Dear Dr. Wolfe and Colleagues

Thank you for your letter to Dr. Francis Collins; you ask the NIH to delay implementation of its policy to assure timely dissemination of clinical trials information "until adequate feedback about its impact is obtained from the affected scientific community." I have been asked to reply.

I am attaching a copy of the final policy, which was released on September 12, 2016, over a year ago. The policy became effective on January 18, 2017. The document includes information (pages 2-3) about the process by which NIH issued (in November 2014) its proposed rule, sought public input (from November 2014 through March 2015), and synthesized ~240 comments from individuals, organizations (e.g. Brigham and Women's Hospital / Massachusetts General Hospital, Children's Hospital of Philadelphia Research Institute), and professional societies (e.g. Association of American Medical Colleges and the Federation of American Societies for Experimental Biology) that together represent large and diverse groups of stakeholders.

I am also attaching a slide presentation based on a meeting with the NIMH Advisory Council. Many of the issues you raise in your letter were discussed at that meeting.

I will now address your specific concerns:

1) "Basic scientists whose research is now deemed a 'clinical trial' may only submit applications for funding through a funding opportunity announcement (FOAs) designated specifically for clinical trials, even though other funding vehicles are more appropriate."

A key function of our policy on designated FOAs is to enable NIH to identify proposed clinical trials. Only by having a reliable way to identify trials will NIH be able to assure the public that all its funded trials are registered and that results from all its funded trials will be reportedwithin one year of completion (see slide 12).

We recognize that there are many types of trials, ranging from exploratory trials to pivotal treatment trials. As we noted in the attached document, we heard concerns that the scope of our proposed dissemination policy was too broad, and conversely that it was too narrow. We stated (page 11) that "We disagree with commenters who suggested that there is no need for coverage of certain types of trials, such as early exploratory trials, small trials, trials assessing only safety, or trials that terminate before reaching enrollment targets. The benefits of transparency and the need to fulfill *the ethical obligation to participants* is as relevant to these types of trials as to any other type."

We appreciate that some trials' primary purpose is fundamental discovery about human biology and behavior. A search on clinicaltrials.gov for "Primary Purpose: Basic Science" and "Interventional Studies" yields 1638 entries. Among these 1638, there were ~1100 that enrolled healthy volunteers.

Some NIH institutes plan to join a "Parent R01 – Clinical Trials" FOA. This FOA will look like the current Parent R01 FOA, with the exception that it will ask for some additional summary information pertinent to studies that meet the NIH definition of clinical trials. At the NIMH Council meeting, Dr. Joshua Gordon stated that NIMH is considering participating in this Parent R01 FOA, as this would be an appropriate venue for basic science trials.

2) "The basic research studies now classified as 'clinical trials' will be reviewed by study sections constituted by clinical trial review and would need to be significantly reconstituted to handle discovery science."

We will assign all proposals to study sections with the most appropriate expertise. For most trials coming in through the "Parent R01 FOA – Clinical Trials," proposals will be assigned to standing study sections in CSR using our current approach. We will not be assigning discovery science proposals to study sections that are used to reviewing Phase 2-3 trials; we agree that would not be appropriate.

3) "Training grants cannot be used to fund 'clinical trials,' so basic research involving humans will be ineligible for T awards."

Basic research involving humans will be eligible for T awards. Appointed trainees will be permitted to obtain research experience in a clinical trial led by a mentor.

4) "Exploratory research, which is the lifeblood of discovery, would be hampered. If exploratory research could be registered at all, such registration is likely to slow the pace of research, impeding innovation and discovery."

We addressed this concern in the attached document (page 16). "With regard to the concern that ClinicalTrials.gov is not set up to accept NIH-funded trials that are small or exploratory in nature or involve behavioral interventions, it is important to note that the ClinicalTrials.gov does accommodate the submission of all trial types and that a variety of study and trial types have been entered into ClinicalTrials.gov since its inception. In addition, ClinicalTrials.gov has resources available to assist investigators in navigating the registration and results information submission processes. These resources will continue to be updated over time to be responsive to investigators' needs…"

5) "The new policies unnecessarily increase the administrative burden on investigators, and this burden will fall disproportionately on researchers at less well-funded universities and colleges, which have fewer administrative resources."

We addressed this concern in the attached document (page 10). "We appreciate those concerns and understand that the policy will create additional work for many investigators. However, we believe that the work should not be seen as a burden, but, rather, an inherent part of an investigator's commitment to the advancement of science. The benefits will, in the long run, accrue to the investigators as well as to the public, patients, and the enterprise as a whole because transparency will improve future research designs and maximize the public's investment – and their trust – in research. Equally important, *it will help investigators fulfill the ethical obligation they have* to clinical trial participants, namely to ensure that the findings from their participation contribute to generalizable knowledge and the advancement of public health …"

6) "Members of the public who seek information in clinicaltrials.gov will find a potentially confusing array of basic science experiments that are not in the clinical trial stage."

As noted, clinicaltrials.gov already has a large body of registered trials whose primary purpose is basic science. While efforts are underway here and elsewhere to help people and patients find trials of interest, our key concern, as we note on pages 10-11 of the attached document is that "A fundamental premise of all NIH-funded research is that the results of such work must be disseminated in order to contribute to the general body of

scientific knowledge and, ultimately, to the public health. The NIH awardees have always been expected to make the results of their activities available to the research community and to the public at large because it is intrinsic to the scientific process. *In research involving human beings, moreover, scientists also have an ethical obligation* to ensure that the burden and risk that volunteers assume by participating in research comes to something, at the very least by ensuring that others are aware of the study and that its findings contribute to the advancement of human health."

7) "Affirm that health-related discovery science is an important part of the NIH research portfolio that enables us to build a foundation of fundamental knowledge that will be needed, in time, to design clinical trials."

NIH leadership has affirmed this publicly – see here and here.

8) "Take this opportunity to invite to NIH representatives from affected basic science communities, listen to the concerns raised, and work with us to shape a policy for this important segment of NIH grantees."

As noted in the attached documented, we have already undertaken an extensive process to solicit public input; we considered the hundreds of comments we received when developing the policy. We are happy to meet with representatives of the extramural science community to discuss ongoing implementation of our policy to assure timely dissemination of NIH-funded trial information.

9) "Specifically develop a protocol for promoting transparency and replicability based on input from the basic science community. A new protocol could be based on existing efforts such as OSF and OpenfMRI."

We would be happy to explore this as a possibility with you, in concert the ongoing evolution and implementation of the NIH policy (attached and see here).

Sincerely yours,

Michael Lauer, MD

Michael S Lauer, MD
Deputy Director for Extramural Research, NIH
One Center Drive, Building 1, Room 144
Bethesda, MD 20892
301-496-1096
Michael.Lauer@nih.gov