

In dialogue with the NIH on clinical trials policy

In his capacity as immediate past president of the Federation of Associations of Behavioral and Brain Sciences, Jeremy Wolfe interviews Mike Lauer about the new NIH clinical trials policy. Mike Lauer is NIH's deputy director for extramural research, serving as the principal scientific leader and advisor to the NIH director on the extramural research programme.

■ **Thank you for taking the time to answer a few of the questions that have been worrying scientists in the basic human behavioural and brain sciences about the implementation of the new clinical trials policy. Perhaps you could start by telling us what the National Institutes of Health (NIH) goals are for this policy?**

Thank you for the opportunity to talk. When we announced our clinical trial policies, we were addressing two major concerns: first, the main results for perhaps as many as half of NIH-funded trials are not publicized within a reasonable time frame (for example, within 2.5 years of completion). Many results are never reported. Second, as the Government Accounting Office pointed out, the NIH as an agency wasn't collecting a minimum amount of data to enable it to function as effective stewards. Our goals are transparency and stewardship.



Left photo: Jeremy Wolfe runs the Visual Attention Lab of Brigham and Women's Hospital, Boston, MA. Right photo: Mike Lauer is deputy director for extramural research at the NIH. Credit: Ernie Branson

The scope of the definition

■ **That makes sense. Our community has been working towards more openness in research and we have been looking for ways to reduce the 'file drawer' effect, where negative findings are not reported. That said, we have been worried about possible adverse consequences of characterizing basic human behavioural and brain sciences as 'clinical trials'. There are two broad areas of concern. First, to what extent is the definition of clinical trial being expanded and, second, what happens if your basic science study is classified as a clinical trial? Let's start with that first question: What is now defined as a clinical trial in the basic behavioural and brain sciences? We have read the 2014 definition but, as you well know, there is a lot of room for interpretation. Can you help us out here?**

We have tried to offer guidance with a set of case studies. If you read through them, that should give you a pretty clear idea. We continue to revise them as we hear questions and feedback. The case studies address a number of points — when is a study observational, what exactly is meant

by an intervention, what is the purpose of a study, and what outcomes are behavioural or biomedical. Some interventional studies are done for the purpose of evaluating the effects of an intervention on an outcome — for example, if a scientist deliberately deprives a person of sleep, does that lead to increased release of stress hormones? That's a trial. In other interventional studies, the scientist's goal is different — for example, does a different pulse frequency lead to better-quality images? That's not a trial. Along the same lines, some pilot studies would not be considered clinical trials — see, for example, case 18g.

■ **This is not intuitively obvious and getting it right is important for grant applications.**

We will continue to try to clarify through the case studies. That said, if you don't come to a clear answer when you consult our decision tool along with the case studies and FAQs, you should ask your program officer — by the way, you should always have a low threshold to ask your program officer questions about anything. If program officers are not sure, they will contact me. If you follow your program officer's opinion,

your grant proposal will not be disqualified for being on the wrong side of the clinical trial definition.

■ **In the 2014 definition, it says that the new definition "is not intended to expand the scope of the category of clinical trials". We certainly feel as though we have been included in a greatly expanded category of clinical trials.**

I understand why you feel that way, but in fact nothing has changed since 2014. In our 2014 guide notice, we wrote, for example, that trial outcomes could include "changes to physiological or biological parameters (for example, improvement of lung capacity, gene expression)". Thus, by what we wrote back in 2014, researchers who prospectively assigned interventions to determine whether those interventions modify physiological or biological parameters were conducting studies that fell within our definition.

■ **I guess we will have to agree to disagree about this. If we are doing clinical trials, we are somewhat confused about distinctions among different kinds of clinical trials. There are 'mechanistic trials' and 'clinical outcome' trials. We are**

particularly nervous about the Food and Drug Administration (FDA)'s 'applicable clinical trials'. We assume that basic science clinical trials are not subject to the oversight and penalties in the FDA system, but could you clarify this for us?

Most of the basic behavioural and brain science clinical trials funded by the NIH are likely to be [mechanistic trials](#). They are not subject to oversight and penalties in the FDA system. Those rules pertain to ['applicable clinical trials'](#). Basically, applicable clinical trials evaluate products regulated by the FDA.

Our definition and guidance is relevant only to studies funded by the NIH. This is entirely independent of whether a trial is an ['applicable clinical trial'](#) under FDA rules and regulations. Our policy does not increase the universe of trials defined as ['applicable clinical trials'](#) under the FDA rule.

