NCI Clinical Trials Terms of Award

Awardees must comply with the NCI Clinical Trials Terms of Award that will be incorporated in their Notices of Award (both grants and contracts.) NCI defines a clinical trial operationally as a prospective study involving human subjects designed to answer specific questions about the effects or impact of particular biomedical or behavioral interventions; these may include drugs, treatments, devices, or behavioral or nutritional strategies. Participants in these trials may be patients with cancer or people without a diagnosis of cancer but at risk for it. (The full 'operational' definition used by NCI in the DSMB guidance can be found at the following website; http://www.cancer.gov/clinicaltrials/conducting/dsm-guidelines/page2#op_def.) Potential applicants and offerors are encouraged to contact National Cancer Institute (NCI) program staff concerning this policy.

NCI's Clinical Trials Terms of Award delineate awardee responsibilities including submission of the required documentation to NCI for all NCI-supported clinical trials. They define specific timelines for approvals related to the initiation of a trial and timelines for reporting events related to its progress. It is the responsibility of the awardee to submit required documentation to the responsible program staff according to these timelines.

These Clinical Trials Terms of Award are in addition to and not in lieu of other NIH policies. Relevant information can be found on cited web sites, including the PHS 398 Grant Application, SF424 (R&R) Grant Application, and PHS 2590 Non-Competing Grant Progress Report and in NCI requests for proposals, applications, program announcements, and funding opportunity announcements. Links to appropriate URLs can be found at http://grants.nih.gov/grants/forms.htm. These Clinical Trials Terms of Award detail the agreement between the NCI and the awardee.

Terms for All Clinical Trial 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 NCI-supported clinical trials in grants and contracts.

A. Reporting Requirements

To aid NCI in fulfilling reporting requirements, the awardee must complete the Inclusion Enrollment Report showing cumulative accrual information for each clinical trial protocol. This should be submitted annually as part of each non-competing renewal or annual progress report.

To aid in monitoring the trials it funds, NCI has developed an electronic database. Initially, reporting will be required for all phase 3 trials of pharmacologic, biological, surgical and radiation interventions. Phase 2 and phase 1 studies will be the next priority. As soon as practical, the database will be extended to include comprehensive information on trials of supportive care, behavioral interventions, screening and detection. Registration of clinical trials (beginning with intervention phase 3 trials) on the database will be required within 21 days of activation and will be updated quarterly, or more often if the status of the trial changes.

Following notification of the award, the responsible NCI program or project officer will advise the awardee regarding submission, according to the procedures of the awarding division. As the initiatives of the CTWG become fully implemented, electronic data reporting compliant with the standards specified by the NCI Center for Bioinformatics (NCICB) will be required. Data will include, but not be limited to, key demographics, treatment, toxicity and outcomes. Details regarding data submission are found at https://cabig.nci.nih.gov.

B. Safety and Monitoring Issues

B.1. Institutional Review Board or Independent Ethics Committee Approval

B.1.1 Initial and Continuing Approval

The awardee will submit to NCI annual documentation of continuing review and approval from the local IRB or IEC. For multicenter clinical trials the awardee institution must ensure that the protocol is reviewed and approved by each participating institution's IRB or IEC and provide each institution's FWA number. When requested, the awardee should submit a copy of all current IRB- or IEC-approved informed consent documents and the OHRP federal-wide assurance (FWA) numbers for the institutions or sites.

To help ensure the safety of participants enrolled in NCI-funded trials, the awardee must maintain documents related to all major changes in the status of ongoing protocols and provide a copy to NCI when requested. This includes:

- 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.

B.1.2 Amendment, Suspension, Termination

The awardee is required to notify the NCI program director or project officer if any of the following occur:

- Unplanned termination or unplanned temporary suspension of patient accrual.
- Unplanned termination or temporary suspension of the protocol.
- Any change in IRB or IEC approval status.
- Any other problems or issues that could adversely 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 principal investigator and 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 maintain information about the initial and ongoing review and approval if any and provide to NCI upon request.

B.2. Data and Safety Monitoring Requirements

NCI 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 3 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).

