DECISION SUPPORT TOOL:
Features to Consider in Determining if a Clinical Trial is Phase II or Phase III

This document is the result of a working group led by the Office of Behavioral and Social Sciences Research, with participants from other Institutes, Centers, and Offices. It is a designed to be a resource to help investigators, program officers, and reviewers determine if a behavioral or social science study is better characterized as a Phase II or a Phase III clinical trial. Distinguishing earlier phases of clinical trials (Phase 0 or I) is not usually difficult but distinguishing between a Phase II and III study can be more challenging, particularly for non-drug trials. Being thoughtful about this distinction is important for a variety of reasons, not least of which is that a Phase III designation for an NIH funded clinical trial generally requires following additional policies and practices beyond those that already apply to Phase II clinical trials, such as the requirement for valid analysis and for a Data and Safety Monitoring Board (DSMB). Data and safety monitoring are required for all clinical trials but for a Phase III trial, the constitution of a board is required.

NIH Definitions

Across NIH and other research or regulatory agencies there are varying definitions for the phases of clinical trials. This resource is directly related to the official NIH definition of Phase III trials as indicated in NOT-OD-18-014 and the Phase II trial definition included in the NIH glossary of terms.

Phase II Clinical Trial:

An NIH defined Clinical Trial that studies the biomedical or behavioral intervention in a larger group of people (several hundred) to determine efficacy and further evaluate safety.

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.

Is it a Clinical Trial?

Before considering what phase a trial is, the first decision is to determine whether a study is a clinical trial. The Office of Extramural Research's website provides additional information on NIH clinical trial requirements and whether a research study meets the NIH definition of a clinical trial.

Comparing General Features of Phase II vs. Phase III Trials

Considerations		Phase II	Phase III
Distinguishing Feature	The study will provide evidence that could lead to a change in health policy or standard of care.	It is not a distinguishing feature.	It is often the aim of the trial. A study is more likely to support a change in health policy or standard of care if the study sample represents the population at risk for the disease/condition of interest and if the study has high power to detect a clinically significant effect.
Features To Consider	**Comparator Condition:** intervention compared to one or more other intervention/control conditions of a trial (e.g., placebo, usual/ standard care, alternative intervention, or other control).	They usually include a comparator condition.	They must include a comparator condition.
	Evaluation of Efficacy/ Effectiveness	A Phase II study is designed to determine efficacy and further evaluate safety.	A Phase III study is designed to confirm efficacy/ effectiveness, monitor side effects, compare it with standard or similar interventions, and collect information about safety.

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Comparing General Features of Phase II vs. Phase III Trials *(continued)*

Considerations		Phase II	Phase III
Features To Consider	Number of Participants	There is no requirement. These are often described as up to a few hundred participants but may be far fewer for some research questions and populations.	There is no requirement. Phase III trials are usually larger than Phase II trials and are often described as a few hundred to several thousand participants but may be far fewer for some research questions and populations.
	Number of Sites	There is no requirement about number of sites, but a single site study is not uncommon.	There is no requirement about number of sites but Phase III trials are usually multi-site studies to enhance broad representation of diverse populations and generalizability so they can provide the scientific basis to support a change in policy, service delivery or standard of care, if effective.
	Duration	No requirement but often shorter trial and follow-up (e.g., 2-5 years).	No requirement but often longer trial and follow-up (e.g., 5-7 years).

A Few Relevant Policies for Phase III Trials

Data and Safety Monitoring:

The current NIH policy for data and safety monitoring states:

- It is the policy of the NIH that each Institute and Center (IC) should have a system for the appropriate oversight and monitoring of the conduct of clinical trials to ensure the safety of participants and the validity and integrity of the data for all NIH-supported or conducted clinical trials.
- The establishment of the data and safety monitoring boards (DSMBs) is required for multi-site clinical trials involving interventions that entail potential risk to the participants.

Analyses by Sex or Gender, Race and Ethnicity for NIH-defined Phase III Clinical Trials (Valid Analysis)

When an NIH-defined Phase III clinical trial is proposed, evidence must be reviewed to show whether or not clinically important sex/gender and race/ethnicity differences in the intervention effect are to be expected. The application or proposal must address plans for the analysis of intervention effect differences on the basis of sex/gender, race, and ethnicity unless there is clear evidence that such differences are unlikely to be seen.

Valid analysis means an unbiased assessment. Such an assessment will, on average, yield the correct estimate of the difference in outcomes between two groups of subjects. Valid analysis can and should be conducted for both small and large studies. A valid analysis does not need to have a high statistical power for detecting a stated effect.

The principal requirements for ensuring a valid analysis of the question of interest are:

- allocation of study participants of both sexes/genders (males and females) and from different racial and/or ethnic groups to the intervention and control groups by an unbiased process such as randomization;
- unbiased evaluation of the outcome(s) of study participants; and
- use of unbiased statistical analyses and proper methods of inference to estimate and compare the intervention effects by sex/gender, race, and/or ethnicity.

Reducing Bias and Examining Intervention Effects

Bias can be reduced using several methods. For example, bias in the evaluation can be reduced by using objective measures and staff who are blind to treatment assignment. Bias in the statistical analysis can be reduced by adjusting for potential confounders. Comparison of intervention effects can be achieved by reporting intervention effects and their confidence intervals separately for each sex/gender and for each race/ethnicity group. Generally, it is not sufficient to adjust the primary analysis for sex/gender or race/ethnicity.