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NIH Policies on Experimental Studies with Humans

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Abstract

The U.S. National Institutes of Health clinical trials policies will apply broadly to studies involving experimental manipulations of humans. These studies will require registration and reporting in ClinicalTrials.gov, grant application submission under a clinical trials funding opportunity announcement, and Good Clinical Practice training for investigators.

Last year, the National Institutes of Health (NIH) issued its clinical trials policies to enhance the accountability and transparency of clinical research (1). These policies, which become effective January 25, 2018, apply to all NIH-supported research that meets the 2014 NIH revised definition of a 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" (https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-015.html). The NIH sought and received input on these clinical trials policies and definition (https://www.gpo.gov/fdsys/pkg/FR-2016-09-21/pdf/2016–22129.pdf). Here we describe these policies and their rationale, and address concerns including the breadth of studies subject to these policies, the additional effort required to adhere to the policies, and how the implementation of these policies may affect basic brain and behavioral research studies included under these policies (2; https://www.nature.com/news/brain-researchers-in-uproar-over-nih-clinical-trials-policy-1.22550).

What is Required under the NIH Clinical Trials Policies and Why?

Transparency

Study Registration.—The International Committee of Medical Journal Editors (ICMJE) recognized the benefits of study registration when it began requiring it over a decade ago (3). Many brain, behavior, and social science journals also have recognized this benefit and have led efforts to promote study preregistration (https://cos.io/rr/)) which, when combined with complete study reporting, minimizes selective reporting of results and publication bias. *The NIH clinical trials policies require studies to be registered in ClinicalTrials.gov within 21 days of the first participant enrollment.* ClinicalTrials.gov already includes registration of thousands of behavioral and social science studies, including many describing their primary purpose as "basic science," and the NIH continues to improve ClinicalTrials.gov for registering a broad array of studies.

Study Reporting

The transparent and ethical conduct of research with humans demands not only study registration but also study reporting. Depending on the data source analyzed, a third to a half of studies fail to publish results in a timely manner (4,5). Among the reasons for this failure to publish results is publication bias against null findings. Taxpayers provide the funds to conduct these studies, and study participants donate their valuable time and accept both known and unknown risks to help advance our understanding of health and disease. These stakeholders rightly expect their sacrifices to benefit scientific progress even if the results are inconclusive or contrary to expectations. *The NIH clinical trials policies require that the primary study findings are reported in ClinicalTrials.gov within one year of the last primary data collection on the last participant.*

Accountability

Submission under Clinical Trials Funding Opportunity Announcement: Last year, the Government Accountability Office (GAO) issued a report on NIH stewardship of clinical trials and recommended that the Health and Human Services (HHS) Secretary direct the NIH to establish and implement a process for monitoring and reporting on the clinical trials that it funds (https://www.gao.gov/products/gao-16-304). To address this directive, *the NIH requires that clinical trials grant applications be submitted to Funding Opportunity Announcements (FOAs) that are specific to clinical trials*, and that applicants complete structured data fields that map to the registration fields in ClinicalTrials.gov (e.g., participants, design, outcomes). Submitting clinical trials applications via this process will allow the NIH to track more accurately clinical trial applications and funded grants.

Training

Good Clinical Practice is an international standard for the conduct and reporting of clinical trials (6). This standard was developed initially for industry trials, but the basic principles of ensuring the protection of participant rights, integrity, and confidentiality, and for ensuring data credibility and accuracy are broadly applicable to most research involving humans. *The NIH clinical trials policies require that all involved in the conduct or reporting of clinical trials obtain GCP training every three years.* Because GCP training available at most institutions is oriented to FDA-regulated clinical research, the NIH Office of Behavioral and Social Sciences Research (OBSSR) has made available the materials for a behaviorally-oriented GCP training that was developed by the University of Michigan with support from the Clinical and Translational Science Awards program funded by the National Center for Advancing Translational Research.(https://obssr.od.nih.gov/training/web-based-learning/good-clinical-practice-for-social-and-behavioral-research-elearning-course/) Professional organizations and academic institutions are encouraged to incorporate these materials into their learning management systems.

Which Studies are Included in the NIH Definition of a Clinical Trial and Why?

To understand the studies subsumed under the NIH definition of a clinical trial, the NIH has provided a decision tree (https://grants.nih.gov/policy/clinical-trials/CT-decision-tree.pdf.) that addresses the four key definitional criteria:

