BRIGHAM HEALTH
BRIGHAM AND WOMEN'S HOSPITAL

MULTI-REGIONAL CLINICAL TRIALS
THE MRCT CENTER of BRIGHAM AND WOMEN'S HOSPITAL and HARVARD

September 28, 2021

Francis S. Collins, MD, PhD
National Institutes of Health
6705 Rockledge Drive, Suite 750
Bethesda, MD 20892
Submitted electronically: SciencePolicy@mail.nih.gov

RE: Request for Information on Developing Consent Language for Future Use of Data and Biospecimens
Notice number: NOT-OD-21-131

Dear Dr. Collins:

The Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard (MRCT Center) appreciates the opportunity to comment on the National Institutes of Health (NIH) Request for Information on Developing Consent Language for Future Use of Data and Biospecimens.

By way of background, the MRCT Center is a research and policy center that addresses the ethics, conduct, oversight, and regulatory environment of international, multi-site clinical trials. Founded in 2009, it functions as a neutral convener to engage diverse stakeholders from industry, academia, patients and patient advocacy groups, non-profit organizations, and global regulatory agencies. The MRCT Center focuses on pre-competitive issues, to identify challenges and to deliver ethical, actionable, and practical solutions for the global clinical trial enterprise. Over the last five years, the MRCT Center has been intimately involved in data sharing, including (1) developing guidance for sharing aggregate plain language summaries for participants and the public, (2) developing guidance for sharing individual results with participants, (3) promoting principles of individual participant data (IPD) sharing including protections of patient/participant confidentiality and privacy and of confidential commercial information, (4) developing template data use agreements and data contributor agreements for IPD and other data sharing, (5) crafting informed consent language to promote participant understanding of the implications of sharing de-identified data, (6) launching Vivli, a platform for global data sharing of IPD data, and (7) furthering the establishment of credit for data sharing for those individuals who choose to share their data, among other efforts. Of note, the responsibility for the content of this document rests with the leadership of the MRCT Center, not with its collaborators, nor with the institutions affiliated with the authors.[1]

[1] Brigham and Women's Hospital, Rope & Gray LLP, Harvard Medical School, and Harvard University.

We have organized the response consistent with the request for information, by question as numbered in the RFI.

Question 1: Utility and useability of this resource:

We believe that a revised document will be helpful and welcomed by the community, and we thank NIH for preparing it. On review, however, there are several additional clarifications and suggestions that would improve its utility and useability. Specifically:

The document should be reviewed for health literacy principles, with specific attention to words and concepts that have a different meaning in regulations than in common use and to words that may not be familiar to all communities.

1. For instance, the use of the term "commercial entities" may be technically with an 8-grade readability score, but "for-profit companies" or "for-profit companies including drug companies" is more precise. Given community concerns, it would be helpful to include whether "government agencies" are included in the list, and what protections there are to re-identification by government entities. "Indefinitely" could be replaced with "forever." When you say, "There are no plans to provide any payment to you should this occur," why not say, "There are no plans for you to be paid should this occur." Or be further direct to say, "You will not receive any payment should this occur." By talking about "plans," there is an implication that plans may change or be developed. Clarity is important.
2. Words such as "biospecimen," "identifiable", "repository", "code," and "coded" should be defined for the reader.
3. You mention the plans to include a time frame, however data is never "used completely" nor are derivative products from biospecimens such as cell lines.

We recommend that there be an introduction in the document, and in the sample language proposed, to explain the value of data sharing and its purpose, value, and utility for science and medicine. Further explanation as to why detailed data is of utility would be beneficial and the fact that efforts are undertaken to protect confidentiality to the extent possible.

Question 2. Gaps or additional components that should be included

We thank NIH for drafting this thoughtful and comprehensive document. We have identified additional components that we believe will strengthen the document and allow its recommendations to be understood in the context of relevant regulatory regimes, including most notably the Common Rule and HIPAA, both of which are administered by other components of the U.S. Department of Health and Human Services.

