Guidance for Reviewers: Clinical Trials Review Criteria

NOTE: this guidance covers clinical trials review criteria BOTH for funding opportunities using the Simplified Review Framework and for funding opportunities not using the Simplified Review Framework.

Requirements and Responsibilities

Clinical trial applications involving grants and cooperative agreements are subject to the NIH clinical trial review criteria as specified in NOT-OD-17-118 or NOT-OD-24-010 (for funding opportunities using the Simplified Review Framework). Clinical trial applications for career development award applications are subject to the clinical trial review criteria specified in NOT-OD-18-109. Please note that the clinical trial review criteria do not apply to a clinical trial research experience which does not involve an independent clinical trial.

Note that some Program Announcements (PARs) and Requests for Applications (RFAs) may include funding opportunity-specific questions in addition to the required clinical trial review criteria. In such cases, the Scientific Review Officer (SRO) overseeing the review meeting will alert reviewers and remind them to consider the review criteria as specified in the individual notice of funding opportunity (NOFO).

Applicant Responsibilities

NIH applicants must ensure that studies which meet the NIH definition of a clinical trial (including BESH) are designated as such in NIH applications and are submitted through an NIH NOFO specifically designed for clinical trials. See the NOFO Types by Clinical Trial Allowability for additional information. Applicants must also ensure that all clinical trial-related information included in the application addresses the specific review criteria.

Scientific Review Group (SRG) Responsibilities

Scientific review groups (SRGs) must consider the clinical trial review criteria in the NOFO when reviewing clinical trial-related information in NIH applications. Their evaluation will contribute to an application's overall scientific and technical merit (overall impact score).

For funding opportunities using the Simplified Review Framework

As part of the Simplified Review Framework, effective for most Research Project Grant (RPG) grant and cooperative agreement applications with receipt dates of January 25, 2025 and beyond, the Scored Review Criteria definitions encompass both clinical trial and non-clinical trial applications. The only criterion where specific review criteria for evaluating applications proposing clinical trials are included is Factor 2 (Rigor and Feasibility):

- For applications involving human subjects, including clinical trials, assess the adequacy of inclusion plans as appropriate for the scientific goals of the research. Considerations of appropriateness may include disease/condition/behavior incidence, prevalence, or population burden, population representation, and/or current state of the science.
- For applications involving human subjects, including clinical trials, evaluate the adequacy and feasibility of the plan to recruit and retain an appropriately diverse population of participants. Additionally evaluate the likelihood of successfully achieving the proposed enrollment based on age, racial, ethnic, and sex/gender categories.
- For clinical trial applications, evaluate whether the study timeline and milestones are feasible.

Under Factor 2 the SRG will also evaluate the plans for human subjects inclusions and the plans for valid design and analysis (for NIH-defined phase III trials). Additional information for reviewing these criteria can be found at Guidance for Review of Inclusion.

Human subjects protections, including the Data and Safety Monitoring Plan/Board, will be evaluated as part of Additional Review Criteria. Additional information for reviewing these criteria can be found at Guidance for Review of Human Subjects Protections.

For funding opportunities *not* using the Simplified Review Framework

Clinical trials specific criteria are located under individual Scored Review Criteria and the Additional Review Criteria section (for the Study Timeline). See Clinical Trial-Specific Review Criteria for examples of Scored Review Criteria that may include clinical trials criteria.

As part of the Additional Review Criteria section, the SRG will also evaluate the plans for human subjects inclusions, the plans for valid design and analysis (for NIH-defined phase III trials), and human subjects protections (including the Data and Safety Monitoring Plan/Board). Additional information for reviewing these criteria can be found at Guidance for Review of Inclusion and Guidance for Review of Human Subjects Protections.

Reviewer Responsibilities

Reviewers **must evaluate NIH applications based on the clinical trial designation from the electronic cover page of the application**, using the review criteria included in the NOFO. Reviewers should not consider whether the application clinical trial designation is correct. There will be no discussion in the meeting or in critique templates of whether that designation is correct.