- Does the study involve human participants research? The terms “research study” and “human subjects” are defined as per the Common Rule (https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html)). It is important to note that the number of human participants is immaterial to this criterion; single case studies and small pilot trials are considered clinical trials if they meet the four criteria. Studies that would be determined by an Institutional Review Board not to involve human participant research (e.g., archival data, educational testing) do not meet this criterion for a clinical trial.
- Are participants prospectively assigned to an intervention? If the investigators are responsible for the intervention the participant receives, then the study meets this criterion for a clinical trial. Assignment does not need to be random or to multiple arms to meet this criterion; single arm, nonrandomized studies are considered prospectively assigned to an intervention. However, if entities other than the investigators (e.g., healthcare systems, policy implementers) assign the intervention, even if randomly, the study does not meet this criterion.
- Is the study designed to evaluate the effect of the intervention on the participants? Although behavioral and social scientists often refer to treatments as interventions, the term “intervention” is interpreted broadly as 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. Non-interventional or observational studies (e.g., cohort or case-control studies) are excluded by this criterion, including when standard measurement procedures within these studies may involve within-subject manipulations to assess a variable of interest (e.g., postural blood pressure, implicit attitudes test).
- Is the effect being evaluated a health-related biomedical or behavioral outcome? The NIH interprets “health-related” broadly to include outcomes that have relevance to health or contribute to a line of research intended to affect health. Many outcomes of interest to behavioral and social science researchers are “health-related,” and the the World Health Organization (WHO) has long encouraged a broad definition of health that includes physical, mental, and social aspects (http://www.who.int/about/mission/en/). While a variety of behavioral and social science outcomes are relevant to areas beyond health, it is reasonable to assume that if an investigator is applying to the NIH for funding, the investigator has determined that the outcomes of interest are health-related. There are two notable exceptions: 1) studies of the measurement properties of assessment instruments (e.g., reliability, validity, or specificity/sensitivity of questionnaires, imaging procedures, or cognitive tests) are excluded because the

study purpose is to evaluate the instrument, not a biomedical or behavioral outcome assessed by the instrument, and 2) feasibility trials of study procedures to test and refine these procedures, not to evaluate the effects of these procedures on a health-related biomedical or behavioral outcome.

As the research community offers examples of what may or may not meet these criteria, the NIH continues to refine case examples, including behavioral case examples, and make them available (https://grants.nih.gov/policy/clinical-trials/case-studies.htm). The following table provides behavioral and social science examples of studies that are or are not clinical trials based on the four decision tree criteria.

Addressing Continuing Concerns with the NIH Clinical Trials Policies

Why do these policies apply to some types of research but not others? The NIH has received comments that the research subject to these policies is too broad (e.g., basic mechanistic studies are not clinical trials) and too narrow (e.g., why are human observational studies and animal studies excluded from these policies?). While the prototypic clinical trial addresses the safety and effectiveness of a treatment for a clinical condition (or to prevent a condition), common definitions do not limit clinical trials to safety and effectiveness questions. For instance, the WHO defines a clinical trial as “any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes” (http://www.who.int/topics/clinical_trials/en/).

The studies subject to these clinical trials policies have different purposes (e.g., mechanistic trials, effectiveness trials) but share the common feature of prospectively assigning humans to interventions to evaluate a health-related biomedical or behavioral outcome.

The benefits of greater transparency and accountability extend beyond the studies subject to these policies, prompting some to comment that these policies are applied too narrowly. Human observational studies also are susceptible to selective reporting and publication bias, and ClinicalTrials.gov provides the capacity to register observational and well as intervention studies (7). The NIH encourages registration and reporting of observational studies, but the clinical trials definition requires prospectively assigned interventions which are not features of observational studies. NIH also has pursued strategies to improve the rigor and reproducibility of animal and other preclinical research (https://www.nih.gov/research-training/rigor-reproducibility), and while there are similar issues with selective reporting and publication bias, there are also unique aspects of molecular and animal research that contribute to rigor and reproducibility problems. The entire scientific enterprise can benefit from greater transparency, openness, and accountability (8), but within the constraints of the NIH clinical trials definition, these policies are being applied only to human interventional studies.

Why require registration and reporting to ClinicalTrials.gov? There are many excellent study registration and reporting systems available, including those listed in the WHO International Clinical Trials Registry Platform (http://www.who.int/ictrp/en/) as well as those managed by nongovernmental organizations, some of which have received support from the NIH (e.g., https://cos.io and https://dataverse.org). The aims of these clinical trials policies, however,

require a centralized registration and reporting system that, among other features, is freely and publicly available, sustainable in perpetuity, and readily linkable to NIH grant application data systems for monitoring purposes, making ClinicalTrials.gov the preferred solution. CClinicalTrials.gov is capable of receiving registration and reporting data obtained by other entities should alternative registration and reporting sites wish to link to ClinicalTrials.gov as a service for their users (https://prsinfo.ClinicalTrials.gov/prs-users-guide.html#section9).

The NIH recognizes that the benefits of greater transparency are not without costs. These policies will require additional time and resources for investigators. The required GCP training involves a few hours of online training to be refreshed every 3 years. The structured data entries in the clinical trials grant application parallel those in ClinicalTrials.gov, and entering these data in structured fields should reduce the narrative research strategy section of the application, but navigating this new application with structured data fields will take additional time to complete, especially for grants that propose multiple experiments. ClinicalTrials.gov already includes registration of a wide variety of human research studies and continues to improve the flexibility of the system for different study types, but registration and reporting still requires considerable time and effort. Adherence to these policies will require additional effort on the part of both investigators and the NIH staff, but registering and reporting these studies also fulfills an inherent commitment to study participants and the public that is shared by the NIH and the research community.

