SACHRP Minutes, July 22-23, 2020

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Secretary's Advisory Committee on Human Research Protections (SACHRP): Minutes

Wednesday, July 21 – Thursday, July 22, 2020

Voting SACHRP Members Present:

Stephen Rosenfeld (Chair), Mary Ellen Allen, Jyoti Angal, Linda Coleman, Douglas Diekema, Janet Freeman-Daily, Robert "Skip" Nelson, Walter L. Straus, Kevin Weinfurt, Consuelo Wilkins, Leslie E. Wolf

Wednesday, July 21

Welcome and Opening Remarks

- *Stephen Rosenfeld, M.D., SACHRP Chair*
- *Jerry Menikoff, M.D., Director, Office for Human Research Protections (OHRP)*

Dr. Rosenfeld welcomed everyone to the call. He observed that virtual meetings are still a learning experience for everyone and asked for patience as participants learn how to make this format work. Members of the public were invited to send questions using the chat feature. The Chair explained that, as time allows, these questions would be addressed during the public comment period. Participants were also steered to the site where meeting materials have been placed for reference.

The Chair voiced an appreciative farewell to former SACHRP members Sandra Berry and Nancy King, both of whom participated in SACHRP during its deliberations on proposed revisions to the Common Rule and later as the committee developed recommendations on the implementation of the new Common Rule. Ms. King continues her service on SACHRP's Subpart A Subcommittee (SAS).

Dr. Rosenfeld welcomed two new members and invited them to say a few words. (Their bios may be reviewed on the SACHRP website.) Dr. Weinfurt and Dr. Diekema both said they were delighted to join the committee.

Dr. Menikoff welcomed everyone and expressed pleasure that SACHRP is tackling the "weighty subjects" on this agenda. He noted that public health surveillance has become a "very hot topic" due to the COVID-19 emergency. He thanked SACHRP members and subcommittee members, as well as ex officios and staff, for their important behind-the-scenes contributions.

The Director welcomed SACHRP's two new members and said he was "thrilled" they were joining. He noted that he had worked with both of them in the past and look forward to working with them in the future.

Dr. Menikoff invited participants to join a one-day online workshop sponsored by OHRP's Division of Education and Development, which will occur on n September 17. The topic is Practical and Ethical Considerations for Single IRB Review.

The Director also highlighted a unique professional opportunity. OHRP is seeking a new Director of Policy and Assurances – one of its most senior positions. The Director will be engaged in rethinking what matters in human subject protection, work that will have a "huge" impact. Dr. Menikoff encouraged any talented people who may be considering what they want to accomplish in life and find this attractive to apply. However, the opportunity to apply will close on July 24 and there is a cap on the number of applications OHRP can receive.

The Minutes from SACHRP's previous meeting, March 11-12, 2020, were approved without changes.

Draft Data Management and Sharing Policy/Discussion

- *Mark Barnes, J.D., SOH Co-Chair*

See Attachment A. Implications of the NIH Draft Policy for Data Management and Sharing on Data Derived from Human Participants (As Approved)

Mr. Barnes presented a set of draft comments on the proposed NIH policy on the sharing and management of data from human participants. The Subcommittee on Harmonization (SOH) has been working on remarks since SACHRP's March meeting. He noted that a good deal of work and many revisions are reflected in the document as presented. He reviewed key points in the document.

I. Data Sharing Provisions. Mr. Barnes observed that, as a research community, we are at the initial stage of trying to understand what data sharing is, including rights of various stakeholders and the protections for human sources of data. NIH has put forward a draft written at what the Co-Chair called a "high level of generality." Similarly, SACHRP's draft response seeks to state principles, values, and points of view. Ms. Barnes called the topic a continuing conversation in which final conclusions are not yet possible. He observed that while NIH's policy is limited to studies funded by NIH, NIH has tremendous funding power and sets a precedent often followed by other public and private funders. SACHRP's comments focus on the implications of the policy for human subjects.

II A. Consent to Data Sharing and Control of Data by Human Participants. SACHRP recommended that people be informed when it is the case that their genomic data may be shared downstream and that promises made to them be honored. Specifically: "NIH should consider implementing a means to track such limitations or require downstream users to enter into data use agreements so that subsequent data requesters are made aware of sharing limitations and held accountable for unauthorized future uses of data derived from human participants."

B. Efficacy of De-Identification and the Heightened Risk of Re-Identification for Smaller Populations. SOH also called attention to the implications of the Health Insurance Portability and Accountability Act (HIPAA) for data sharing. Mr. Barnes noted that covered entities must give subjects a notice of privacy practices and should inform them that their data, once de-identified, may be used for secondary research purposes. Even identifiable information may be used in some circumstances without individual consent or authorization. Even identifiable information may be

used in some circumstances without individual consent. SOH suggests that NIH work with HHS's Office of Civil Rights (OCR) to develop standard text or templates for consent and notice documents to promote transparency. Subjects should also be aware of limitations on their ability to revoke permission to use their data.

Since re-identification of data is often possible even when it has, theoretically, been anonymized, SACHRP recommends that NIH provide minimum standards investigators must meet when de-identifying data, suggest data types that might be excluded to reduce the risk of re-identification, and require investigators to include a provision in data use agreements "in which the data recipient agrees not to attempt to identify individuals who are subjects of the data." SOH also proposed that NIH provide additional guidance when data are derived from small underserved populations (such as the Havasupai) that could suffer dignitary harms from certain uses of their data. Genomic data in particular require additional safeguards to prevent data from being reidentified and shared without subjects' consent.

C. Controlled Access to Data Derived from Human Participants. Mr. Barnes said that issuing a Certificate of Confidentiality to protect human participants' data is insufficient to safeguard the data from inappropriate use, since it still permits further disclosure of this information in certain cases. SOH suggested providing controlled access to certain data. For example, "sandbox" environments can be created that allow scientists to use the data in a controlled space without being able to receive portable copies.

D. Downstream Sharing and Efficacy of Sanctions. Mr. Barnes stressed the need for sanctions for individuals who obtain data and do not respect the terms and conditions placed on the use of these data. He argued that there should be tangible and significant consequences to such misuse, as well as a more rigorous enforcement mechanism than currently exists. Sanctions could include fines or civil monetary penalties for each instance of non-compliant use or data sharing. Ideally, SOH would like to see such measures applied universally, not simply in the context of NIH-sponsored research.

E. Resolution of Discrepancies Created by Ex-U.S. Standards. SOH noted that while NIH's draft document highlights a number of U.S. policies, laws, regulations, statutes, and guidance that may apply to data sharing, it makes no mention of international standards that may also apply. Mr. Barnes argued that NIH should bring these to the attention of researchers.

Discussion

Dr. Nelson noted that throughout the document, a range of terms introduce recommended NIH actions, including recommend, suggest, believe, and urge. He asked whether the various terms have different meanings. Mr. Barnes said all of them really mean "recommend." Mr. Barnes revised the document to replace all these similar terms with the single term, "recommend," to avoid the possible interpretation that there are subtle differences among the recommendations.

Ms. Wolf questioned the statement that the sharing of human data "should be dictated" by applicable laws, regulations, statutes, guidance, and institutional policies, noting that the reality is

more complicated than this implies. Dr. Rosenfeld suggested alternate wording, "is governed by," which was accepted.

Also, in regard to the first paragraph of Section A, Ms. Wolf said the point made is currently framed as retrospective (asking investigators to "evaluate the underlying consents of data derived from human participants") and should instead ask them to consider the implications of consent prospectively. Mr. Barnes's revision recommends that NIH policy require investigators to "carefully craft consents" to communicate possible subsequent uses of subjects' data.

Ms. Wolf also thought it was worth reinforcing the fact that obligations related to the Certificate of Confidentiality do follow the data. Mr. Barnes added a footnote that makes the point: "As discussed in Section D. Certificate of Confidentiality requirements attach to, and follow, identifiable human data collected in the course of NIH-funded research."

Dr. Straus noted that the NIH document provides an opportunity to educate investigators on the risks posed by the reidentification of data. He said many of them will still be unaware of the issue and those that are may falsely believe that the concern applies only to genomic material.

Dr. Straus agreed with the recommendation that there should be consequences for inappropriate data sharing. Some purposes may be altruistic, while others may be inappropriate. Potential consequences should be clearly delineated.

Ms. Wolf suggested defining the terms "de-identified," "anonymized," and "sensitive." These terms could be confusing and should be distinguished. Mr. Barnes added a footnote defining all three terms.