In addition, reviewers **should not discuss** in the meeting whether the applicant used the correct NOFO, or correct FORMS package. Reviewers may bring potential discrepancies regarding clinical trial designations, NOFO, or FORMS packages to the attention of the SRO. Ideally, this should be communicated well in advance of the meeting. The SRO will follow up as appropriate.

Funding Opportunities for Clinical Trials

Clinical Trial NOFOs will use one of the following designations:

- Clinical Trial Required or Independent Clinical Trial Required
- Clinical Trial Optional
- Basic Experimental Studies with Humans Required (BESH)

A link in the Internet Assisted Review (IAR) module will take the reviewer to the appropriate review criteria in the NOFO for each application or component.

Clinical Trial-Related Information in NIH Applications

Clinical trial-related information is found in the Research Plan Section (PHS 398 Research Plan Form) and the PHS Human Subjects and Clinical Trials Information Form, or as otherwise indicated in the NOFO.

Research Project Applications & Study Records of the PHS Human Subjects and Clinical Trials Information Form:

For single-project applications:

- Reviewers must address all study records in a single critique template.

For multi-component applications:

- Reviewers must follow NOFO-specific instructions for each of the components.

Resources and Definitions

1. Clinical Trial Resources Website:
   - https://grants.nih.gov/policy-and-compliance/policy-topics/clinical-trials
2. NIH Application Guide Instructions:
   - https://grants.nih.gov/grants-process/write-application/how-to-apply-application-guide

Clinical Trial

A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.

- The term "prospectively assigned" refers to a pre-defined process (e.g., randomization) specified in an approved protocol that stipulates the assignment of research subjects (individually or in clusters) to one or more arms (e.g., intervention, placebo or other control) of the clinical trial.
- An “intervention” is defined as a manipulation of the subject or subject's environment for the purpose of modifying one or more health-related processes and/or endpoints. Examples include, but are not limited, to: drugs/small molecules/compounds, biologics, devices; procedures (e.g., surgical techniques); delivery systems (e.g., telemedicine, face-to-face); strategies to change health-related behavior (e.g., diet, cognitive therapy, exercise, development of new habits); and, treatment, prevention, and diagnostic strategies.

- A "health-related biomedical or behavioral outcome" is defined as the pre-specified effect of an intervention on the study subjects. Examples include positive or negative changes to physiological or biological parameters (e.g., improvement of lung capacity, gene expression); psychological or neurodevelopmental parameters (e.g., mood management intervention for smokers; reading comprehension and/or information retention); disease processes; health-related behavior; and, well-being or quality of life.

For official definition, see here.

NIH-Defined Phase III Clinical Trial

An NIH-defined Phase III clinical trial is a broadly based prospective Phase III clinical investigation, usually involving several hundred or more human subjects, for the purpose of evaluating an experimental intervention in comparison with a standard or controlled intervention or comparing two or more existing treatments. Often the aim of such investigation is to provide evidence leading to a scientific basis for consideration of a change in health policy or standard of care. The definition includes pharmacologic, non-pharmacologic, and behavioral interventions given for disease prevention, prophylaxis, diagnosis, or therapy. Community trials and other population-based intervention trials are also included.

Basic Experimental Studies Involving Humans (BESH)

Studies that prospectively assign human participants to conditions (i.e., experimentally manipulate independent variables) and that assess biomedical or behavioral outcomes in humans for the purpose of understanding the fundamental aspects of phenomena without specific application towards processes or products in mind. BESH are studies that meet both the federal definition of basic research and the NIH definition of a clinical trial.

Clinical Trial Research Experience

The involvement of a student, postdoctorate, or early career faculty member in a clinical trial led by their mentor or other investigator, with the goal of obtaining clinical trial experience relevant to their research interests and career goals. A clinical trial research experience is one in which the participant is supervised by a more experienced investigator and is intended to prepare the participant to potentially lead an independent clinical trial in the future. The applicant can be part of the clinical trial team and can use the data generated during the clinical trial research experience in his/her proposed research project. NIH expects the mentor to assume overall responsibility of the trial including registering and reporting in clinicaltrials.gov and obtaining IRB approval.