August 14, 2018

Lawrence Tabak, DDS, PhD
Principal Deputy Director, National Institutes of Health
Building 1, Room 126A
1 Center Drive
Bethesda MD  20814

Re: Request for Clarifying Clinical Trial Case Study

Dear Dr. Tabak,

I am writing on behalf of the American Society for Investigative Pathology (ASIP), a nonprofit educational 501(c)(3) organization primarily representing the academic pathology research community. We are a society of biomedical scientists who investigate disease, linking the presentation of disease in the whole organism to its fundamental cellular and molecular mechanisms. Our members use a variety of structural, functional, and genetic techniques, seeking to ultimately apply research findings to the diagnosis and treatment of patients. Our society represents approximately 1,000 physicians and doctoral scientists who perform or are involved with pathology research in academic medicine, government, and private industry. We are one of the earliest members of the Federation of American Societies for Experimental Biology (FASEB).

We have appreciated your ongoing leadership regarding the recent expansion of the definition of a clinical trial. Indeed, that is why the ASIP is writing today to request that an additional case study be added to the current website. ASIP members believe strongly that the following (or comparable) case study should fall outside of the definition of a clinical trial:

A research study is being conducted comparing fluorescence in situ hybridization probe (FISH probe) type A with FISH probe type B to determine which probe is better able to detect mutations associated with a specific gene. Identifiable biospecimens will be used (for purposes of this example it should not matter whether the sample is from previously consented archived biospecimens or whether the sample is gathered under the appropriate consent with the specific intent to use it in this research example). The identifiable biospecimens are randomly assigned to be either type A or type B. For comparison, the same gene region is analyzed using direct DNA sequencing. Conclusions are drawn as to the accuracy of each type of FISH probe.

It is inappropriate to call the above study a clinical trial, nor is it a prospective basic science study involving human participants. There is no intervention at the level of the individual research participant or their physical environment other than to gather consent if needed. Hence there is no “involvement.” There is no potential harm nor potential benefit to the donor of the specimen regardless of which arm of the study the biospecimen is assigned to. There is no clinically-relevant information obtained. There is no plan to return results. Furthermore, if the researcher were to design the research study instead to take samples and analyze them with FISH probe A and then by DNA sequencing and, in a separate research project, take samples and analyze them with FISH probe B and then by DNA sequencing, you would get to the same research conclusion – which FISH probe is most accurate. Yet this second, more cumbersome research project would not be considered a clinical trial as it lacks prospective assignment.
It seems to the ASIP that the crux of the challenge is in the definition of prospectively assigned. As currently defined, prospectively assigned is “as related to the definition of a clinical trial, a pre-defined process (e.g., randomization) specified in an approved protocol that stipulates the assignment of research subjects (individually or in clusters) to one or more arms (e.g., intervention, placebo, or other control) of a clinical trial.”¹ This does not specify that the research is directly on the individual research subject or their environment – as opposed to physically removed from the subject and their environment as would be the case with a biospecimen.

There is also the second challenge of the definition of “involvement,” which is currently an undefined term on the ClinicalTrials.gov definitions webpage.² Research where the participation is the important, but limited, act of donating a biospecimen does not “involve” a research participant in the research and the participant is not directly affected by procedures performed in the research study or the outcome of the study.

As an organization, we are committed to rigorous science that is both transparent and reproducible. We also support data sharing obligations as set forth by NIH through platforms appropriate to the nature of the research. Our desire for this clarification is based in a common-sense approach that such a research example is true basic science and not a clinical trial nor a prospective basic science study involving a human participant.

As this is a specific situation, the ASIP believes this is most appropriately addressed through an updated case study and not necessarily to the recently issued Request for Information. We would be pleased to discuss this with you in more detail should you have questions. We appreciate your willingness to consider an additional case study that would be most helpful to those researchers working with identifiable biospecimens. If the ASIP may be of further assistance, please contact Dr. William B. Coleman at wbcoleman@asip.org.

Sincerely,

William B. Coleman, PhD
Executive Officer

¹ From NIH website: https://grants.nih.gov/policy/clinical-trials/glossary-ct.htm#P
² From NIH website: https://grants.nih.gov/policy/clinical-trials/glossary-ct.htm#I