Dr. Wilkins felt the document skirted issues related to the use of data associated with minoritized and racialized groups. She suggested it should be more specific about what kinds of groups were included in the term "underserved" and address the issue of what should be disclosed to them. The revised document Mr. Barnes presented later in the meeting states the following:

> *While sharing of data for additional research uses may often be beneficial, there are circumstances in which the sharing of certain data may increase the risk of harm to human participants, particularly for populations with unique sensitivities, such as those who have historically been the subject of discrimination or lack effective representation in the political process, or who may suffer dignitary harms as a result of the use of their data for certain types of research projects. SACHRP recommends that the Policy provide additional guidance on how investigators might navigate exceptions to sharing certain data derived from defined, vulnerable* ~~***small or underserved***~~ *populations.*

Dr. Rosenfeld found the examples in Section A confusing. He noted that they refer to clinical rather than research contexts and would not fall under NIH's policy guidelines. Mr. Barnes responded that since research may be done on clinical data sets created before the investigators begin their work, the collection of data in a clinical context is also relevant. He said the possible downstream uses of

data should be transparent, beginning with their collection and continuing when they are passed to a researcher who then shares them with additional researchers. The intent is to invite NIH to think more deeply about creating an "ethical universe" in which researchers have a greater ability to share data appropriately.

Mr. Paine, *ex officio* representative for NIH, thanked the committee. He said he was interested in SACHRP's comments and appreciated their review. NIH is moving toward finalizing the policy.

Mr. Paine noted that SACHRP's document refers to the type of consent needed to accommodate "broad data sharing," which might be taken to imply that NIH is requiring or expecting people to obtain broad consent in all cases. NIH is aware of challenges related to broad consent and does not want to force its researchers to go that route. Mr. Barnes said he is a passionate opponent of broad consent and will revise the draft to make sure the document cannot be read as promoting or requiring broad consent. That was not SOH's intention. In the final draft approved by SACHRP, the word "broad" was removed.

Mr. Paine also called attention to the final sentence of Section A, which states that "participants should also be informed of mechanisms through which they may themselves seek to make their data available to third-party researchers." He asked whether this provision refers to data participants might have themselves or data generated in the course of the study. Mr. Barnes said it could refer to either. It is common, for example, that members of a rare disease community want to share their data with the institution where they receive care. The intention is not to imply that NIH should itself share these data, but rather that it should make researchers aware of this possibility and encourage them to think it through.

Mr. Paine asked, in regard to sanctions for those who misuse data, whether the subcommittee considered a legislative change necessary. Mr. Barnes said that SOH had considered the many different kinds of sanctions debated by Public Responsibility in Medicine and Research (PRIM&R). Most thought there should be a range of graduated sanctions, starting with a fine. The government needs the ability to identify those who abuse data and harm individuals or groups, especially if this is done for commercial purposes. The subcommittee did not have a specific recommendation on how this should be implemented.

Discussion of Revised Document

Mr. Barnes presented a revised version of the document reflecting SACHRP's input and addressing Mr. Taunton's concerns. He explained where he had made these changes and highlighted alternate wording.

Dr. Straus felt additional discussion was needed on how best to hold organizations accountable for violating agreements related to the use of human subjects' data. The issue is complex, in that what might be a substantive penalty for one investigator might seem trivial to a large corporation. He said he would be supportive of SACHRP addressing the issue of sanctions as a separate topic. Dr. Nelson felt the document had sufficient specificity for its purpose, adding that he did not feel he had

the expertise to be more specific.

Ms. Wolf noted, in reference to the footnote defining terms (footnote 8), that sensitive data might confer other types of injury or harm besides "reputational" ones. She asked that the word "reputational" be removed. Mr. Barnes said he would do so.

Action

- SACHRP approved Implications of the NIH Draft Policy for Data Management and Sharing on Data Derived from Human Participants. (See Attachment A.)

Deceased Donor Intervention Research

- Stephen Rosenfeld, M.D.

See Attachment B. Issues Surrounding Deceased Donor Intervention Research under 45 CFR part 46 (As Approved)

Dr. Rosenfeld noted that SACHRP has been dealing with the topic of Deceased Donor Intervention Research (DDIR) for about a year and a half. He particularly thanked subcommittee members Michelle Russell-Einhorn and Nancy King for their contributions.

SACHRP's deliberations were most recently informed by comments from a panel of organ recipients and a transplant surgeon. After hearing their experiences, committee members disagreed about whether a surgeon should be able to overrule a patient's decision not to receive the offer of a research organ and offer it anyway. The debate continued on the subcommittee, where many members felt this action would violate the patient's autonomy. The subcommittee reached a compromise that entails emphasizing the importance of providing many opportunities for patients to receive additional information about research organs and revisit their decision not to receive such offers.

The transplant surgeon expressed concern about institutional risk aversion. He feared that if patient consent were required, institutions would not want to receive research organs as a matter of institutional exposure. The Chair observed that there is no perfect answer to this concern other than to create a culture and community where openness to participation in research is the expectation.

Other changes the Subpart A Subcommittee (SAS) was asked to consider included clarification of the terms of the consent process and a clearer discussion of waivers of consent in this context. The Chair noted that issues related to the consent of family members are not addressed in the document. Most of the document was unchanged.

Review of Key Points

Dr. Rosenfeld reviewed the document, clarifying SAS's response to questions posed by OHRP.

He explained that the introductory material was intended to explain what makes DDIR such a difficult problem and why problems exist in carrying out such research under the regulations. He

noted that there is no way to determine who might be offered a research organ and which research protocol might have been followed, and therefore there is no way to prepare transplant teams and subjects in advance in sufficient detail to meet the regulatory criteria for informed consent to participate in research. Severe time constraints follow from the limited time that the organ is viable.

A report by the National Academy of Medicine (NAM) on the subject concluded that people who receive research organs from deceased donors should be considered research participants. The Academy recommended a two-step process for consent, which would include initial discussions with subjects to provide general information (step one) and specific information about the research protocol associated with an organ at the time it is offered (step two). Dr. Rosenfeld said since there are no time limits for the first step, as much weight should be placed on it as possible. SACHRP should also encourage transplant teams to continue to brief potential organ recipients periodically about the possibility of accepting a research organ.

In regard to whether some research might be considered minimal risk, the Subpart A Subcommittee (SAS) concluded that some protocols might conceivably meet the criteria for minimal risk research while others would not. If the research is truly minimal risk, then the IRB could consider the possibility of a waiver of consent as it would for any other research. The primary concern here is the inconsistency in the decision-making process from one IRB to another.

SAS considered whether it is permissible to waive consent under 45 CFR 46.116 (e) or (f), which addresses situations in which it is not "practicable" to get consent for a study that is not greater than minimal risk. The document notes that "DDIR presents unique circumstances in which consent may not be practicable despite the opportunity for interaction. This concern is the basis for the recommendation that a Secretarial waiver be required."

In seeking the simplest path forward to address an obviously urgent issue, SAS "swung 180 degrees a couple times" on the issue of whether a Secretarial waiver was required. It concluded, however, that it was simply "too much of a stretch" to think that all the elements of informed consent for research could be addressed in the "call in the middle of the night" in which an organ offer is made. They concluded that there was simply no way to share all the elements of consent in a way that would facilitate understanding and provide "sufficient opportunity to discuss and consider whether or not to participate." However, the proposed document underlines the importance of education, both for transplant teams and patients, to take full advantage of the time available in "step one" of the consent process.

Recommendations

SAS recommended the following:

(1) The three structures recommended by the NAM report – a single IRB, a Donor Research Oversight Committee (D-ROC), and one or more data and safety monitoring boards with special expertise – would "improve the quality of the system of human research protection programs for DDIR" and should be created. However, SAS proposed that implementation of SACHRP's

recommendations should not depend on these structures being in place. In the meantime, DDIR protocols should continue to be reviewed by single IRBs. In this review, the IRB must determine whether or not the protocol complies with "all of the regulatory criteria for approval of research."

(2) A Secretarial Waiver of 45 CFR 46.116(a)(2) and (b) at the time of the organ offer consent process is necessary. A "clear and robust key information summary" that satisfies 45 CFR 46.116(a)(5)(i) is essential and must be used during the organ offer call. Complete consent forms should be signed by organ recipients to attest to their receipt and discussion, but they do not need to be signed prior to surgery.

Conditions for use of the Secretarial Waiver are described in subsequent recommendations. They include specific requirements for the initial education session and subsequent clinical interactions, standardized education about DDIR for potential transplant recipients and transplant teams, and the development of additional resources to inform potential organ recipients of DDIR protocols. (See Attachment A for details.)

Justification for the Secretarial Waiver

Dr. Rosenfeld reviewed the proposed Secretarial Waiver in light of the key principles established in the Belmont Report. In regard for respect for persons and beneficence, the document concludes that the time available during the organ offer call will give prospective recipients "a minimally sufficient opportunity to decide whether to accept a DDIR organ." SAS also felt the principle of "justice" was relevant, in that the current system of decentralized management and oversight of the organ transplant process "is a barrier to successful and equitable implementation of DDIR."

