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Subject: "... brain scans (e.g., fMRI)" is *not* a clinical trial, but "fMRI ... during [a] gambling task" *is* a clinical trial? Revisions to official guidance increase confusion.

Date: January 8, 2018 at 9:22:30 AM EST

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Dear Dr. Collins,

Unfortunately, you really ought to look into this right away. Just weeks before the (self-imposed) deadline for rollout of new policies on clinical trials, Dr. Michael Lauer has released a re-revision (third version) of the example "Cases" at <<https://grants.nih.gov/policy/clinical-trials/case-studies.htm>>. Remarkably, this new version actually **adds** a great deal of unnecessary and harmful confusion.

Please consider the distinction between Case 18A (an fMRI study that is **not** a clinical trial) and 18C (an fMRI study that **is** a clinical trial):

- In case 18A, fMRI is used ("Participants are administered ... brain scans (e.g., fMRI)"), and the determination is made that the research project is **not** a clinical trial.
- In case 18C, fMRI is used ("The investigators will measure the comparative effects of 'wins' and 'losses' on brain function (fMRI in striatal regions) during the gambling task."), and the determination is made that the research project **is** a clinical trial.

This naturally raises the question: Would the findings of case 18C apply if the (unspecified) fMRI task in case 18A involved 'wins' and 'losses' or 'gambling'? If so, then how (and by whom) shall fMRI studies be assessed? Do all tasks designed to probe (say) working memory and early visual processing fall under case 18A, while tasks designed to probe the reward system are to be considered clinical trials, per Case 18C? Will NIH publish an annotated catalog of fMRI tasks, to inform researchers which ones are clinical trials?

How did we get here?

Such nit-picking arguments should be unnecessary, given the clear divide between basic research and clinical trials. In biology, the idea of a manipulation is fundamental to the definition of experimental (vs. observational) science. Basic science relies upon seeing how manipulations affect measurements, while clinical trials are about seeing how interventions affect health or biomedical-related outcomes.

Historically, there has been little confusion regarding these distinctions, but Dr. Lauer's "Cases" avoid this historical understanding, and instead manifest expansive readings of "intervention" and "health outcomes", so as to create a vast enlargement of the category of clinical trials, in a manner that diverges from NIH's 2014 statement that new definition "is not intended to expand the scope of the category of clinical trials" (<<https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-015.html>>).

The threat to American science and public health posed by the looming reclassification as clinical trials of so much of what has long been recognized as basic research has been well documented by others, in the form of letters, petitions, scientific papers, and news articles. I am writing today to point out, urgently, that NIH's amiable rhetoric of progress-towards-shared-goals cannot be sustained by last week's release of a mystifying new version of the "Cases".

The "Cases" continue to disregard historical understanding, remain inconsistent with NIH's 2014 statement of purpose, and greatly increase unnecessary and harmful confusion. (Again, please consider: "... brain scans (e.g., fMRI)" is **not** a clinical trial, while "fMRI ... during [a] gambling task" **is** a clinical trial!) The re-revised "Cases" violate the first rule of holes, which is "Stop digging."

Basic research and clinical trials both serve public health, and respecting the distinction between the two is valuable. The NIH should slow down and take time to fulfill the good intentions and laudable goal of increasing transparency and reporting in clinical research, without the harm to science, health, and trust that the unintended consequences of the new policies will bring.

Sincerely yours,

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