NIH Clinical Trials - Best Practices and Resources

In preparation for the 2016 NIH clinical trial stewardship reforms, NIH revised its definition of Clinical Trial? in October of 2014, which applies to applications submitted on and after January 25, 2015. The revised NIH definition of Clinical Trial is:

*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 outcome.*

Commencing with applications due on and after January 25, 2018 it is critical that investigators determine if their study/ancillary study meets the NIH definition of clinical trial in order to:

- Select the correct Funding Opportunity Announcement (FOA).
- Ensure the application includes all information required for Peer Review.
- Ensure that they are in compliance with appropriate policies and regulations.

**Does Your study meet the NIH Definition of Clinical Trial?**

**Recommended Best Practice** ? follow all these steps:

**STEP-1**

You must answer all four questions below to determine if your study meets the NIH definition of clinical trial. For ancillary studies take into account only the work proposed in the ancillary study, not the work being done in the parent project.

**NOTE:**

- If applying for a Career Development Award (K series), proceed to STEP-3.
- If applying for an Individual Fellowship (F-series), proceed to STEP-4.

1. Does the study involve human subjects?

2. Are the participants prospectively assigned to an intervention?
3. Is the study designed to evaluate the effect of the intervention on the human subjects?

4. Is the effect that will be evaluated a health-related biomedical or behavioral outcome?

   - If you answer YES to all four questions, your study meets the NIH definition of Clinical Trial.
   - If you answer NO to any of the four questions, you study does NOT meet the NIH definition of Clinical Trial.

Proceed to STEP-2.

STEP-2

In ALL cases, it is recommended that you consult with and/or seek confirmation from the NIH Institute/Center Program Official/Director for the program that you are applying to before proceeding with the application process.

REMEMBER NOT-OD-18-106

   - If you have confirmed that the study MEETS the NIH definition of clinical trial be sure to use a Parent FOA designated as ?Clinical Trial Required.? For Parent R01 Clinical Trial Required and Parent R21 Clinical Trial Required FOAs, check with the NIH Institute/Center that you are applying through to see if they have published IC-Specific Clinical Trial FOAs before proceeding (NOT-OD-18-010).
   - If you have confirmed that the study DOES NOT MEET the NIH definition of clinical trial, ensure that the FOA that you apply through (parent or other) is designated as ?Clinical Trial Not Allowed? before proceeding.

STEP-3

If applying for a Career Development Award (K series), and

1. Independently Leading a clinical trial, you MUST-

   a. Have answered YES to the four questions.
   b. Have NIH Institute/Center Program Official/Director confirmation that the study meets NIH definition of clinical trial.
   c. Apply to a FOA that states, ?Requires Clinical Trial? in the title and Section II.
   d. Follow application instructions carefully, as well as all NIH policies related to clinical trial applications and awards.
2. Working on a Clinical Trial that is led by another investigator or another investigator has ultimate responsibility, you must apply to a FOA that does NOT require clinical trials.

   a. The FOA Title will state, ?No independent clinical trials.?
   b. Section II will indicate that applicants may propose to gain experience in a clinical trial led by a mentor/co-mentor as part of their career development.

STEP-4

If applying for an Individual Fellowship (F series), independent Clinical Trials are NOT supported and a specific Clinical Trial FOA does not exist:

1. Section II of the FOA will clarify that the applicant can propose their intent to experience a mentor-led Clinical Trial.
2. IMPORTANT: Follow application instructions carefully for guidance to complete the PHS Human Subjects and Clinical Trials Information form.
3. The Research Strategy section of the application should include applicant?s role and details of clinical trial.
4. Ensure mentor/co-mentor statements address oversight of the trial.

TERMS DEFINED:

45 CFR 46.102(d) Common Rule Definition of Research

Research means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities.

45 CFR 46.102(f) Common Rule Definition of Human Subject

Human subject means a living individual about whom an investigator (whether professional or student) conducting research obtains:

   (1) Data through intervention or interaction with the individual, or
   (2) Identifiable private information.

   Intervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. Interaction includes communication or interpersonal
contact between investigator and subject. Private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

**Prospectively Assigned**

As related to the definition of a clinical trial, 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 a clinical trial.

**Intervention**

As related to the definition of a clinical trial, a manipulation of the subject or subject’s environment for the purpose of modifying one or more health-related biomedical or behavioral processes and/or endpoints. Examples include: drugs/small molecules/compounds; biologics; devices; procedures (e.g., surgical techniques); delivery systems (e.g., telemedicine, face-to-face interviews); strategies to change health-related behavior (e.g., diet, cognitive therapy, exercise, development of new habits); treatment strategies; prevention strategies; and, diagnostic strategies.

**Health-related Biomedical or Behavioral Outcomes**

As related to the definition of a clinical trial, the pre-specified goal(s) or condition(s) that reflect the effect of one or more interventions on human subjects' biomedical or behavioral status or quality of life. Examples include: positive or negative changes to physiological or biological parameters (e.g., improvement of lung capacity, gene expression); positive or negative changes to psychological or neurodevelopmental parameters (e.g., mood management intervention for smokers; reading comprehension and/or information retention); positive or negative changes to disease processes; positive or negative changes to health-related behaviors; and, positive or negative changes to quality of life.

**RESOURCES:**

NOT-OD-15-015  (Related Guide Notice)

NIH Clinical Trial Requirements for Grants and Contracts
NIH GLOSSARY DEFINITION OF 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.

See Common Rule definition of research at 45 CFR 46.102(d)

See Common Rule definition of human subject at 45 CFR 46.102(f)

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.

Biomedical clinical trials of an experimental drug, treatment, device, or behavioral intervention may proceed through four phases:

Phase I. Tests a new biomedical intervention in a small group of people (e.g. 20-80) for the first time to determine efficacy and evaluate safety (e.g., determine a safe dosage range and identify side effects).
Phase II. Study the biomedical or behavioral intervention in a larger group of people (several hundred) to determine efficacy and further evaluate safety.

Phase III. Study to determine efficacy of the biomedical or behavioral intervention in large groups of people (from several hundred to several thousand) by comparing the intervention to other standard or experimental interventions as well as to monitor adverse effects, and to collect information that will allow the interventions to be used safely.

Phase IV. Studies conducted after the intervention has been marketed. These studies are designed to monitor the effectiveness of the approved intervention in the general population and to collect information about any adverse effects associated with widespread use.