Additional Considerations

The Chair noted that the Secretarial waiver will apply only to HHS-funded research and not to FDA-regulated DDIR, since FDA regulations do not allow for a Secretarial waiver. The document states that SACHRP does not believe that DDIR fits the intent of existing exceptions from the complete requirements for informed consent in the relevant FDA regulations, including 21 CFR 50.23 and 24. Accordingly, rulemaking is probably necessary to avoid further delays and barriers to DDIR.

Discussion

Ms. Levy (HRSA) asked for further clarification of the subcommittee's conclusions regarding the applicability of criteria to be considered minimal risk research. Dr. Rosenfeld explained that the presumption is that a person is being offered a manipulated organ because the investigator wants to know if that manipulation is beneficial or not. It cannot be assumed that the answer to that question is yes. He said he had difficulty imagining circumstances in which the transplantation of a research organ would truly qualify as a minimal risk intervention. A transplant surgeon might see a cooled organ as a minimal risk intervention, but this would not be consistent with the way IRBs interpret the concept. Specifically, IRBs have avoided interpretations that calibrate risk to the unusual risks

faced by specific populations, such as children with leukemia.

Dr. Nelson said he thought that the applicable concept in regard to manipulation of the organ in research is "incremental risk." He felt the IRB should focus on evaluating the incremental risk associated with accepting the manipulated organ over what would otherwise be happening. Dr. Rosenfeld agreed, but he noted that as a practical matter, clinicians will take into account the risk background associated with the individual.

Ms. Levy then asked whether a central IRB's determination as to whether an intervention is minimal risk would fall under the Secretarial Waiver. Dr. Rosenfeld said the waiver applies to requirements for informed consent to research, which would be necessary only if the IRB found the intervention to be greater than minimal risk. If the research were minimal risk, the IRB could waive or alter the consent without the Secretarial Waiver.

Ms. Levy noted that the NAM report considers transplant teams who implant a manipulated organ to be co-investigators in the research. She asked whether that was SACHRP's interpretation as well. Dr. Rosenfeld said the document does not address that issue and he could see an argument for both sides. However, he found it hard to consider someone a co-investigator "after the fact" even though they are administering a consent form and collecting information. Clearly, the team needs to ensure that the organ is appropriate for an individual and to do that, it must know enough to make a responsible decision. However, the SACHRP recommendations do not specify how this should be done.

Ms. Wolf complemented the committee on a "fantastic job" with a challenging topic and said she felt they had ended up "in the right spot." However, in regard to the issue of the practicability of a waiver in such cases (question 7), she noted that practicability is usually applied when an individual is not available to be consulted. DDIR poses a different kind of constraint on practicability. The document should acknowledge this difference. Dr. Rosenfeld agreed.

Mr. Paine (NIH) said he had been in conversation with groups at NIH that are interested in this area. A question raised in these consultations was the potential applicability of an alteration of the elements of informed consent rather than a waiver. Dr. Rosenfeld responded that an alteration would be possible only if the research is less than minimal risk; the Secretarial Waiver would be invoked only when this is not the case. He agreed to clarify this point.

Mr. Paine also asked whether the committee had considered implementation challenges stemming from the centralized resources recommended in the document, including ways to assure quality. Dr. Rosenfeld said SACHRP recognized the burden associated with creating these entities but it did not consider it within its charge or expertise to recommend specific sponsors, funding strategies, and means of implementation. He noted that pursuing DDIR equitably *without* these central mechanisms would likely require even more resources than creating them.

Second Discussion

Dr. Rosenfeld implemented requested changes and reviewed the revised document with the full committee.

In response to Ms. Wolf's concern regarding the customary interpretations of the concept of "practicability," the discussion of Question 3 concedes that "it may be 'practicable' for clinicians or investigators to have the conversation that constitutes the second step in the NAM process, but the IRB will face real difficulty in determining that this conversation, while adequate for clinical consent, fulfills regulatory requirements for research informed consent as usually interpreted." A similar clarification was required in the response to Question 7.

Dr. Rosenfeld said the revisions also reflected Mr. Paine's request for clarification around waivers of consent. The revised document makes clear that minimal risk research that is eligible for a waiver of consent under the regulations does not require the Secretarial Waiver. None of the conclusions was changed. He noted that SACHRP was asked not to comment on the charged issue of how to assess minimal risk in this context. However, the following clarification was added to the recommendation to create a Secretarial Waiver: "SACHRP believes it will be difficult to find that DDIR presents no more than minimal risk to participating organ recipients but recognizes that this determination will be made by the IRB on a study-by-study basis."

The revised draft also moves material originally presented later in the document to clarify the conditions required for the organ offer call to be "deemed adequate in terms of both regulatory compliance and ethics." These include the use of the Secretarial Waiver, the development and use of a "clear and robust key information summary," the development and approval of "complete consent forms" to be signed by organ recipients (but not before surgery), education for potential transplant recipients and transplant teams, and additional resources designed to enable potential recipients to stay apprised of current DDIR protocols if they so choose. (See Appendix A.)

Dr. Nelson called attention to the wording of Recommendation 2, which states that the determination that research is minimal risk "will be made by the IRB on a study-by-study basis." This makes it sound as if they will often do this or always do this. Dr. Rosenfeld suggested the word "should" rather than "will." Dr. Nelson concurred with this change.

Dr. Nelson also questioned the wording of condition (D) for use of the Secretarial Waiver, which calls for study PIs to prepare "complete consent forms" to be signed by organ recipients sometime after surgery. He suggested that this should be called something other than consent form. Dr. Rosenfeld said the document would be modeled after regulatory informed consent requirements but could be called something else. Dr. Nelson suggested calling the document "an **information form** to be given to the participant that fully satisfies 45 CFR 46.116." In response to questions from Ms. Levy, he further clarified that this document would come from the study team, is a "subject-facing" document, and would only be used when research is greater than minimal risk.

Dr. Nelson thought it should be sufficient to say that the fact that the recipient has received the informed consent/information form should be documented. Dr. Rosenfeld said he assumed that the signed form would be retained by the study team, since the research may significantly exceed minimum risk.

Ms. Freeman-Daily asked whether there was a time limit within which the form should be signed, and Dr. Rosenfeld said this was not specified. Any time constraint would be too rigid, given many unknowns. However, it is a condition of the Secretarial Waiver that it be signed at some point (if necessary, by the patient's Legal Authorized Representative). Ms. Levy agreed; some patients will be ready to sign the document the morning after surgery, while some will need much longer. Dr. Rosenfeld further opined that it would be unethical to require a signature from someone who did not have the mental capacity to understand what was being signed. SACHRP agreed to specify that the document should be signed "when clinically practical."

Action

Issues Surrounding Organ Intervention Research was approved as modified during the meeting. It is understood that the document will be reviewed by Dr. Rosenfeld to identify needed grammatical and other nonsubstantive changes.

Interpretation of Public Health Surveillance, 45 CFR 46.102(1)(2) and 46.102(k)

- David Forster, J.D., SOH Co-Chair

See Attachment C (1). Interpretation of *Public Health Authority* and *Public Health Surveillance Activities*, 46.102(k), 46.102(l)(2) – Version Showing Revisions Made in the Meeting

See also Attachment C(2). Interpretation of *Public Health Authority* and *Public Health Surveillance Activities*, 46.102(k), 46.102(l)(2) – Clean Version With Meeting Revisions Accepted

See also Attachment C(3). Complete Decision Tree

Recorder's Note: Two versions of the attachment are presented because revisions were so heavy the document became unreadable. For complete versions of the algorithms (decision trees), please email SACHRP's Executive Secretary, Julia Gorey, at *Julia.gorey@hhs.gov.*

Dr. Menikoff noted that the exclusion for public health surveillance activity under the new Common Rule has become relevant with the COVID-19 epidemic. In response to questions directed to OHRP, the agency issued guidance to clarify when and how the exclusion applies. OHRP asked SACHRP to "independently deliberate" certain questions and "come to its own objective recommendations." This includes assessing OHRP's guidance on the topic.

Mr. Forster said that SOH reviewed OHRP's guidance on the topic and basically thinks the

guidance is fine. Two possible algorithms have been developed to illustrate the guidance and help agencies determine whether an activity can be considered a public surveillance activity.

Introduction and Opening Comments

Mr. Forster observed that research and public health surveillance activities may look very similar and could even be the same activity. They are distinguished by their purpose. SOH also concluded that the fact that an agency is designated as a public health agency does not mean that everything that agency does is public health surveillance. Activities that do not meet the criteria to be considered public health surveillance may require the oversight given to research activities.

Dr. Nelson found the opening comments confusing; even though the draft document acknowledges that some activities can be both public health surveillance and research, it attempts to make a distinction between these terms. Public health surveillance can result in generalized scientific knowledge. He opined that the entire section needs "more careful exposition." He also "took some umbrage" at the characterization of Food and Drug Administration (FDA) regulations as focused on "social utility" rather than "broad scientific progress." Ms. Allen held that the reference to FDA should be deleted; she noted that the agency's entire purpose is to protect public health.

