SUMMARY GUIDANCE ON
THE NATIONAL INSTITUTES OF HEALTH DEFINITION OF A CLINICAL TRIAL

The National Institutes of Health (NIH) defines a clinical trial as a research study in which:

- one or more *human subjects*
- are *prospectively assigned* to one or more i*nterventions* (which may include placebo or other control)
- to evaluate the effects of those interventions on *health-related biomedical or behavioral outcomes*

NIH's current interpretation of this definition means that some social and behavioral research previously considered to be basic research will now be categorized as a clinical trial and trigger a variety of requirements specific to clinical trials. Contact your NIH Program Manager for assistance in determining if a study will be categorized as a clinical trial.

NIH states that four questions must be asked to determine if a study will be considered a clinical trial:

1. Does the study involve human participants?
2. Are the participants prospectively assigned to an intervention?
3. Is the study designed to evaluate the effect of the intervention on the participants?
4. Is the effect being evaluated a health-related biomedical or behavioral outcome?

If the answer to all four of these questions is yes, NIH would consider the study to be a clinical trial. There is a tool on NIH's website intended to guide researchers through these questions.

An understanding of the specific terms used in NIH's definition is critical to correct categorization. Key terms used by NIH are described as discussed below.

Prospectively Designed

The design of the study must include:

- a pre-defined process (e.g., randomization) that is specified in an approved protocol ; and
- 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

An intervention is 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;
- diagnostic strategies.

Health-Related Biomedical or Behavioral Outcome

These outcomes are defined as 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;
- positive or negative changes to quality of life.

Criteria to determine if a study will be considered a clinical trial are further discussed in a number of recently issued NIH notices. NIH Notice NOT-OD-18-010, *NIH Plans for Clinical Trial Specific Parent R01 and Parent R21 Funding Opportunity Announcements* is one such notice. Excerpts from this notice are below.

> "NIH defines a clinical trial as "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." (NOT-OD-15-015)"
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> "NIH not only supports trials of safety and efficacy, it also supports mechanistic exploratory studies that meet the definition of a clinical trial and are designed to explore or understand a biological or behavioral process, the pathophysiology of a disease, or the mechanism of action of an intervention".
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> "These studies may focus on basic and/or translational discovery research in healthy human subjects and in human subjects who are affected by the pathophysiology of diseases and disorders. By addressing basic questions and concepts in biology, behavior, and pathophysiology, these studies may provide insight into understanding human diseases and disorders along with potential treatments or preventive strategies".
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> "NIH thus supports studies that meet the definition of clinical trials (as noted above) but do not seek to establish safety, clinical efficacy, effectiveness, clinical management, and/or implementation of preventive, therapeutic, and services interventions".
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> "Examples of mechanistic clinical trials include but are not limited to:
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> - Studies that use a manipulation (physiological or behavioral) to answer basic science questions about normal functions.
> - Studies that use an experimental manipulation in order to understand normal functioning or the pathophysiology of a disease or disorder, but do not aim to demonstrate clinical improvement.
> - Studies that involve the prospective use of efficacious interventions where the intent is to obtain and analyze biospecimens to identify genetic risk associations, novel biomarkers, examine the disease process, or characterize mechanisms of therapeutic response.
> - Studies in which an intervention with demonstrated efficacy for a population is being studied to understand mechanisms of response, non-response, or risk of adverse effects of the efficacious intervention".

NIH has posted Case Studies **and** FAQs **that are very helpful. Also, see** NIH's main page on Clinical Trials

CMU's ORIC website **has additional information.**