A Data and Safety Monitoring Plan (DSMP) must be included in any application or proposal that proposes research involving more than minimal risk. Final decisions regarding the type of monitoring will be made jointly by NCI and the awardee before trial initiation. Discussions with the responsible NCI program or project officer 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 NCI 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 monitoring board is organized by the awardee, a roster of proposed members and their CVs must be submitted to and approved by NCI before trial initiation. In addition, awardees should provide the charter or operating procedures (including a proposed meeting schedule, plan for review of adverse events, and management of potential conflicts of interest) to NCI on request.

B.3. Assuring Data Accuracy and Protocol Compliance

Institutions should describe quality-control procedures for assuring data accuracy and completeness in trials funded by NCI in their Data and Safety Monitoring Plan (DSMP). If an IND is in place, quality-control procedures are generally stipulated by the IND sponsor and may be simply referenced or summarized in the DSMP. For trials not done under an IND, the institution should describe the procedures in place to assure data integrity and protocol

adherence. Appropriate procedures may range, for example, from regular data verification and protocol compliance checks performed by a data manager and a principal investigator, to a formal external data-audit process by an agent external to the institution.

Detailed policy and guidance for monitoring of clinical trials is available at the following URLs:

- NIH Policy for Data and Safety Monitoring: http://grants.nih.gov/grants/guide/notice-files/not98-084.html

- Further NIH Guidance on Data and Safety Monitoring for Phase 1 and Phase 2 trials: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html

- Essential elements of data and safety monitoring plans for clinical trials funded by the NCI: http://www.cancer.gov/clinicaltrials/conducting/dsm-guidelines

- NCI Cooperative Group Data Monitoring Committee Policy (Phase 3 Trials): http://ctep.info.nih.gov/monitoring/index.html

C. NCI Review Process before Trial Initiation

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

- Documentation of IRB or IEC approval, including OHRP federal-wide number and IRB or IEC name.

- 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. It must include a copy of each IRB- or IEC-approved informed consent document identified by version number, date, or both

- Where other institutions are involved in the research, e.g., a multicenter trial, each institution should obtain IRB or IEC approval of the protocol. Written documentation of approval from each institution must be maintained by the awardee and provided to NCI upon request and must include a copy of each IRB- or IEC-approved informed consent document identified by version number, date, or both.

- 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.

D. Investigational New Drug or Investigational Device Exemption Requirements

All NCI-funded and/or sponsored research will be conducted in accordance with applicable federal regulations governing clinical research. Trials involving the use of investigational therapeutics, vaccines, or other regulated medical interventions will be conducted under a research protocol approved under a U.S. Food and Drug Administration (FDA) IND or IDE,

and/or under the regulation of the appropriate regulatory authority in cases where the research is being conducted in a foreign country.

Note that, under certain circumstances, licensed products or devices used for a purpose other than that for which they were licensed may require an IND or IDE in accord with applicable FDA regulations.

If the proposed clinical trial will be performed under an IND or IDE held by the NCI, then the NCI must approve the protocol and protocol related documents, such as the informed consent, and all protocol amendments before they are activated.

If the proposed clinical trial will be performed under an IND or IDE held by a sponsor other than the NCI, the awardee must provide NCI with the name and affiliation 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 the written responses to those comments. The awardee must notify NCI if FDA, and/or other regulatory authorities, place the study on clinical hold and provide NCI any written comments from FDA, written responses to the comments, and documentation in writing that the hold has been lifted.

- In the case of a foreign regulatory filing, the awardee must provide NCI with written documentation from the regulatory body that the awardee is in compliance with local regulatory laws.

- Risk information regarding the intervention being studied (e.g., product development plan, investigator's brochure, or information obtained through published literature review or other venue) must be maintained by the awardee and supplied to the NCI upon request.

Regardless of who holds the IND or IDE, the investigator is required to follow all government regulations.

D.1. IND/IDE Safety Reporting Requirements when NCI is the Sponsor

As the IND/IDE sponsor, it is NCI's responsibility to provide the FDA with safety reports of serious and unexpected adverse events that occur on trials that it sponsors. The awardee must report all adverse events to the appropriate NCI officials in compliance with the reporting instructions contained in the protocol for each clinical trial to ensure that NCI is able to meet its FDA reporting requirements.

Other adverse events documented during the course of the trial should be reported in accordance with the standard data reporting requirements established for the trial.

In case of specific problems or issues, the awardee will be required to respond in writing to concerns raised by NCI staff responsible for monitoring the trial in a timely manner as established by NCI staff on the basis of the seriousness of the issues or concerns.

E. Other Requirements

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