Dr. Rosenfeld said this was an important point. He added that since the word exclusion is not used in the new Common Rule, public health surveillance is simply characterized as "not research" – even though it can be used to produce generalizable knowledge. If that knowledge is used for a public health purpose, it is nevertheless "off the table" in terms of the requirements for research under the new Common Rule.

Dr. Nelson observed that poison control reporting and surveillance of those data can enable a researcher to draw conclusions about a population larger than the one in the data base. It therefore fits the definition of research, but it is not covered under the regulations because of its public health purpose. The Centers for Disease Control (CDC) and the FDA routinely draw generalized conclusions from data like this. Dr. Rosenfeld rejoined that he was not sure the philosophical issues behind the distinction actually matter; it just has to be clear when the exclusion applies.

Ms. Wolf questioned whether the broad statements characterizing the purpose of the Common Rule were necessary or helpful.

Dr. Straus referred SACHRP to a helpful white paper, "Health-Related Activities Along the Boundary Between Research and Practice: When to Take Alternate Approaches to Providing Ethical Oversight."[1] He encouraged SOH to think expansively about the topic and address the interface between public health surveillance and quality improvement (QI) activities.

[1] Capron, A. M, Tilson, H.H., Davis, A.L. (2020). Health-Related Activities Along the Boundary Between Research and Pactice: When to Take Alternate Approaches to Providing Ethical Oversight. A White Paper by the PRIM7R Project on the Boundary Between Research and Practice. Public Responsibility in Medicine and Research (Internet link broken).

Question 1
What entities should be considered to meet the Common Rule definition of a "public health authority"?

Mr. Forster said that SOH felt the exclusion should be narrowly interpreted. If a private institution has a partnership with a public health authority, all the activities carried out through that contract are not necessarily public health surveillance activities. Subsequent use of data or samples gathered under the exclusion need to be further examined to determine whether these activities should remain under the exclusion. Also, the specific authority given to the private entity should be formally documented in the legal document.

Mr. Forster also highlighted the subcommittees' conclusion that while a foreign government may be a public health authority, it is a public health authority only for the purposes of research in its own country.

Ms. Wolf considered how the exclusion might apply to academic institutions preparing to open in the fall, which will undoubtedly be tracking and testing students for COVID-19. Nevertheless, the activity does not make them public health agencies. Dr. Rosenfeld agreed. Dr. Straus also found SOH's approach to the question persuasive. Mr. Barnes noted, however, that one strategy in university testing is to get a letter from the state public health department under which results are reported back to the authority. It could be argued that the university is acting as an agent of the public authority, which gives it some shielding from a legal perspective.

Question 2
How should the exclusion operate when the public health surveillance activities will be wholly carried out by an entity outside of the Federal, State, or local government?

Mr. Forster said the definition of a public health authority, as SOH understood it, does include contractors, grantees, or members of a public-private partnership if they are given authority to conduct public health surveillance activities by a public health authority. SOH had a long discussion on whether such an entity could conduct such activities and never give any information back to a public health authority itself; while they felt that would be wrong, they could not see that it was prohibited or would make the entity ineligible to be considered a public health authority by delegation. Dr. Rosenfeld said that raising the question of how findings are disseminated is "going down a rabbit hole."

Dr. Nelson commented that contracts and grants differ in terms of the obligation to deliver a product to the agency issuing the contract or grant. Based on his experience with the National Institutes of Health (NIH), he held that a grantee may have more leeway in this regard. Dr. Straus agreed, noting that a contract is an agreement to conduct a body of work and report back, but a grant is generally more permissive. Mr. Forster said many people on the subcommittee thought that such an open approach should not be allowed. Dr. Nelson agreed that the public health agency should monitor the tasks it assigns and receive the data. He further noted that all Common Rule signatories may not distinguish between grants and contracts in the same way.

Mr. Barnes clarified that the draft was not intended to imply that a public health authority cannot issue a contract for a private entity to do a public health surveillance activity on the authority's behalf. Rather, the subcommittees intended to make clear that any grantee of a public health authority is automatically exempt from complying with the Common Rule when conducting public health surveillance activities.

Ms. Wolf felt that clearer distinctions were needed to delineate the various circumstances described in the second part of OHRP's question. She suggested that one important consideration might be who is "driving" the activity – the grantee or the public health agency.

Question 3
What type of activities should be considered to be "public health surveillance activities" for purposes of this exclusion?... Please also consider developing illustrative case studies that describe the creation of a repository as the primary study, as well as a repository embedded within a trial.

Mr. Forster observed that a lengthy list of activities that fall within this definition is offered in the preamble and in OHRP draft guidance; SOH did not have any activities to add. The preamble also identifies activities that should *not* be considered public health surveillance, and SOH chose to reference but not expand them.

In regard to the second part of the activity, he noted that OHRP guidance said that it was possible to carve out activities such as a research trial that was intended for use as a public health surveillance activity; SOH agreed that this approach was permissible. However, such a carve-out would be different from an exemption.

Ms. Freeman-Daily said SOH's draft makes it sound as if some elements of such a repository would be considered research. This seems contradictory. Mr. Forster said the intention was to distinguish between a data repository as a stand-alone project as opposed to a data depository as part of a project with several components.

Dr. Straus observed that most of the types of surveillance described can be categorized as "passive" as opposed to "active" surveillance activities. An example of active surveillance system would be a contract with a number of hospitals to provide information about all cases of a particular pathogen. Other examples may include prospective surveillance to monitor and report the impact a particular mitigation strategy, such as the impact of wearing masks or of social distancing. Mr. Forster asked Dr. Straus to draft and send proposed wording for this addition.

Ms. Freeman-Daily commented, in regard to activities designed to enable the public health agency to identify the prevalence of a known risk factor, that this might not be an obvious public health surveillance activity if the agent in question is a new one. Approaches to measuring this agent might be developed by individuals using devices of undetermined accuracy. Would that be considered research or PH surveillance? Mr. Forster opined that the tests themselves would be research projects that would fall under the FDA device regulations. Dr. Nelson said he considered the definition of research in the Common Rule to be ambiguous. Ms. Freeman-Daily agreed and opined that the

ambiguity should be more thoughtfully addressed in the document.

Dr. Straus said that in the context of COVID-19 the situation described by Ms. Freeman-Daily could be described as "characterizing" risk factors. She further observed that the field is at the stage where research is still being done to identify risk factors so that public health surveillance can keep track of them. Dr. Nelson said that devices used in this type of activity would fall under parts 50 and 56 of the FDA regulations. As a result, even if they were excluded from oversight through the Common Rule, they would not be exempt from oversight by the FDA.

In response to a question from Dr. Nelson, Mr. Forster noted that SOH has not yet crafted responses to two of OHRP's questions: "Should the purpose of the surveillance activity be solely to inform the decisions or actions that must be made by a public health authority, or to apply study findings to public health practice? Should activities that do not meet this exclusion include disseminating findings to stimulate public health action by others, but not informing the public health authority of actions that it would take to improve public health?" Dr. Nelson said the answer should be that such a "carve-out" should apply only to public health agencies or entities to whom such agencies have formally delegated their authority. The answer is an extension of the earlier question about what constitutes a public health authority.

Question 4
The regulatory language of the exclusion provides that "[t]he activity must be conducted, supported, requested, ordered, required, or authorized by a public health authority. What do each of these actions entail, and how do they differ? Please consider developing suggested examples illustrating each of these scenarios.

Mr. Forster stated that SOH's response basically used plain dictionary definitions of the terms. Ms. Freeman-Daily suggested, however, that the word "required" is different from "ordered": "required" might mean that the charter of an organization says it must do something, while "ordered" might mean that an external entity is mandating that activity.

Dr. Rosenfeld said the definition of terms should not be limited to the list supplied by OHRP but should be as expansive as possible. However, he was not sure that parsing out all of these terms really served a purpose because if the activity is done in the context of delegated authority from the public health agency, the distinctions don't seem relevant.

Question 5
While this exclusion clearly may apply in the context of a public health emergency, it is not limited to the emergency context. What are the pros and cons involved in broad application of this exclusion?

Mr. Forster said that a positive feature of broad application is increased flexibility to perform needed activities, but on the negative side, if the exclusion is applied to research activities that should be done following IRB review, this could harm public trust. During an emergency, broader application may be appropriate.

Dr. Nelson observed that it would be helpful to prepare for an emergency in a nonemergency context. He also noted that while the assumption is that informed consent is not secured in an emergency context, this assumption needs to be more carefully "unpacked." If someone is drawing blood, the investigator still need the person's consent. Unless there is a grant of authority, emergency public health activities will not qualify for the exclusion and will be subject to the Common Rule.

