



September 17, 2017

Michael S. Lauer, M.D.  
Deputy Director for Extramural Research  
National Institutes of Health  
9000 Rockville Pike, Bldg. 1  
Bethesda, MD 20892

Dear Dr. Lauer,

The Association of American Medical Colleges, Association of American Universities, Association of Public & Land-grant Universities and Council on Governmental Relations collectively represent hundreds of institutions that employ tens of thousands of researchers. We write to convey the concerns of our members that the definition of *clinical trial* has been significantly expanded through the set of case studies<sup>1</sup> recently published by NIH as a means to assist investigators in determining whether proposed research meets the NIH definition. The definition, issued in October 2014,<sup>2</sup> is the foundation for several policies administered by NIH. The three primary concerns of the research community are 1) that the case studies have themselves modified the definition so it now includes fundamental and basic health-related research, 2) that inconsistencies and insufficient clarity in the analysis may lead to different conclusions from institution to institution about which research will now constitute a clinical trial, and 3) that the impact on an investigator and research study of designating research as a clinical trial is more significant than has been acknowledged.

We appreciate your willingness to speak with us generally about these concerns and recognize that the NIH has a goal to demonstrate more transparency and accountability, under the principle that the outcomes of federally-funded research should be made available to the public. The website developed to explain the many changes to the NIH clinical trial policies states: “NIH has had difficulty reporting how many clinical trials it has funded and results from many NIH-funded clinical trials are never published or reported in a public database. Consequently, the Government Accountability Office (GAO) recommended NIH improve clinical trial data collection and establish and implement a process for using this data effectively.”<sup>3</sup> **The associations and our members share with you the goals of ensuring that the results of federally-funded clinical trials are made available to the public and expanding results reporting for federally-funded basic research involving humans.** As further detailed in this letter, and consistent with the feedback we have provided to you directly, with respect to basic health-

<sup>1</sup> Available at <https://grants.nih.gov/policy/clinical-trials/case-studies.htm>, revised September 8, 2017.

<sup>2</sup> “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.” Notice of Revised Definition of “Clinical Trial,” October 23, 2014, NOT-OD-15-015, available at: <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-015.html>.

<sup>3</sup> <https://grants.nih.gov/policy/clinical-trials/why-changes.htm>.

related research involving humans, we believe there is a more productive way to improve statistical rigor and results reporting that leverages existing resources and is less disruptive to the entire research enterprise. We are dedicated to working with the NIH to identify alternative approaches.

**1. The case studies posted by NIH demonstrate a change in the interpretation of the 2014 definition of *clinical trial*.**

In the October 2014 notice announcing a revised definition of *clinical trial*, the agency indicated that “the revision is designed 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.” Although similar intentions have been expressed in more recent presentations, several of the case studies have reached unexpected conclusions, encompassing as clinical trials research that has been considered to be basic or fundamental health-related research.

While we appreciate NIH’s efforts to provide clarity, some of the case studies recently published seem inconsistent with the original discussion of the definition in the 2014 notice. Specifically, many of the case studies designated as clinical trials are not consistent with the definitions or examples of an “intervention” or “health-related biomedical or behavioral outcome” provided in that notice. These case studies would in fact significantly expand the scope of what is defined as a clinical trial and subject health-related basic research to unnecessary oversight and restrictions that we believe would only serve to hinder scientific progress. We have included in the appendix a number of examples to illustrate the specific concerns outlined in this letter, but have not provided here a comprehensive analysis of each of the proposed and revised (as of September 8, 2017) case studies. If such an analysis would be useful to NIH, we would gladly provide one to your office.

The October 2014 notice announcing the new definition of a clinical trial defined *intervention* 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.” The case studies suggest that a manipulation that may result in a temporary physiological and/or behavioral change solely during the course of research participation for the purpose of measuring a physiological and/or behavioral response is a clinical trial, even when the studies are not designed to alter participants’ health or behavior. *Health-related biomedical or behavioral outcome* was defined in 2014 as “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.” Further, the provided examples of an “intervention” and “health-related behavioral outcome” did not suggest that basic health-related research that does not modify a health-related biomedical or behavioral outcome (i.e., the intent is not to change health or behavior but to measure a physiological and/or behavioral change strictly during the course of an experiment) would be considered a clinical trial.

The attached appendix includes several examples of case studies involving a manipulation only during the course of research and solely for the purpose of understanding physiology and/or behavior that NIH has indicated would now be considered a clinical trial.

**2. The case studies lack sufficient clarity, and may well lead researchers, institutions, program officers, reviewers, and policy experts to come to different conclusions as to whether or not some proposed research will be determined to be a clinical trial.**

With the significant consequences of research being designated as a clinical trial, that designation should be unambiguous in every case. Ongoing, robust discussions throughout the research community over the

past few weeks have demonstrated that even with these case study examples and explanations of the responses to each of the four questions, research activities may well be classified differently depending on who is undertaking that analysis. We are concerned that this would pose precarious conditions for the administration, funding, and oversight of research.