Application and review process

■ **Let's talk about the application process. Early on, we heard that grants that included clinical trials needed to be submitted under different funding opportunity announcements (FOAs). How does that work?**

Yes, it will be important to submit your grant under the right FOA. There is a [parent R01 announcement](#) for clinical trials and another [parent R01 announcement](#) for proposals that do not include clinical trials. Importantly, some institutes and centres are issuing their own announcements — for example, the National Eye Institute, whose announcement is [here](#). Many new FOAs and request for applications (RFAs) come in two versions, one allowing clinical trials and another excluding them. Basically, if your grant includes a clinical trial, you will submit under an appropriate clinical trial FOA. Again, when in doubt, ask your program officer.

■ **And how will this change the review of our grants? Will they be reviewed by clinical trials study sections that don't understand our science?**

Your proposal will not be sent to an inappropriate study section just because you have submitted in response to a clinical trials FOA. We anticipate that a proposal whose primary purpose is basic science will go to existing Center for Scientific Review study sections. Most likely, the study section that you would have gone to before the policy changed will be the study section you go to now. At that study section, we will not be 'clustering' trials. That means that

applications that include clinical trials will be mixed in with other applications (as is the case now). So, for the most part, we will be assigning applications to study sections exactly as we do now — but again, if you have concerns, never hesitate to ask your program officer.

■ **New review criteria are listed for clinical trials grants. Can you describe how those will affect basic behavioural and brain science?**

In practice, you will probably not notice any substantive change in the way that your grants are reviewed. We describe our review criteria for clinical trials [here](#). While I encourage readers to look there, here are two questions that reviewers will be asked to answer for basic science proposals that include clinical trials:

- Is the scientific rationale supported by preliminary data, information in the literature or knowledge of biological mechanisms?
- For trials focusing on mechanistic, physiological, biochemical or other biomedical endpoints, is this trial needed to advance scientific understanding?

I think you will agree that these are questions that any proposal should be able to answer. I had more to say about this topic [here](#).

Training grants

■ **We had a specific concern about training grants, as we understood that these could not propose clinical trials. Many of our postdocs are funded by F32 National Research Service Award individual postdoctoral fellowships. The research plan is an important part of those proposals and would typically include what might now be considered a clinical trial. We understand that it was not the intent of this policy to make it harder for our students to get postdoctoral fellowships. Can you explain how this will work?**

Yes, that's absolutely right — the policy is not intended (nor should it) make it harder for students to get support for postdoctoral fellowships. As we say on [our website](#), "NIH encourages fellows to receive training in clinical research, however, NIH supported fellows are not permitted to conduct a clinical trial independently." What does that mean? It means that "NIH expects the mentor or individual receiving support for the clinical trial to assume overall responsibility for the trial." We will ask applicants for F- and T-series

awards to provide details of their planned contributions to the study in the research strategy section of their application. For the sort of basic behaviour research that we are discussing here, this means that you, the postdoctoral applicant, will propose a programme of research and, if that work is classified as a clinical trial, your mentor will confirm that s/he accepts overall responsibility.

K-awards are a bit different in that some K-award FOAs will support independent clinical trials conducted by the applicant. Other K-awards will be just like F- and T-awards, where the mentor or individual receiving support for the trial must assume overall responsibility. For details, see [notice NOT-OD-18-001](#).

More on application and review

■ **Quite a few new RFAs say, "clinical trials not allowed". For example, consider the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) initiative RFA, 'Proof of concept development of early stage next generation human brain imaging' (RFA-EB-17-003). Would we be correct to assume that if someone proposed to test one of these new technologies, that would not be a clinical trial because methodological studies would not be classified as clinical trials? Yes, that's right. It's not a trial if the purpose of the study is to develop or evaluate a method.**

■ **Some FOA's require clinical trials, others exclude them. What happens if your proposal includes both clinical trials and studies that are not clinical trials? That could easily happen if, for example, experiment 1 is a methodological study and experiment 2 is a clinical trial. That's a great question. Briefly, if any of the proposed experiments are classified as clinical trials, you would submit to a FOA that accepts trials. Go [here](#) for an illustrative graphic.**

■ **In the application process, a proposal for a traditional clinical trial might just describe a single trial. However, basic behavioural and brain science usually involves a string of experiments, each of which could be a clinical trial. The new FORMS-E grant proposal asks for a separate form for every clinical trial. Is there some way to avoid or streamline the filling-out of what could be a couple of dozen pages of forms? Your question gets to the tension between lumping and splitting. We would encourage**

lumping. That is, to the extent possible, describe a series of experiments as a set of variants of a single design. Then one registration can cover all of them. The FORMS-E grant proposal will work in a similar way; you could describe several studies as variations of one basic experiment.