Ms. Wolf expressed concern that the "cons" as presented assume that the activities are really research activities. It is important to think through the question as presented and be careful of the language.

Ms. Coleman suggested adding some language related to verification of findings.

Question 6
What entity or involved individual may or should decide whether a planned activity meets the requirements of this exclusion? Are there any recommended considerations involved with this decision, and do they differ depending on what entity or individual might be making this decision?

Clearly, Mr. Forster said, the investigator should not be the one to make this decision. It might be made by an IRB office or by a government agency. Often, many institutions will be involved in carrying out an activity. Dr. Nelson agreed, but said he did not think the answer in the document was as clear as Mr. Forster's oral presentation. He added that if his institution were offered a contract to carry out a public health surveillance activity and assured that it met the exclusion, he would want to see the grant of authority. For transparency, the criteria used in making the determination should be readily available.

Ms. Wolf noted that the response uses the term "principal investigator," which invokes the research context. This would not apply to a public health surveillance activity.

Ms. Coleman noted that in order to determine whether criteria for the exclusion were met, an institution would need to verify that this is the case. She suggested the answer should address the types of information needed to make this verification. Also, she felt it should address how the decision-making process might be reached when the activity is one that might be either a public health surveillance activity or a research activity.

Question 7
Should documentation be recommended or required regarding each of the decision points involved with this exclusion? If so, please consider providing specific suggestions as to documentation and how entities or individuals should accomplish this.

Members concurred with SOH's response, which was that "the decision that an activity is a public health surveillance activity should be documented with specific reference to how it meets 45 CFR 46.102(l). This documentation should be publicly available, and easily accessible."

Question 8

This exclusion will not apply to activities dually regulated by FDA and OHRP. Are there any useful recommendations for involved institutions and individuals in such circumstances? (If not, feel free not to further consider this point.)

SOH noted, "SACHRP does not agree that it is universally true that "this exclusion will not apply to activities dually regulated by FDA and OHRP." For instance, if a public health authority used HHS funding to conduct or support a surveillance program that involved return of COVID-19 test results to subjects, it seems that the project would meet the exclusion at 45 CFR 46.102(l)(2) and simultaneously require FDA review under 21 CFR 812 as an investigational diagnostic device."

Dr. Straus suggested that the response include examples of FDA public health surveillance activities such as the Sentinel project, the FDA Adverse Event Reporting System (FAERS), and the Vaccine Adverse Event Reporting System (VAERS).

Dr. Nelson observed that surveillance related to biologics would fall under the Public Health Service Act, which is a separate authority. Otherwise, he thought SOH's draft response was fine.

OHRP Guidance

Mr. Forster said that though SACHRP was invited to comment on OHRP's guidance on the topic, SOH members thought it was a good document and did not disagree with any of its points.

Algorithms

For complete versions of the algorithms (decision trees), please email SACHRP's Executive Secretary, Julia Gorey, at *Julia.gorey@hhs.gov.*

Mr. Forster presented two algorithms depicting the flow of decision making around whether or not an activity can be considered public health surveillance. Dr. Straus noted that a graphic is often more easily followed than a text-based presentation.

Ms. Freeman-Daily suggested placing "Could this be public health surveillance" as the first question. Dr. Rosenfeld observed that this was not a straightforward question because answering it requires additional steps. Also, he suggested it would be good to avoid forcing people to answer difficult questions if the possibility is ruled out by easier ones earlier in the decision process.

Ms. Freeman-Daily suggested phrasing the first question, "Could it be considered research?" Dr. Rosenfeld noted that research and public surveillance activities might actually be the same activity but have a different purpose.

Dr. Nelson observed that the definition of research presented in the decision tree does not discuss the fact that research has "generalizable results." He thought the algorithm worked well but the text was problematic. Dr. Rosenfeld disagreed with Dr. Nelson with the utility of invoking

"generalizable knowledge" in this context. He wanted to stick to a practical approach that takes into account the fact that all learning is not research.

Second Discussion

Mr. Forster revised the document to take SACHRP's input into account. He explained that the term "grant of authority" will be used to distinguish any grant (*i.e.,* funding) given by a public health authority from a specific grant of authority that enables the grantee to act on its behalf. He removed a sentence that said they were identical.

Mr. Forster also rewrote the answer to Question 2 to clarify common distinctions between grants and contracts. A previous statement that data should be provided to the public health authority when these mechanisms are used was removed. Mr. Forster also added a brief statement that stressed the need for mechanisms that ensure the surveillance activity is "limited to that necessary to identify, monitor, assess or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance."

Dr. Nelson said it should be clearer that this could only apply to a contract when there is an explicit grant of authority. Dr. Rosenfeld said that either a contract or a grant would require a grant of authority. This typically would be specified through a letter or a memorandum of understanding. Activities that exceed that grant of authority may be considered research. Dr. Nelson saw a distinction between the two mechanisms. Not following the terms of a contract may result in a penalty, but a grantee might have the flexibility to make an argument as to why they did something different. Dr. Rosenfeld said the exclusion would only apply to public surveillance activities.

Ms. Wolf asked SAS to "think conceptually about the scope of the activity and who is controlling it." True public health surveillance activities must come from the legal authority of the public health agency and are carried out as an extension of that authority. Another SACHRP member observed that many entities may engage in public health practices but not under the authority of such an agency. Schools might engage in such practices, for example, but without a formal delegation of authority.

Ms. Freeman-Daily cited instructions to IRBs on the Johns Hopkins University site regarding what constitutes a public health surveillance activity. She found the language used concise and helpful: "The difference between public health surveillance and research in this context is that the purpose of the surveillance is to inform the decisions or actions that must be made by a public health authority." She concluded that if the information gathered will not be used by a public health authority, the activity cannot be considered public health surveillance. She sent the link to Mr. Forster for reference by the subcommittee.

Dr. Straus encouraged people to read a 2014 white paper from Public Responsibility in Medicine and Research (PRIM&R) on "Health-Related Activities Along the Boundary Between Research and Practice: When to Take Alternate Approaches to Providing Ethical Oversight."

Dr. Wilkins posed the example of a public health agency that hires a company to use its proprietary software for contact tracing. A private company with such a limited scope may not have expertise in public health, and giving them an exception regarding the use of their data would give the public pause.

Dr. Rosenfeld read a comment from Dr. Bass, on staff at the Centers for Disease Control (CDC). Dr. Bass confirmed that a public health authority such as CDC will engage in a broader universe of public health activities that are not necessarily public health surveillance. CDC would not want SACHRP to consider all of those activities to be surveillance. Dr. Bass also noted that CDC often uses "cooperative agreements" to support activities. She felt the use of the term "support" would enable SACHRP's response to the questions posed to be more consistent with Common Rule requirements.

Dr. Straus said he would provide additional examples of passive and active surveillance for use in SACHRP's response to question 3. He conceded this might be more "granular" than necessary but felt the distinction was important to illustrate. Dr. Nelson commented that he did not consider FDA activities such as FDA's Adverse Event Reporting System (FAERS) a research activity. Dr. Straus agreed, but noted that the data collected in such surveillance can be used to generate questions that might lead to additional research.

Public Comment

One substantive question received through the "chat" feature was read. It related to DDIR:

- Does the committee's work address prior consent or ethical considerations from the perspective of the deceased donor?

Dr. Rosenfeld said this was not part of the scope of the committee's consider. The Common Rule addresses research involving human subjects. Even though there are clear ethical obligations, manipulation of an organ in a deceased individual does not fall under Common Rule.

Dr. Rosenfeld also noted, in response to a question, that OHRP will post final approved documents after the meeting. He said that if there were urgently needed before that occurs, members of the public could request them by emailing the Executive Secretary for the committee, Julia Gorey.

Thursday, July 22

Welcome and Opening Remarks

- *Stephen Rosenfeld, M.D., SACHRP Chair*
- *Jerry Menikoff, M.D., Director, Office for Human Research Protections (OHRP)*

Dr. Rosenfeld welcomed everyone to the meeting and determined which SACHRP members and ex officios were present. He asked members of the public to use the link provided to submit comments, some of which will be addressed later in the public comment period.

The Chair observed that SACHRP is addressing many issues of "immediate and pressing relevance"

at this meeting. It is an "extraordinary moment we are living through," he said. Dr. Menikoff in turn, said that HHS is "thrilled to have SACHRP weighing in on relevant issues" and thanked the committee for its work, especially its deliberations on deceased donor interventions. The committee's work is crucial to HHS moving forward, and the agency does want to enable these studies to take place. He expressed the hope that the committee's work on the public surveillance issue will be useful in itself as a reference available through OHRP, whether or not the agency provides further guidance.

Consideration of the Role of Justice as an Ethical Principle in 45 CFR Part 46

- Stephen Rosenfeld, M.D., SACHRP Chair
- Panelists:
    - Jyoti Angal, B.H.M.S., M.P.H.
    - Linda Coleman, J.D.
    - Martin Mendoza, Ph.D.