The NIH clinical trials definition has been interpreted broadly to apply these transparency, accountability, and training requirements to NIH-funded studies in which humans are prospectively assigned to interventions. The studies subject to these requirements have diverse aims, and the broad interpretation of the clinical trials definition is not intended to redefine basic human research as clinical research or to convey that these studies have similar purposes. Although this clinical trials definition has been adopted elsewhere for other purposes (e.g., under the revised Common Rule for posting informed consent), other agencies and entities may adopt different clinical trials definitions or interpretations of this definition. The NIH also does not intend for these policies to change the types or proportion of studies we fund. There will be a period of adjustment to these policies during which we will monitor any changes in the types of research proposals we receive, and the NIH remains committed to supporting a strong basic research portfolio (9).

Whether submitted under a clinical trials FOA or not, grant applications will continue to be assigned and reviewed by study sections with appropriate expertise. Basic behavioral and social sciences research applications, for example, will continue to be reviewed by basic behavioral and social scientists with appropriate scientific content expertise, not by clinical trialists. The NIH will continue to encourage reviewers to evaluate the proposed scientific approach in the context of the project aims, regardless of if the application is submitted under a clinical trials FOA or not. Investigators continue to have the option of contacting the Scientific Review Officer or the Project Officer if their application is assigned to a study section that does not appear to have appropriate expertise.

The NIH has developed a standard protocol template for Phase 2 and 3 clinical trials, and is working to adapt the template for comparable behavioral clinical trials. However, the extensiveness of the protocols submitted to ClinicalTrials.gov and to the NIH institute/center funding the grant will depend on the aims and risks of the proposed research. For most basic research, the protocol submitted to the IRB will be sufficient. The NIH recognizes that under the Revised Common Rule (https://www.gpo.gov/fdsys/pkg/FR-2017-01-19/html/2017-01058.htm), benign behavioral interventions may be exempt from IRB review, and NIH clinical trials policies do not require IRB review when the study is exempt from IRB review, but investigators still will be required under these circumstances to produce and submit a protocol to ClinicalTrials.gov and to the funding institute.

The NIH will continue outreach and communication with the research community regarding these policies and refine our implementation accordingly. The NIH also will continue to expand outreach efforts to the public and relevant research stakeholders. ClinicalTrials.gov is evaluating and refining its database filtering capabilities so that patients seeking active experimental treatments for their condition will be able to do so without scrolling through numerous basic science studies or studies involving healthy volunteers. The NIH also will continue to be clear with various stakeholders that the clinical trials data we monitor and report includes the broad definition of interventional studies (e.g., experimental manipulations) and is not limited to treatment safety and effectiveness studies only.

We look forward to working with the scientific community toward the common goal of producing rigorous and transparent health research that advances scientific progress and ultimately enhances health, lengthens life, and reduces illness and disability. For the purposes of the clinical trials policies addressing additional requirements for training, applying, registering, and reporting, the NIH's intent is to apply these policies broadly to research involving experimental manipulations of humans (i.e., interventional or non-observational human research). The implementation of these policies is not without effort and cost, and the NIH is committed to working with the research community to facilitate adjustment to these new policies. In addition to encouraging a more open, transparent, and efficient scientific enterprise, the result of these policies will be a comprehensive repository of NIH-funded interventional human research which can be accessed by the research community for meta-analyses and other scientific purposes.

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Table 1

NIH Clinical Trials Definition Criteria with Behavioral and Social Science Examples

Criterion	Is Not a Clinical Trial	Is a Clinical Trial
Human Participants Research	Longitudinal social network and physical activity data from an existing cohort are obtained and analyzed to assess how social networks and physical activity levels covary over time.	A sample of cohort participants are sent a fitness tracker and randomly assigned to have the information from the tracker sent to key social network connections to determine how this information influences physical activity among those within the social network.
Prospectively Assigned	A school system with limited resources provides an early childhood intervention only in some schools. Five years later, investigators evaluate health status and social functioning of the children in the schools who did and did not receive this intervention.	Investigators assign schools within a school system to deliver an early childhood intervention program. Over the next five years, the investigators assess health status and social functioning of those who did or did not receive the intervention.
Evaluate the Effect of the Intervention	Healthy volunteers and patients with Generalized Anxiety Disorder (GAD) are evaluated using a standard decision under ambiguity laboratory procedure that involves repeated within-subject trials (e.g., Iowa Gambling Task). fMRI, cortisol, electrodermal response, and perceived stress also are assessed, and healthy and GAD participants are compared on these measures and on the associations within each group.	Healthy volunteers are randomly assigned to a stress induction procedure prior to being evaluated using a standard decision under ambiguity laboratory procedure that involves repeated within-subject trials (e.g., Iowa Gambling Task). fMRI, cortisol, electrodermal response, and perceived stress also are assessed, and participants under stress induction and no stress induction conditions are compared on these measures.
Health-related Biomedical or Behavioral Outcome	Investigators compare an opt-in vs. opt-out method for establishing and contributing to health savings accounts. The investigators evaluate the effect of these two approaches on income stability, financial status, and net assets.	Investigators compare an opt-in vs. opt-out method for establishing and contributing to health savings accounts. The investigators evaluate the effect of these two approaches on healthcare access and health status.

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