Guidelines for Reviewers: Clinical Trials Review Criteria

Revision Notes — November 2021

- Added information about how reviewers should consider clinical trial review criteria in applications submitted in response to clinical trial-specific Funding Opportunity Announcements (FOAs) (e.g., Clinical Trial Required, Clinical Trial Optional, and Basic Experimental Studies with Humans (BESH) FOAs).
- Reorganized the layout of the previous clinical trial guidance for reviewers and updated the information and considerations that reviewers need to know.
- Added links and resources for reviewers.

Requirements and Responsibilities

Clinical trial applications involving grants and cooperative agreements submitted to the NIH for due dates on or after January 25, 2018 are subject to the NIH clinical trial review criteria as specified in NOT-OD-17-118. 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 clinical trial research experience (see definition below) which does not involve an independent clinical trial.[1]

Some Program Announcements (PARs) and Requests for Applications (RFAs) may include FOA-specific questions in addition to the required clinical trial review criteria. Reviewers should consider the review criteria as specified in the FOA.

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 FOA specifically designed for clinical trials. Applicants must also ensure that all clinical trial-related information included in the application addresses the specific review criteria. See the FOA Types by Clinical Trial Allowability and clinical trial-specific review criteria for additional information.

Scientific Review Group (SRG) Responsibilities

Scientific review groups (SRGs) must review the clinical trial-related information in NIH applications and must evaluate the clinical trial review criteria into their overall evaluation of an application's scientific and technical merit and overall impact score.

[1] *Applicants proposing to gain clinical trial research experience (i.e., not conducting an independent clinical trial) may be able to apply to a Clinical Trial Not Allowed FOA permitting clinical trial research experience under a clinical trial conducted by a sponsor or mentor. Additional review criteria about clinical trial research experience will apply (see "Independent Clinical Trial Not Allowed" review criteria specified in NOT-OD-18-109).*

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 from the FOA. Reviewers should not consider whether the application clinical trial designation is correct. There will be no discussion in the meeting or in the critique templates of whether that designation is correct.

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

Funding Opportunities for Clinical Trials

Reviewers will use the review criteria and critique template that correspond to the designation and FOA used by the applicant.

- For reviews using Word critique templates:
    - A link in the Internet Assisted Review (IAR) site will take the reviewer to the review criteria in the FOA for each application or component.
    - The SRO will provide the correct critique templates in IAR for the reviewer.

- For reviews using online critique templates:

    - A link in the IAR site will take the reviewer to the online critique for that application, which will display Section V details from the FOA.
    - A link to the full FOA will appear as well.

For applications submitted on or after January 25, 2018, FOAs may be designated as follows:

- Clinical Trial Required or Independent Clinical Trial Required
- Clinical Trial Optional
- Clinical Trial Not Allowed or Independent Clinical Trial Not Allowed
- Basic Experimental Studies with Humans Required (BESH)

Reviewers must evaluate the information in the application using the clinical trial review criteria as specified in the Clinical Trial Required and BESH FOAs.

For applications submitted in response to a Clinical Trial Optional FOA, reviewers must note the clinical trial designation from the electronic cover page of the application and apply the clinical trial criteria only to applications designated as clinical trials.

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 FOA.

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 FOA-specific instructions for each of the components.

Resources

1. Information for Reviewers:
    - https://grants.nih.gov/grants/policy/review.htm
2. Review Criteria & FOA Guide Notices:
    - https://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-147.html
    - https://grants.nih.gov/grants/guide/notice-files/NOT-OD-17-043.html
      https://grants.nih.gov/grants/guide/notice-files/NOT-OD-18-106.html
    - https://grants.nih.gov/grants/guide/notice-files/NOT-OD-18-001.html
3. Clinical Trial-specific Review Criteria Webpage:
    - https://grants.nih.gov/policy/clinical-trials/review-criteria.htm
4. Clinical Trial Resources Webpage:
    - https://grants.nih.gov/policy/clinical-trials.htm
5. BESH Resources Webpage:
    - https://grants.nih.gov/policy/clinical-trials/besh.htm
6. NIH Application Guide Instructions:
    - https://grants.nih.gov/grants/how-to-apply-application-guide.html
7. Clinical Trial Policy for Appendix Materials:
    - https://grants.nih.gov/grants/guide/notice-files/NOT-OD-17-098.html

NIH Definitions

- **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.

  Note: reviewer guidance for NIH-Defined Phase III Clinical Trials is found in the *Guidelines for the Review of Inclusion on the Basis of Sex/Gender, Race, Ethnicity, and Age in Clinical Research* at https://grants.nih.gov/grants/peer/guidelines_general/Review_Human_subjects_Inclusion.pdf

- **Basic experimental studies involving humans (BESH)**
  Basic experimental studies involving humans (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.