See Attachment D. Charge to SACHRP: Consideration of the Role of Justice as an Ethical Principle in 45 CFR Part 46

Dr. Rosenfeld introduced the panel by sharing that after posting the Charge to SACHRP to address this issue, he prepared by reviewing the Belmont Report for guidance – his usual starting point. It was, he said, "the first time I've been disappointed in that document." The discussion of exclusion and diversity largely addresses personal vulnerabilities at the individual level. Nothing acknowledges where group vulnerabilities may arise and the duty to address them at a different level. He was struck by the characterization of the subjects of the notorious Tuskegee and Nazi experiments as "populations of convenience" when the truth was in fact much more egregious. Nuremberg and the Tuskegee experiment were the impetus for the federal human subject protection regulations, yet the fundamental issue of how we treat a population we regard as "other" was not addressed. The Chair also noted that the criteria for research approval at §46.111(a) discuss vulnerability, but requirements related for protection of such populations actually fall outside these criteria and arise in §46.111(b), leaving IRBs with "ambiguity as to their role in upholding the rights of so-called 'vulnerable' populations." SACHRP's charge calls attention to this.

Another place the regulations address diversity is in the discussion of requirements for IRB membership, which raises practical issues related to running an IRB and recommends that, if the IRB regularly reviews research on a group of people, a representative knowledgeable about that group should sit on the IRB. In many cases, in practice, IRBs choose someone who may be knowledgeable about a group but who is not a member of the group in question. This, too, deserves discussion.

Dr. Rosenfeld reviewed the four components of SACHRP's charge:

1. §46.111(a)(3) requires the IRB to take into account "the setting in which the research will be conducted." SACHRP was asked to consider:

- What is the role of the IRB in ensuring that research conducted in this setting appropriately protects the rights and welfare of research participants?

- In particular, how can research be conducted so that it does not implicitly inherit the injustices of the healthcare delivery system (*e.g.,* restricting participation to individuals who are insured and able to afford copays)?

Dr. Rosenfeld observed that many protocols have barriers to participation that affect the generalizability of the science across populations. Some people cannot afford to pay copays, for example, and have less access to insurance.

2. §46.111(b) asks the IRB to ensure that "additional safeguards" are in place to protect research subjects "vulnerable to coercion or undue influence." SACHRP was asked to consider:

- What measures constitute adequate safeguards in these circumstances, and how should their adequacy be assessed?

- Should the requirement for such safeguards be limited to those "vulnerable to coercion or undue influence" (*i.e.,* populations with diminished autonomy), or are there concerns of social justice that should lead to a more expansive interpretation of vulnerability to exploitation?

Dr. Rosenfeld noted that there is no specificity about what "additional safeguards" might mean. This brings up the issue of vulnerability and what it means for human subject protection.

3. §46.107(a) requires that the IRB "consider inclusion" of individuals who are "knowledgeable about and experienced in working with" disadvantaged populations if it regularly reviews research involving such groups. SACHRP was asked:

- This language is often interpreted to apply when research targets a specific group, but given the diversity of the U.S. population, should the language be interpreted more broadly to require that inclusion of such members be the rule, rather than the exception?

- And, given the awareness of ubiquitous structural racism, is it sufficient to rely on expertise and experience rather than representation to "promote respect for (the IRBs) advice and counsel?"

The Chair explained that the thrust of this element of the committee's charge is to explore what it means for a population to have "a seat at the table."

4. The fourth area to explore is:

- Is there any additional guidance, training, or resources that can be helpful to IRBs in raising awareness of and responding to ethical issues involving disadvantaged populations in research?

This is in effect a "catch-all' for everything else that should be considered.

Dr. Rosenfeld introduced the panelists, who each briefly shared their perspectives.

Remarks by Jyoti Angal

Ms. Angal said her insights were informed, in part, by her experience as the Director of the Regulatory Knowledge Core within the Collaborative Research Center for American Indian Health, which "provides a platform to bring together tribal communities and health researchers from multiple disciplines to work together in the development of cutting-edge transdisciplinary research that will address the significant health disparities experienced by American Indians in South Dakota, North Dakota and Minnesota." She noted that multiple violations of ethical constraints on research are well documented in tribal history. The approval of research on genetic samples that was contrary to the wishes and consent terms of Havasupi subjects is only one example. Researchers often do "helicopter" research on tribes with no accountability or feedback to benefit to the tribe. In addition, they frequently pursue research that stigmatizes tribal communities. Tribal oversight and participation in the research are essential to counter these practices.

The speaker observed that there are 573 federally recognized tribes and 50 known entities that provide oversight for research. Tribes want to self-govern their research because in their experience the existing review boards do not provide sufficient accountability. Some lack an understanding of indigenous cultures and the ability to discern whether or not the proposed research aligns with the culture's priorities. It is important to consider the issues of both individual and group benefit when research on a tribe is proposed.

Ms. Angal pointed to the *4 Rs framework,* developed in the 1990s, as an appropriate way of looking at requirements for research in indigenous communities. Its key principles include: Respect, Relevance, Reciprocity, and Responsibility.

Remarks by Linda Coleman

Ms. Coleman works closely with Yale University's Center for Clinical Investigation, which collaborates with community partners. It seeks to foster inclusion and diversity through sound recruitment methods.

SACHRP's charge focuses on the ethical principle of justice and includes consideration of such key concepts as equitable selection, inclusion, vulnerability, and diversity. In order to look at these things, she said, it is essential also to consider the Belmont principles of respect for persons and beneficence. She noted that agency expectations and requirements, as well as research standards,

have evolved over time, and participants' perceptions of research have also changed. She noted that IRBs are limited in their capacity to supervise research implementation, which involves education about the research and issues of trust. Research sites and teams have an obligation to the communities that participate in their research to gain and hold the trust of those communities.

The applicable definitions of terms such as "diverse" and "inclusive" will depend on the nature of the research. The principles of respect for persons and beneficence are relevant to equitable selection of subjects and should affect the approvability of proposed research. When an investigator says, for example, that the study will make no attempt to enroll anyone who does not speak English, these principles require the IRB to ask for the rationale for the exclusion.

The principle of beneficence is relevant to considerations of risk-benefit and scientific merit. The soundness of the science depends on ensuring that subjects are appropriately representative. If they are not, a drug or therapy could conceivably jeopardize patient safety when it goes on the market. To achieve the objectives of appropriate inclusion and diversity, research teams need to engage communities, educate proposed subjects, and address issues of trust so that people are comfortable volunteering. They should also carefully consider barriers to participation, such as those that stem from economic disadvantage.

Researchers can be successful in addressing these principles by paying attention to what communities want and care about. For example, subjects typically care about access to health care and overcoming health disparities. They want information they can take back to communities and share. Research teams should be sure there is meaningful collaboration with subjects' communities. IRB chairs might reach out through "cultural ambassadors" and hold town halls to educate community members. There are many successful models of how true engagement can be achieved, and they should be more widely used.

Remarks by Martin Mendoza

Dr. Mendoza expressed his appreciation to SACHRP for giving the HHS Office of Minority Health an opportunity to be part of the panel. He explained that the office is "dedicated to improving the health of racial and ethnic minority populations through the development of health policies and programs that will help eliminate health disparities." His remarks focused on challenges and opportunities related to including racial and ethnic minority populations in clinical trials.

Note: This PowerPoint presentation is available upon request to Julia.gorey@hhs.gov. Please see the PowerPoint for more detailed information.

The speaker gave four reasons that the participation of these populations was necessary:

- Minorities have been historically under-represented in clinical trials.
- Their representation is needed to study the effects of medical products in the people who will ultimately use them.
- Minorities may respond differently to medical products.

- The participation of minorities is needed to understand health disparities (diseases that occur more frequently or appear differently in diverse populations).

Dr. Mendoza noted that one-fifth of the guidance on FDA-approved product labels is specifically directed to racial and minority groups. He also expressed concern that 60 percent of clinical trial data are from sites outside the U.S., which may be less diverse than the U.S. population. He believed that "the trend toward globalization is not helping the representation of minority groups."

The speaker cited concerning data on drug trial participation in 2017 made available through the Center for Drug Evaluation and Research (CDER). These data showed that of various demographic groups participating in trials to develop novel drugs, 77% were white, 11% were Asian, 7% were Black or African American, and 14% were Hispanic. Oncology trials in the same period – trials that led to the approvals of 12 new drugs – had the following demographics: 74% white, 12% Asian, 2% Black or African American, and 4% Hispanic. U.S. Census data for 2019 show the population as 76% white, 6% Asian, 13% Black or African American, and 19% Hispanic or Latino.