It is not clear whether investigators considering research activities similar but not identical to one of the case studies would know how to classify their research. As an example, case study 18b, describes an activity that would result in a change in brain activity during the course of the experiment but is not designated a clinical trial, while 18c and 18e, which are designated clinical trials, also involve only a physiological change during the course of an experiment to understand a physiological system. None of these activities are aimed at modifying a health-related biomedical or behavioral outcome with the goal of directly using that intervention to improve a participant or other person's health and well-being.

We have heard from institutions that have concluded they will be unable to provide any additional assistance to investigators attempting to determine whether their proposed research will need to be submitted under a clinical trial specific Funding Opportunity Announcement (FOA) due to the institutions' uncertainty about whether the NIH would come to the same conclusion. Instead, those wishing to apply for NIH funding will be directed to submit all inquiries to the NIH or relevant IC for guidance about whether the research (other than FDA-regulated clinical trials conducted under an IND or IDE) meets the clinical trial definition. This seems to be an inefficient and potentially burdensome approach to making these decisions, both for the NIH and for investigators.

### **3. The consequences of fundamental research being designated a “clinical trial” are significant.**

To underscore why absolute clarity in the definition of clinical trial is necessary, we remind you of the significant consequences of having research be declared a clinical trial, and why some of these requirements are inapplicable to or inappropriate for basic health-related research that isn't designed to change or affect health or behavior of the study participants. Once designated a clinical trial, the research is subject to the following requirements:

- **Registration and reporting requirements in ClinicalTrials.gov.** Clinical trials are subject to the HHS regulations on Clinical Trials Registration and Results Information Submission and the NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information.<sup>4</sup> In addition to the concerns echoed throughout the community that the current configuration of ClinicalTrials.gov is cumbersome to use and ill-suited in some respects for entering registration and results information for fundamental research, the utility of the database as a public resource for information about trials can be diluted with an expanded definition. Even with fields that could help to distinguish certain types of research from others, including basic research studies involving humans in a public repository called “ClinicalTrials.gov” is likely to cause confusion among the public as to which studies are clinical trials and appropriate or available for enrollment and participation. We share the goal of making ClinicalTrials.gov as useful and accurate as possible and are concerned that the incorporation of large numbers of fundamental health-related research studies into the database could have the unintended consequence of rendering it less effective as a communication tool.

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<sup>4</sup> “NIH Policy on Dissemination of NIH-Funded Clinical Trial Information,” September 16, 2016, NOT-OD-16-149, available at <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-149.html>. See also the NIH discussion of the relationship between the NIH policy and the regulations related to ClinicalTrials.gov, at <https://grants.nih.gov/policy/clinical-trials/reporting/understanding.htm>.

- **Good Clinical Practice (GCP) training for all investigators and “clinical trial staff.”** While all researchers should have the requisite training to ensure rigor and reproducibility of research results and appropriate methodological training to address the design and conduct of research, whether basic or pre-clinical, many of the elements of GCP training<sup>5</sup> are not applicable to the types of research designated as a clinical trial in some of the case studies.
- **Limitations on the ability to apply for grants other than through clinical trial-specific FOAs.** Researchers have expressed concerns about reduced funding opportunities if their ability to apply for grants from NIH is restricted to clinical trial specific FOAs<sup>6</sup> and the relevant institutes issue insufficient or inconsistent FOAs. A lack of clarity on whether specific research meets the definition of *clinical trial* would further compound the issue, with some investigators’ applications potentially being rejected because they should have classified their research as a clinical trial and applied through an FOA and other possible rejection or funding limitations because they should not have applied through a clinical-trial specific FOA.
- **Training awards will not be able to be used for clinical trials.** Research currently considered basic research on fundamental health-related systems is at times led by qualified trainees. Designating this same research as a clinical trial would prevent trainees from leading the project, ending or hampering some research, under new NIH policy.<sup>7</sup>
- **New human subjects and clinical trials forms.**<sup>8</sup>
- **A single IRB review for collaborative research.**<sup>9</sup>

Reclassifying and regulating basic research as clinical trials would subject both faculty and research administrators to additional regulatory requirements, a change that runs counter to the agency’s other broader efforts to streamline and identify administrative efficiencies, an effort that both Congress and the executive branch are advancing. Furthermore, many institutions, especially those without a substantial biomedical research community, simply do not have the resources or experience to address all these additional requirements that would result, and the administrative burden would be greater for researchers at institutions lacking these resources. Particularly for these institutions, the barriers to applying for and obtaining NIH funding is likely to become substantially more significant.

We appreciate your continued efforts to engage and inform the research and higher education communities in this process and look forward to continued conversations about how best to assist the NIH in reaching the laudable goals of transparency and accountability, consistent with the principles that have been articulated, the tools available to the agency and community, and the constraints that are already imposing challenges to the research community as a whole.

