all NIAID-supported clinical research involving human subjects, including the development of new technologies using human subjects or materials derived from patients or volunteers; studies into the mechanisms of human disease using patient or volunteer samples; therapeutic interventions, clinical trials, and any studies that require institutional review board (IRB) or independent ethics committee (IEC) approval to collect samples from patients or volunteers; epidemiologic and behavioral studies; and outcomes and health services research. These Clinical Terms of Award define specific timelines for approvals related to the initiation of a trial or study and timelines for reporting events related to its progress. It is the responsibility of the awardee to submit required documentation to the responsible program or project officer according to these timelines.

NIAID Clinical Terms of Award

These Clinical Terms of Award are in addition to and not in lieu of other NIH policies, such as a written assurance of compliance with the Department of Health and Human Services (DHHS) Office of Human Research Protection (OHRP) 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.

In accordance with OHRP regulations for the protection of human subjects (45 CFR 46) and ensuring objectivity in research (42 CFR 50, subpart F), these Clinical Terms of Award detail the agreement between the NIAID and the awardee.

Terms for All Clinical Research Awards

NIH policy requires certain information regarding research that involves human subjects, such as reporting of demographics in the noncompetitive renewal application or annual report, and annual IRB or IEC review. The terms outlined here supplement these normal requirements; they apply to all grants and contracts that involve human subjects.

A. Reporting

To aid NIAID in fulfilling reporting requirements, the awardee must complete the Inclusion Enrollment Report showing cumulative accrual information for each study or clinical trial protocol. This submission should be submitted annually as part of each noncompeting renewal

or annual progress report. Find the format for the Inclusion Enrollment Report at http://grants.nih.gov/grants/funding/phs398/enrollmentreport.pdf.

B. Safety and Monitoring Issues

Institutional Review Board or Independent Ethics Committee Approval

The awardee will submit to NIAID annually documentation of continuing review and approval from the local IRB or IEC, including a copy of the current IRB-or IEC-approved informed consent document and the OHRP federal-wide assurance number for the institution or site. Where other institutions are involved in the research (e.g., a multicenter clinical trial or study), the protocol must be reviewed and approved by each institution's IRB or IEC. Initial and annual documentation of continuing review and approval, including the current approved informed consent document and federal-wide number from each institution, must also be provided to NIAID.

For international sites, approval from a national IRB or IEC, if applicable, may be required in addition to or in lieu of approval from the local 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.

Notification of any of the above changes must be made within three working days by email or fax, followed by a letter cosigned by the principal investigator and 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.

Data and Safety Monitoring Requirements

Independent safety monitoring is strongly recommended for all clinical trials involving investigational drugs, devices, or biologics and other clinical research perceived to involve more than a minimal risk.

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).

- Monitoring plans must be included in any application or proposal that proposes research involving more than minimal risk. However, final decisions regarding the type of monitoring to be employed will be made jointly by NIAID and the awardee before study initiation. Discussions with the responsible NIAID program officer regarding appropriate safety monitoring and approval of the final monitoring plan by NIAID will 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 (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. All phase III clinical trials must be reviewed by a DSMB; other trials may require DSMB oversight as well.

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 study initiation. 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.

C. NIAID Review Process Before Study Initiation

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 will 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 federal-wide 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 the NIAID before patient accrual or participant enrollment can begin.

D. 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 or investigational device exemption (IND or 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.

Required Time-Sensitive Notification

Under an IND or IDE, the sponsor is required to provide FDA safety reports of serious adverse events. Under the 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, enumerating 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 will be made jointly by the NIAID and the awardee.

E. Other Requirements

Other requirements may be determined on a case-by-case basis.

NIAID Clinical Terms of Award Checklist

This checklist serves as a reminder of information that must be submitted to NIAID. This checklist may be completed by the investigator and attached to a submission to the responsible program or project officer according to the review mechanisms applicable to the awarding division.

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.
- Federal-wide 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 OffBA: _____ 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 federal-wide 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.

Please note that for the duration of the award it is the responsibility of the awardee to notify NIAID of subsequent protocol amendments or changes in IRB or IEC approval status within three working days of IRB or IEC decision. Documents related to an

amended protocol must be submitted to the NIAID prior to implementing changes, except in the case of imminent danger to participants.

☐ 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 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 reports of adverse events 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.