Dr. Mendoza saw several possible explanations for decreased participation by minority groups in clinical trials. These include:

- Many members of these populations may harbor distrust of the medical system due to historical abuses.
- Researchers' recruitment and retention efforts may be inadequate.
- Patients may lack awareness of clinical trials.
- These populations may have concerns about their privacy.
- Researchers may misunderstand the beliefs and values that contribute to the decision-making process in various minority groups.
- Researchers may believe that minorities do not want to participate.
- Physicians may not talk to these patients about clinical trials.
- Results are often not returned to the individual or community.
- Researchers may believe that minorities are ineligible for enrollment.
- There are too few minority physicians, researchers, and clinical investigators.

The speaker then turned his attention to various policy strategies to support diverse participation in clinical trials. He first pointed to the FDA Safety and Innovation Act (FDASIA) of 2012, Section 907, which includes a provision to include reporting of race and ethnicity, a requirement for an initial public report on inclusion data from medical product applications, and an action plan to

address any deficiencies. The agency's 2018 action plan calls for three priorities:

1. *Improve the completeness and quality of demographic subgroup data collection, reporting and analysis.* To accomplish this priority, FDA has issued two guidance documents: Collection of Race and Ethnicity Data in Clinical Trials and Evaluation and Reporting of Age, Race, and Ethnicity Data in Medical Device Clinical Studies. The first guidance document articulates – for the first time – FDA's expectation that sponsors will enroll participants who "reflect the demographics for clinically relevant populations." Sponsors are required to submit a plan to ensure this objective is accomplished before the first patient is enrolled.

2. *Identify barriers to subgroup enrollment in clinical trials and employ strategies to encourage greater participation.* To accomplish this, FDA envisions public meetings and the use of tools. Dr. Mendoza stressed the need for effective communication and outreach strategies to address this priority.

3. *Make demographic subgroup data more available and transparent*. The Drug Trials Snapshot is one way this priority is being addressed.

Discussion

Ms. Coleman noted that the ethical principles of justice and beneficence both come into play in the effort to ensure that drugs work well for minority populations. Members of tribes, for example, are motivated to participate in studies that benefit their population, but they may not wish to put themselves at risk without benefit. Considerations related to possible benefits to participants should be part of study design.

She also stressed that while people who are "knowledgeable" about certain communities are considered acceptable IRB representatives, she felt strongly that actual members of the communities will be more respectful of the community and more in touch with community concerns. The use of community advocates to help in recruiting can have a huge impact. This strategy requires finding "champions" who are familiar with the research as well as their community.

In terms of barriers to participation, Ms. Coleman observed that copays are not the only financial barrier to be considered. Many policies have "huge" deductibles and for many people, travel to a site where their disease is being researched is not affordable. In-person interactions may be costly, and she held that they may not always be necessary. Finally, she commented that people with limited resources or life-threatening illnesses may be relatively easy to coerce. Are we educating people about the trials that make the most sense for them?

Dr. Straus highlighted a significant new resource under development: Achieving Diversity, Inclusion, and Equality. The document is substantial and will include tools to help broaden inclusion in clinical research.

Dr. Wilkins expressed appreciation for Dr. Rosenfeld's opening remarks. She said that the current time is one of heightened awareness of injustice, and she is grateful so many people are open to

rethinking policies that perpetuate inequities. While she did not want to discount any of the efforts to increase diversity, she stressed that key systems designed to protect human subjects are flawed. An example is the focus on research protections on individuals rather than oppressed and racialized communities. So long as we continue to look at individual benefits and fail to recognize how whole populations are disadvantaged, equal opportunity to benefit will never be achieved.

She agreed with Ms. Coleman that the issue of community benefit must be addressed to increase participation. It is also essential to determine how to address the systemic challenge of protecting groups, not just individuals. She highlighted additional systemic challenges related to the health care system itself, noting that many studies are not designed to include subjects regardless of payer status. She also agreed with Ms. Coleman that the practice of placing a person with "expertise" on a population on an IRB instead of one who has the lived experience of belonging to a disadvantaged and oppressed population fails to put an appropriate value on the level of understanding that only members of a population can possess.

Dr. Wilkins observed that "we have biologized race and baked that concept into research." Nevertheless, there is no clear definition of what it is, how it will be captured in studies, how findings should be interpreted, or how they should be disseminated. Many research studies fail to focus on the populations that have the greatest burden of the disease that is the studies' focus; sometimes, this is because of challenges related to language. Systemic problems will continue to make much of the research that we conduct inappropriate for broad dissemination. There is "plenty of opportunity to step back."

Ms. Wolf expressed appreciation for the opportunity to take up this topic. She said she had always considered "justice" the underdeveloped principle in the Belmont Report and believes that SACHRP can offer a great service by fleshing out what it can mean in the context of research. For example, the committee might suggest questions an IRB could ask of researchers when appropriate, such as, "Why are you recruiting only in this academic center?"

Turning her attention to the participation of minority communities, Ms. Wolf recalled the significant contributions made by Community Advisory Boards during the HIV/AIDS epidemic. Some of those affected by the disease or at high risk of contracting it became experts and helped design meaningful studies. She also observed that when there is only one community member on a Board, that person's voice may be discounted. She was impressed at how clearly community voices came through in peer reviews conducted by the Department of Defense's Congressionally Directed Medical Research Program .

Dr. Rosenfeld observed that the issues raised are large and overlap with bioethics concerns such as the therapeutic misconception. There is an increasing perception that clinical trials offer therapeutic opportunities that would not otherwise be available.

Dr. Nelson reflected on two threads of the conversation that are woven into SACHRP's charge: the idea that additional safeguards are needed for vulnerable populations (for example, that children should only be enrolled in a trial if it is relevant to them) and equitable selection. IRBs tend to think

more about participant protection and less about adequate participation and applicability of the research. He noted that, arguably, few FDA trials include the full range of individuals who might be exposed to that drug. The issue is made more complex by the fact that race is not a simple biological construct, but at least in part a social one.

Dr. Rosenfeld agreed that this aspect of the topic was challenging. He added that while it is possible to look at the principle of justice only through the lens of science, this is not all there is to it. He noted that it is not possible to represent the biology of everyone who might be offered a drug, but it is likely that researchers will get much closer by trying than by ignoring the issue.

Dr. Wilkins stressed that when conditions disproportionally affect certain groups, there should be a minimum bar to ensure they are adequately represented. She noted that participants in the first vaccine study related to COVID-19 were 89% white, yet the mortality rate from the disease is much higher in Native American, Black, and Latino communities.

Dr. Rosenfeld observed that this discussion is only the beginning, and SACHRP will continue to address the issues raised at its October meeting.

Consideration of Risks to Non-Subjects in Human Subjects Research

- *Dave Borasky, M.P.H., SAS Co-Chair*

See Attachment E. Consideration of Risks to Bystanders Posed by the Research Setting

Mr. Borasky presented a "relatively young" document for SACHRP's feedback. The issues it addresses were spotlighted by COVID 19 but the subcommittee found it easy to identify other examples in which such risks could occur.

Mr. Borasky noted that the Belmont Report is subject-centered in its discussion of risks, and regulations provide no "guide star." The issues raised are largely extra-regulatory. Is there agreement that SACHRP should address this topic? If so, what should its output look like? What should the final document tell stakeholders?

The Co-Chair observed that subcommittees have fairly broad representation, and members of SAS who "spend their days in the IRB trenches" acknowledge that some research poses risks to bystanders. However, they were uncertain how best to "layer the burden of responsibility" to address these risks. In some cases, for example, there are non-IRB oversight bodies that can address these concerns. Community advisory boards, for example, may have a role is shaping protocols that may affect communities. He further noted that there is extensive literature on risks to bystanders, proving that they are neither unknown nor hidden.

The current document offers background on relevant regulatory requirements and follows the model of points to consider, including both areas in which there may be risks worth considering and others in which the IRBs need not become involved. Its current introduction frames the document in the context of the COVID-19 pandemic.

Dr. Rosenfeld said the need for guidance related to bystander risk is most likely to arise in novel situations. If a protocol fails to address obvious risks, the IRB is likely to notice them. IRBs are used to reviewing and assessing protections put in place by investigators. SACHRP's document should describe the level of risk that should set off alarm bells and distinguish this from the risks of everyday life, such as driving a patient to a medical appointment. Dr. Nelson agreed that SACHRP should not assume that IRBs are new to the idea that risks like these should be taken into account.

Ms. Wolf saw a "disconnect" between the COVID-19 crisis and other examples, such as psychiatric washout studies. She said her IRB had protocols in place for permission to talk to family members in cases where they could be exposed to risk. She also had the experience of sitting on a Community Advisory Board that addressed issues related to vaccines and preventive research through counseling and consent processes that stressed both the risk of contracting the disease and the risk of passing it on. She suggested it would be helpful to acknowledge the fact that there are already good examples of how to handle bystander risk, then go on to illustrate what IRBs should be thinking about. She was uncertain about whether there was really something important to say on the subject.