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<sup>5</sup> <https://grants.nih.gov/policy/clinical-trials/good-clinical-training.htm>

<sup>6</sup> <https://grants.nih.gov/policy/clinical-trials/specific-funding-opportunities.htm>

<sup>7</sup> See “Special Considerations for Training, Fellowship, and Career Development Awards,” at <https://grants.nih.gov/policy/clinical-trials/specific-funding-opportunities.htm>.

<sup>8</sup> <https://grants.nih.gov/policy/clinical-trials/new-human-subject-clinical-trial-info-form.htm>

<sup>9</sup> <https://grants.nih.gov/policy/clinical-trials/single-irb-policy-multi-site-research.htm>

**About the Signatory Associations**

The Association of American Medical Colleges is dedicated to transforming health care through innovative medical education, cutting-edge patient care, and groundbreaking medical research. Its members comprise all 147 accredited U.S. and 17 accredited Canadian medical schools; nearly 400 major teaching hospitals and health systems; and more than 80 academic societies. The Association of American Universities is an association of 60 U.S. and two Canadian preeminent research universities organized to develop and implement effective national and institutional policies supporting research and scholarship, graduate and undergraduate education, and public service in research universities. The Association of Public and Land-grant Universities (APLU) is a research, policy, and advocacy organization with a membership of 235 public research universities, land-grant institutions, state university systems, and affiliated organizations in the U.S., Canada, and Mexico, that is dedicated to strengthening and advancing the work of public universities. The Council on Governmental Relations (COGR) is an association of over 190 leading research universities and affiliated academic medical centers and independent research institutes. COGR concerns itself with the impact of federal regulations, policies, and practices on the performance of research conducted at its member institutions.

## Appendix: Selected Case Study Examples

Case #9: The study involves the recruitment of healthy volunteers who will be randomized to different durations of sleep deprivation (including no sleep deprivation as a control) and who will have stress hormone levels measured. It is designed to determine whether the levels of stress hormones in blood rise in response to different durations of sleep deprivation.

In this case study, NIH has designated the research as a clinical trial because it has been determined to include an *intervention* (“the participants are prospectively assigned to an intervention, different durations of sleep deprivation followed by a blood draw”) that has a health-related biomedical or behavioral outcome (“stress hormone levels”). In this case study, there is a manipulation but not for the purpose of modifying a health-related biomedical or behavioral process or endpoint. The manipulation may result in a temporary physiological change during study participation (i.e., a possible fluctuation in stress hormone levels) but it will not modify the biomedical or behavioral status or quality of life of those participating in the research. The intervention serves only to determine whether stress hormones levels in blood rise in response to different durations of sleep deprivation. This basic research study can improve our understanding of the physiological effects of sleep deprivation and ultimately human health, but does not seek to demonstrate whether any particular intervention has an effect on sleep disorders or has an effect on health or behavior. **We believe that this case study should not be designated a clinical trial.**

Case #14: The study involves the recruitment of healthy volunteers for a respiratory challenge study; participants are randomized to receive different combinations of allergens. The study evaluates the severity and mechanism of the immune response to different combinations of allergens introduced via inhalation.

Again, this intervention does not modify a health related biomedical or behavioral process and/or endpoint. The intervention serves only to determine the severity and mechanism of the immune response to different combinations of allergens introduced via inhalation. The study will not address a participant’s allergies or attempt to alter health or behavior. This basic research study can improve our understanding of the immune response to combinations of inhaled allergens and ultimately affect human health through the development of treatments or hypotheses based on this research. **We believe that this case study should not be designated a clinical trial.**

Case #18c: The study involves the recruitment of healthy volunteers who are randomly assigned (either between-subject or with-in subject in a counterbalanced design) to one of two experimental conditions to enhance or interfere with cognitive performance. The effects of these conditions on cognitive performance (e.g., working memory) and brain function during the cognitive performance task are measured (e.g., fMRI).

In this context, the study is designed to determine if performing the cognitive task under conditions hypothesized to enhance or interfere with the task will alter cognitive task performance and associated brain activity. It is not being used to modify a participant's health-related biomedical or behavioral outcome but to temporarily modify a behavioral and/or physiological response to better understand conditions under which cognitive task performance could be enhanced or compromised and the associated physiological response. **We believe that this case study should not be designated a clinical trial.**

Case #18e: The study involves the recruitment of healthy volunteers. Half of the volunteers are randomly assigned to an MRI in a real MRI scanner, then perform a working memory task outside of the scanner. The other half will have an MRI in a mock MRI scanner, then perform a working memory task outside of the scanner. It is designed to determine if exposure to the magnetic field impacts working memory performance.

Here, there is a manipulation but not an intervention for the purpose of modifying a health-related biomedical or behavioral process or endpoint. The manipulation may result in a temporary physiological or behavioral change (i.e., a change in working memory performance during the course of fMRI) but it will not impact the biomedical or behavioral status or quality of life of those participating in the research. **We believe that this case study should not be designated a clinical trial.**