Changes in your research plan

■ **In what we can call 'discovery science', we don't necessarily know all of the specific experiments that we will do over the course of a grant. Experiment 2 might depend on the outcome of experiment 1 or a journal editor might require a new experiment. Whole new lines of experiments, related to the current aims but unmentioned in the grant, may emerge during the course of our work. Will this be a problem?**

I don't think so. If a new study is defined as a clinical trial, you will need to register it within 21 days of the start of data collection and you will need to report results in a timely way. Beyond that, you will need to report you plans in your annual non-competing renewal. Your program officer will need to be convinced that the work is within the scope of the grant, but that is the case now.

■ **What if we change a clinical trial after it has started (for example, abandoning a version that isn't working and starting a new one).**

The most important consideration is the need to document what you did. Report the result in ClinicalTrials.gov, even if that result was that the method didn't work.

Remember, at all times, you should never hesitate to contact your program officer. This is especially true if you are thinking of making a substantial change in the nature of your work. We have a [dedicated section](#) in our NIH Grants Policy Statement about our policy on change in scope. When in doubt, ask!

Institutional review board issues

■ **Under the new Common Rule, many of our studies will be exempt from institutional review board (IRB) oversight because they involve 'benign behavioural interventions'. Will that be a problem in the application and review process? We are also concerned about possible a public relations problem if someone learns about "NIH clinical trials that do not require IRB-approved informed consent"? Will it be possible to register in ClinicalTrials.gov**

with a basic science clinical trial that is exempt from a requirement for full IRB approval?

Yes, that is not a problem. We understand that certain studies that meet the definition of a clinical trial will at the same time be exempt from a requirement for full IRB approval.

■ **Does clinical trial status require that we have a data and safety monitoring board like a drug trial would have?**

Our policy, as we've [issued before](#), is that "safety monitoring should be commensurate with risks". If your study did not require a data and safety monitoring board before, it in all likelihood would not now.

Required training

■ **Researchers involved in clinical trials will be required to take Good Clinical Practice (GCP) training. We understand that this refers to an online course that might take an hour or two. That seems reasonable. Can you give us a link to a list of courses that would satisfy this requirement and, better yet, would be relevant for basic science researchers?**

We posted on [our website](#) the specifics of our policy on GCP training. Our policy does not specify that a particular GCP course or programme be taken. There are many available programmes, including [one offered by the National Institute on Drug Abuse](#) and [another by the Office of Behavioral and Social Sciences Research](#). And I know that a number of institutions offer GCP courses for behavioural researchers, like [the one offered by the Collaborative Institutional Training Initiative](#).

■ **If undergraduate students are helping with a study as many students do, for a few hours a week during term, do they need to satisfy the GCP training requirement?**

Our [policy on GCP training](#) states that the expectation for training applies to "Individuals, identified by the investigator, who are responsible for study coordination, data collection and data management . . . These individuals may also seek informed consent from prospective participants, enroll and meet with research participants, and collect and record information from research participants." So if undergraduate students engage in these activities, then, yes, they should spend the few hours it takes to complete GCP training.

Indeed, a course like the Office of Behavioral and Social Sciences Research [GCP](#)

course might be interesting, important and well-suited for students who are new to the world of human experimentation. Topics include the elements of protocols (including IRB protocols), standard operating procedures, fidelity, protocol deviations, best practices for recruitment and retention, the informed consent process, confidentiality and privacy, safety and adverse event reporting, quality control, and research misconduct.

Public relations

■ **Thank you. We have one last concern today. We think that there is a real possibility for confusion and worse when the public encounters studies that are labelled as clinical trials under the new NIH definition but that are not clinical trials under a more traditional definition. For example, we worry that a congressional staffer, looking for waste, might target a basic science study that is funded as a clinical trial. We can defend the value of basic discovery science. We can defend the value of clinical trials. We are concerned about having to defend basic discovery science as a clinical trial. What would you suggest?**

This is an important question. I don't think this will emerge as a problem, though, since our overarching message is that our goal — and by that I mean the goal of all of us in the biomedical research enterprise — is to foster transparency and quality. By assuring the public that scientists will, in a timely manner, report the results of all human subject experiments, no matter how different scientists might classify them, we will increase accountability of and confidence in our work.

We may not agree with all aspects of this policy, but we appreciate your willingness to work with us to make the policy function as well as possible. Thank you for your time.

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