General Points to Consider

We have identified additional components for inclusion in the 'General Points to Consider' section. Because much of the research in which samples are collected for future research will involve samples that are collected in multiple states and in foreign counties, we suggest that in addition to referencing consideration of the laws/regulations/policies of cultural/donor/sovereign groups, the document should encourage the consideration of relevant state laws, including state genetic privacy and omnibus privacy laws, as well as foreign research and privacy laws, such as the European Union's General Data Protection Regulation. We think the document will do a disservice to the research community if it does not reference these important topics given that in our experience, researchers often interpret the omission of references to such laws in federal guidance documents to mean that they do not need to concern themselves with such laws.

Because many U.S. researchers and institutions who use this document will be "covered entities" that are subject to the Health Insurance Portability and Accountability Act of 1996 ("HIPAA"), we also recommend that the document reference the intersection of HIPAA with the topics discussed in the document. Specifically, the document should note that in implementing consent language for future research, the consent language needs to be consistent with the language in the HIPAA authorization that participants sign to authorize the use and disclosure of their protected health information ("PHI") in connection with the research. While the document contemplates that many identifiers will be shed from any data and biospecimens that are maintained for future research, in our experience HIPAA identifiers such as dates of collection are often retained on such samples, meaning that HIPAA will remain relevant for future use of such materials. Notably, the HIPAA Omnibus Rule and subsequent guidance from the U.S. Department of Health and Human Services Office for Civil Rights provide that potential future uses should be adequately described "such that it would be reasonable for the individual to expect that his or her protected health information could be used or disclosed for such future research" (see Modifications to the HIPAA Privacy, Security, Enforcement, and Breach Notification Rules Under the Health Information Technology for Economic and Clinical Health Act and the Genetic Information Nondiscrimination Act; Other Modifications to the HIPAA Rules, https://www.govinfo.gov/content/pkg/FR-2013-01-25/pdf/2013-01073.pdf 78 FED. REG. 5612 (Jan. 25, 2013); Guidance on HIPAA and Individual Authorization of Uses and Disclosures of Protected Health Information for Research, https://www.hhs.gov/sites/default/files/hipaa-future-research-authorization-guidance-06122018%20v2.pdf). This standard should be referenced when discussing the description of future research.

In the last bullet point in the 'General Points to Consider' section, which begins with "As technology advances for coding and deidentifying data and biospecimens," we recommend referencing the provision of the revised Common Rule (see 45 C.F.R. § 46.102(e)(7) (2018)) requiring Federal departments and agencies periodically to revisit the meanings of "identifiable private information" and "identifiable biospecimen" and the technologies generating these data. The preamble to the revised Common Rule notes that whole genome sequencing is likely to be one of the first technologies analyzed under this process. Mentioning this fact will help

the research community anticipate upcoming regulatory changes that may affect their approach to future research.

As a further general point, it would be helpful to address genetic and genomic data sharing more explicitly. This document references but does not integrate the detailed suggestions (and requirements) of the NIH Genomic Data Sharing Policy. For example, the NIH Genomic Data Sharing Policy suggests that the consent should include whether participant's individual-level data will be shared through unrestricted or controlled access repositories, a topic not mentioned in the model language here. In addition, the revised Common Rule requires research involving biospecimens to include a statement in the informed consent about whether the research will or might include whole genome-sequencing (45 CFR 46.116 (c)(9).

Component 1

We have identified additional components for inclusion in the Component considerations and sample language.

For the Component 1 sample language, we recommend the inclusion of customizable brackets for a user of the NIH document to specify what data and biospecimens will be made available for other research studies. We also recommend the inclusion of a statement that the parties with whom data and biospecimens are initially shared may share data and biospecimens further unless there is a contractual limitation against further sharing.

The Sample Language suggests specifying where the data and biospecimens will be stored, imposing a significant limitation on future use. We suggest that the informed consent describe the protections over future use (regardless of location) and whom participants should contact regarding withdrawal of their biospecimens and data. Further, this section says that "To use your data and biospecimens, researchers must get approval and they must agree not to try to identify you." However, researchers using anonymized data do not necessarily need to "get approval." This statement is misleading.

