

Questions and Answers Regarding the Revised NIH Definition of “Clinical Trial”

1. Why did NIH revise the NIH definition of “clinical trial”?

The definition was revised to make the distinction between clinical trials and clinical research studies clearer and to enhance the precision of the information NIH collects, tracks, and reports on clinical trials. It is not intended to expand the scope of the category of clinical trials.

2. When will the revised definition be implemented?

NIH announced the revised definition on October 23, 2014. It will replace the current clinical trial definition in relevant extramural and intramural NIH policies, guidance, and instructional materials.

It will apply to competing grant applications that are submitted to NIH for the January 25, 2015 receipt date and subsequent receipt dates and contract proposals that are submitted to NIH on or after January 25, 2015.

3. How is the clinical trial definition used by NIH?

NIH uses the definition of clinical trial for a number of purposes. It is used to help track the progress of research projects involving clinical trials, and to analyze the NIH research portfolio and respond to requests for information about the NIH clinical trial portfolio.

In addition, because clinical trials are subject to additional oversight, a clearer definition will help investigators ensure that they are meeting all of their obligations, and it will help NIH ensure that the additional oversight is occurring when it is needed. For example, NIH policy requires clinical trials to be monitored, and applicants and offerors seeking NIH support are expected to describe their plans for data and safety monitoring in their applications and proposals. Final data and safety monitoring plans must be approved by the NIH prior to award. In addition, throughout the life of the award, NIH staff monitors the clinical trial’s progress to ensure that milestones are met and that any safety concerns are addressed.

4. How does the definition of “clinical trial” differ from definition of “clinical research”?

Clinical research is defined as any research involving human subjects, including human specimens and data. Specifically, NIH defines “clinical research” as:

- Patient-oriented research. Research conducted with human subjects (or on material of human origin such as tissues, specimens, and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. Excluded from this definition are in vitro studies that utilize human tissues that cannot be linked to a living individual. It includes: mechanisms of human disease, therapeutic interventions, clinical trials, development of new technologies,
- Epidemiological and behavioral studies.
- Outcomes research and health services research.

Clinical trials are a subset of clinical research. To be classified as a clinical trial, a clinical research project must involve the following three key characteristics:

- Prospective assignment of subjects through a pre-defined process;
- An intervention; and,
- Evaluation of a health-related biomedical or behavioral outcome.

5. Is randomization a defining element of a clinical trial?

No. All clinical trials, by definition, involve a pre-defined process of assignment of research subjects, but the process may involve methods other than randomization.

6. In a clinical trial, should the health-related outcome(s) be directly linked the study intervention?

Yes. Clinical trials are used to study the effects of an intervention(s) on health-related outcome(s).

7. Do single arm trials meet the NIH definition of clinical trial?

Yes. Clinical trials may be have a single arm or multiple arms.

8. Is the use of a control a defining element of a clinical trial?

No. A study need not include a control to be a clinical trial.

9. Does the revised NIH definition encompass trials using behavioral interventions?

Yes, if a trial prospectively assigns human subjects to a behavioral intervention to evaluate a health-related biomedical or behavioral outcome, then it is a clinical trial under the NIH definition.

10. Does the revised NIH definition encompass comparative effectiveness studies?

It depends on whether the study involves prospective assignment of an intervention. Comparative effectiveness studies are sometimes carried out through observation of patient outcomes. A comparative effectiveness study that evaluates health outcomes through observation only, i.e., does not involve prospective assignment to an intervention, is an observational study, not a clinical trial.

11. Does the revised NIH definition encompass observational studies?

No. Observational studies do not meet the definition of clinical trial.

12. Does the revised NIH definition encompass symptom provocation studies?

It depends. A challenge study evaluating whether an intervention can provoke symptoms could be a clinical trial if it is evaluating a change in a health-related biomedical or behavioral outcome. If the study involves prospective assignment to an intervention for which the health-related effects will be evaluated, the study is a clinical trial. However, if the study involves prospective assignment of an intervention to evaluate a biomedical or behavioral outcome that is not health-related, the study is not a clinical trial.

13. Does the revised NIH definition encompass studies involving retrospective analyses?

It depends. A study involving only retrospective or historic cohorts would not meet the NIH definition of clinical trial unless it also involved a prospective intervention arm designed to evaluate a change in a health-related biomedical or behavioral outcome would meet the NIH definition of a clinical trial.

14. If a proposed study involves prospective assignment of human subjects to one or more interventions that trigger a short term physiologic response, e.g., if a study involves providing a drug one time to see whether it increases blood flow in the brain, is such study a clinical trial?

It depends. The goal of a clinical trial is to show or lead to an impact on the health of individuals. In order to be a health-related outcome, the benefit of the intervention should be expected to extend past the end of the study even if the same beneficial intervention needs to be provided as clinical therapy after the study is over. If the intervention is diagnostic, a diagnosis that results in evidence-based treatment is a health-related outcome.

Health-related outcomes are not typically temporary in nature. Temporary effects rarely have a health impact. For example, a temporary increase of blood flow in the brain observed by MRI after the administration of buspirone is not a health-related outcome because the increase in blood flow is not necessarily associated with changes in health. (Case study #13).

On the other hand, if an investigator describes a study in which human subjects will be prospectively assigned to an intervention, and where the short-term effects of the intervention will be used to inform the course of therapy or establish the stage of a pathology, the study would be a clinical trial.

15. Does a study involving a single research participant meet the revised NIH definition?

It depends. If a study involving a single participant otherwise meets the definition of a clinical trial, it is a clinical trial.

16. Will the revised NIH definition capture more clinical studies not encompassed by the prior definition?

The revised definition is not intended to change the scope of the clinical trial category, and it shouldn't result in an increase or a decrease in the clinical trial portfolio.

17. Do changes to the definition of clinical trial affect the determination of whether a trial is subject to IRB review?

No. The Common Rule, 45 CFR Part 46, subpart A, determines whether research is subject to IRB review. See <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html>.

18. Does the revised definition of clinical trial affect the requirements for clinical trial monitoring?

No. According to NIH policy, all clinical trials must be monitored to ensure the safety of participants and the validity and integrity of the data. The level of monitoring depends on the nature of the clinical trial. See *NIH Policy for Data and Safety Monitoring* at <http://grants.nih.gov/grants/guide/notice-files/not98-084.html> and *Further Guidance on Data and Safety Monitoring for Phase I and Phase II Trials* at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html>.

19. Does the revised NIH definition of clinical trial apply retroactively?

No.

20. Has NIH's definition of a phase III clinical trial also changed?

No. NIH's definition of a phase III clinical trial has not changed. It is:

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.