The concept of a "locked location" implies a physical location and the language mandates that the code and identifying data be separated. Currently, use of secure electronic systems are utilized such that the code is secure (but not locked); the same cloud service vendor may hold both code and data.

Component 2

In the first bullet point in the Component 2 considerations ("In general, participants should be given the option to"), we question whether the potential benefit of the study should be the dividing line between when sharing of data and biospecimens is mandatory and when it is optional. Because we understand that the specimens at issue here will either be completely de-linked from identifiers or subject to a coding system in which the key needed to re-identify

the data is stored separately from the research information, consent to future use of the data would not generally be required from a Common Rule perspective. Thus we think that the document should note those instances in which consent to future research is not required from a Common Rule perspective and any decision by the researcher to obtain consent would exceed what is required by the Common Rule.

The Common Rule requires only that potential participants be informed about this possibility (45 CFR 46.116(b)(9)(i)). In Component 2: Voluntary Participation, NIH recommends that participants be given the opportunity to provide their informed consent for future research in which their data or biospecimens might be stored or shared for future research, even if identifiers will be removed before doing so. Is this intentional? We recommend that the document conform to the Common Rule, and if not, explain the reasons for its departure.

In addition, we recommend that NIH acknowledge the potential burden related to providing participants with the option to agree to, or disagree to, having their data and biospecimens stored and shared for future research. While the document references the ethical reasons for providing this option, it should also be recognized that tracking individual participant preferences over a long period of time can be challenging, especially for institutions with fewer resources available to conduct such tracking, and researchers and institutions should be aware of this challenge when deciding whether to provide this option. Indeed, in our experience, it is the challenge of operationalizing such tracking that has dissuaded many institutions from implementing the "Broad Consent" provision of the revised Common Rule.

Component 3

We suggest renaming Component 3 to "Withdrawal of Consent" for clarity.

The Component 3 sample language helpfully includes the disclosure of the potential limitations facing an institution's ability to retrieve or discontinue others' use of data and biospecimens that have already been shared. The sample language could also state that HIPAA allows covered entities with whom data are shared "to use and disclose protected health information that was obtained prior to the time the individual revoked his or her authorization, as necessary to maintain the integrity of the research study" (see Frequently Asked Questions HIPAA Privacy Rule for Researchers, https://www.hhs.gov/hipaa/for-professionals/faq/316/if-a-research-subject-revokes-authorization-can-a-researcher-continue-using-information-obtained/index.html). We think that this same standard could be referenced here with respect to retention of biospecimens and data following a participant's withdrawal of consent for storage and sharing of their data.

The sample language is not clearly stated and can be simplified. We propose: "You can change your mind about sharing your data and biospecimens at any time. If you change your mind, please contact the study team to let us know. We will not share your data and biospecimens after we hear from you. However, it may not be possible to get data and biospecimens back if

they have already been shared with other researchers. For example, we will not know which data and biospecimens are yours if the identifying information was removed. Also, if some research with your data and biospecimens has already been done, the information from that research may still be used."

Component 4

We appreciate the identification of "stigma or the ability to obtain certain types of insurance" as specific risks associated with the loss of privacy in the 'Considerations-Risks' section of Component 4. To further facilitate the identification and disclosure of specific risks associated with the loss of privacy of data and biospecimens, we recommend that NIH specify additional risks in this section, such as risks to the ability to gain certain types of employment or implications for civil and criminal liability. Additionally, we recommend amending the first bullet point in this section to read (suggested text in brackets): "Ensure that the safeguards listed are consistent with language addressing the storage and sharing of data and biospecimens in the introduction [and the research protocol]." In our experience, the data protections described in the informed consent are sometimes inconsistent with the protections described in the protocol, and thus inclusion of such language could be a helpful reminder to researchers in drafting their consent forms and protocols. Finally, we recommend that NIH add a bullet point to this section to encourage the disclosure of the specific risks raised by the use of the data and biospecimens that are being stored and shared; these risks can vary significantly based on the type of biospecimens and data at issue.

In the Component 4 sample language, we recommend adding a statement that the ability for data and biospecimens to be re-identified may change over time as technology advances and permits the re-identification of data through comparison of the data with reference databases.

As a final point, we recommend that NIH add a component to the document that provides guidance and sample language on what information regarding the future use of data and biospecimens should be included in the "key information" section of an informed consent form. The addition of this component will be helpful to users in developing an informed consent form that is consistent with the revised Common Rule's requirements that "informed consent must begin with a concise and focused presentation of the key information that is most likely to assist a prospective subject or legally authorized representative in understanding the reasons why one might or might not want to participate in the research," and this key information section "must be organized and presented in a way that facilitates comprehension (see 45 C.F.R. § 46.116(a)(5)(i) (2018)).

Question 3. Specific language proposed in the informed consent sample language

The sample language proposed by NIH will be helpful to the research community. We offer general suggestions in response to Question1 (including examples for replacement of terms, definitions) and include here minor suggestions to strengthen the sample language. In

Component 1 Option #1, we recommend changing "other identifying information" to "directly identifying information." Some information that is considered identifiable by the HIPAA Privacy Rule, such as specimen collection dates, is frequently attached to data and biospecimens that are stored and shared for future research (see Guidance Regarding Methods for De-identification of Protected Health Information in Accordance with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule, https://www.hhs.gov/hipaa/for-professionals/privacy/special-topics/de-identification/index.html#standard). To maintain consistency with HIPAA, we would suggest referring to "directly identifying information," as dates are not considered "direct identifiers" for purposes of HIPAA and thus a promise to remain "directly identifying information" would permit dates to remain on the specimens in a way that a promise to remove "other identifying information" may not.

In the Component 2 Option #2 directions, we recommend clarifying the meaning of "studies where sharing is integral to the purpose of the study." We presume that this statement refers to studies in which biobanking for future research is a key component of the study. Explicitly stating the intended meaning of this statement would clarify when to use Component 2 Option #2.

In Component 4, we recommend deleting the phrase "as much as possible." The parties storing and sharing data and biospecimens are oftentimes not taking the most extreme measures possible to protect data and biospecimens but rather taking reasonable measures based on the resources available.

Question 5. Other considerations relevant to this resource (limit: 8000 characters; current: 256 characters with spaces)

Of central importance to the document is to clarify whether this document is intended to cover both identifiable and de-identified data and biospecimens, since there is a lack of clarity (and some inconsistency) in the document.

In the Background and Instructions for Use sections, we recommend acknowledging that institutions and research organizations, in addition to investigators and IRBs, share the responsibility for compliance with various regulations and standards for informed consent.

It is important for the document to include a "Whom to Contact" section clearly in the event of a participant's withdrawal of consent or request for further information, or in the event of an unanticipated problem (e.g., concern or evidence of re-identification).

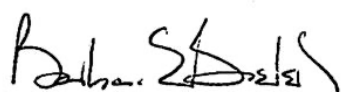
In an effort to have comprehensive sample policy and language, we recommend including model statements that are required by the revised Common Rule. For instance, 45 CFR 46 116(b)(9) requires a statement about any research that involves the collection of identifiable private information or identifiable biospecimens to state whether or not the data and biospecimens will be used or distributed for future use, and whether identifiers will be

removed. Consideration of the applicability of broad consent therefore in this document is also important. If this document is to provide model language for broad consent, the required elements of consent contained in 45 CFR 46.116(d) should be included. This policy should address the requirements of the Common Rule.

Thank you again for the opportunity to comment on this important issue. We believe that the NIH is in a unique position to provide guidance not only for investigators and their study teams, but also importantly for participants and the public on the importance and value of data sharing, advanced through clarity, health literacy, and respect for participants and their communities.

We are available to discuss our comments with you if that would be helpful and would be happy to work with you on any of the aforementioned items. Please feel free to contact the MRCT Center or Barbara Bierer, MD, bbierer@bwh.harvard.edu; (617) 827-7413. We are at your service should we be able to be helpful.

Respectfully submitted,



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