Dr. Nelson also wondered whether there was a problem here that SACHRP needed to address, though he acknowledged a lack of specific language in the regulations. He was interested in hearing of examples that highlight related issues. He noted that some challenge studies are done under circumstances in which the problem of transmission to a third party is a concern.

Dr. Straus was "more enthused" about the value of taking on the topic. In reference to the effort to find a vaccine that is effective against COVID-19 as swiftly as possible, people are being exposed to the virus. There is significant dialogue in the vaccine community about the ethics of exposing people intentionally to a pathogen we are only beginning to understand. If the vaccine fails, there may be risks not only to the volunteer but to others. He felt the subject merited careful thought and believed that IRBs might benefit from points to consider.

Ms. Angal agreed with Dr. Straus that providing guidance for IRBs on how to consider risk to bystanders in research was a useful activity. She suggested addressing examples such as the risks posed to bystanders by the use of wearable sensor technology that may capture data from bystanders without their knowledge.

Ms. Allen noted that IRBs are already engaged in identifying risks to family members in genome research and certain pregnancy risks, but risks to members of research team may not be considered. She expressed concern that using the examples of mental illness and HIV-AIDS to highlight risks to bystanders may have unintended consequences; they may perceived as biased and fuel stigma and discrimination in these populations.

Dr. Rosenfeld noted that some type of protocol review often occurs before the protocol reaches the IRB (for example, review by a biosafety committee). However, in many cases there is no regulatory requirement for this to occur. In the rush to COVID-19 trials, some were not thought through as well as they might have been, and there was often no standing body prepared to do the necessary

pre-review.

Dr. Wilkins said the document should pay attention to community risks, including those related to racial or ethnic groups. Higher household densities in some communities might elevate bystander risk, for example. She was not sure what kind of prompts might be useful, but it would be helpful to emphasize the importance of consultation with affected groups or communities. Dr. Rosenfeld observed that her comments could be addressed as "points to consider," adding that "there is no harm in repeating things we already do" while addressing new concerns and strategies.

Dr. Straus also thought the "points to consider" format would be appropriate. Reflecting on COVID-19 virus studies, he said he could not think of other examples in which researchers might intentionally expose individuals to a pathogen, with attendant bystander risks.. He thought IRBs might benefit from a checklist. He also expressed curiosity about the origins of mechanisms for separate review such as radiation safety committees, noting that a similar review mechanism might be needed for exposure to pathogens.

Mr. Borasky agreed that there was work to be done to address such issues but was not sure the IRB was the right place for this burden. He did not want to encourage unnecessary "expeditions" to explore potential risks to bystanders in cases when there was no real cause for concern. Ms. Wolf cautioned that in many cases the IRB should not be addressing this type of issue on its own, but rather should be working with other committees and partners.

Dr. Rosenfeld agreed that this point was well taken; "mission creep" on the part of IRBs poses an unnecessary burden on research. He said the document should be very clear that in the majority of cases the issue of bystander risk does not arise and IRBs should not "go looking for it." However, some smaller IRBs may lack the volume of protocol reviews needed to recognize and address this type of issue. Mr. Borasky agreed that "the size and resources of the institution will affect how it addresses the issue." Dr. Wilkins said, however, that these were not the only considerations. IRBs that are more accustomed to community engagement, especially engagement with racialized or marginalized groups, will be better equipped to address bystander risks.

Dr. Nelson raised the question of audience, noting that in many ways this could be a document directed to researchers designing protocols rather than to IRBs. Mr. Borasky noted that some FDA documents are targeted to specific audiences.

In closing, Mr. Borasky noted that a few voices questioned the necessity of the document and others cautioned that the document might be useful but should be limited in scope. The subcommittee discussed the fact that if the focus were placed on COVID-19 research, it might not be recognized by the research community as a topic that merits broader consideration. Further, there might be limits on the longevity of recommendations that are so contextualized.

Mr. Borasky thanked the committee for "good food for thought." He said he would take the document back to the subcommittee and begin to refine it.

Public Comment

Consideration of the Role of Justice as an Ethical Principle. SACHRP responded to several questions:

- There have been policies and guidelines for minority inclusions but it is not enforced. So how do you purpose enforcing?

- Investigators include minorities in the design but does not do subgroup population analyses so inclusion means nothing - how do you purpose to enforce that the IRB approval was based on design that wasn't fulfilled?

- This is the same discussion we had in research over 10 years ago. Nothing presented today is new. These are the same issues and elements.

- Where is this speaker from? She obviously has no experience with VA studies that have a strong inclusivity approach to minority research and inclusion in general population studies.

- One cannot say that drug development, thus efficacy, is not dependent on race until it has been demonstrated that it is not – i.e., Warfarin. This is another problem with finding justice in clinical trials.

- The single IRB requirement: what challenges does it pose for the topics being discussed? How to deal with those challenges? *E.g.*, IRB members' knowledge of the specific population and study context and implications for justice, beneficence, etc.? Risk of slippage in adequacy of IRB review as move from local context to an IRB dealing with a national or global context?

Dr. Rosenfeld agreed that enforcement of any aspects of a protocol is always a concern. He noted that failure to fulfill requirements for a representative population would have implications for FDA labeling of products.

Dr. Rosenfeld said he could see both strengths and weaknesses related to the single IRB requirement and justice issues. Single IRBs would be better able to review the inclusion plans at several sites overall. However, community engagement may be more challenging for a distant single IRB. Some of these questions may help inform the work of SACHRP's subcommittees on this issue.

Dr. Nelson noted, regarding the reference to Warfarin, that decisions must always be driven by data. It is important to recognize that there are important population characteristics that may not be related to race.

Ms. Coleman said that Yale University's Human Research Protection Program has a cultural ambassador program that facilitates protocol review. Researchers get advice on design, improvements, and operational changes appropriate for target populations. Whether the IRB is doing a review for another institution or relying on another institution's IRB, it is important to

provide the IRB of record with information on the community. They have sometimes facilitated conversations between the local community and another IRB conducting research on that population. Real understanding goes beyond a simple form or checklist.

Dr. Wilkins reported that the Meharry-Vanderbilt Alliance has a National Advisory Board that includes minoritized groups. It is able to convene virtual engagement opportunities with people around the country, using a variety of strategies. Clearly, however, this approach is not perfect. She stressed that regardless of the location of the IRB of record, every site should have its own recruitment plan, which should include an opportunity to work with community partners and the local population.

Bystander Risk. A participant asked:

- Is the intention of the "Considerations of Risks to By-Standers" to cover risks to those who may be affected by the recommendations of machine learning or artificial intelligence systems under investigation? For example, a fully consented research subjects; (subject A) data is loaded into an AI/ML system which, because of the subjects' data, now produces a recommendation based upon the adapted gradients. A patient/subject (subject B) that has not consented to participate in that component of the study has their care now subject to the researcher's interpretation of the new recommendation provided by the AI/ML system. Is subject B a by-stander here? If so, is this the person whose risk and benefit profile needs to be reviewed by the IRB under this proposal?

Dr. Rosenfeld opined that it should not be possible to use such a device in medical care until it has been approved by FDA, at which point it would no longer be research. Therefore, the situation described did not sound to him like bystander risk.

Closing Remarks

Dr. Rosenfeld observed, in closing, that SACHRP approved two key documents at the meeting – its comments on NIH's proposed data sharing strategy and its recommendations on DDIR. He was thankful that SACHRP can now pass its recommendations on DDIR to HRSA and others who can implement the recommendations. He said addressing the complex issues around DDIR had been a "real learning experience" for him and for the committee.

The Chair observed that SACHRP has just begun to address its charge to consider the role of justice as an ethical principle and is far from having final recommendations to present. He hoped that by SACHRP's October meeting the committee would benefit from another panel on the subject and a first-pass document that frames related issues.

The subcommittee's work on public health surveillance will be returning with revisions for further considerations by the parent committee. He would have liked to move faster on this topic of current interest but hoped that new insights had been gained through discussion.

SACHRP's work on bystander risk may also be relatively urgent but is less so that public health surveillance. He hoped that the committee's work would contribute by, at least, providing "guideposts" for IRBs to consider.

The Chair noted that a public comment observed that the discussion of this principle was unchanged from what might have been said many years ago. He pointed to the Black Lives Matter and other civil rights movements as having placed issues in focus for reconsideration. Ms. Wolf observed that the fact that such conversations have been going on for a long time does not mean there is no need to continue to have them.

Ms. Gorey, SACHRP's executive secretary, reminded everyone of the dates of SACHRP's next meeting – October 20 and 21 – and asked everyone to put these dates on their calendars. She thanked the Chair and SACHRP members, noting that they were all getting better at using this technology. Dr. Menikoff also offered his thanks for a "great meeting."

Attachment A. Implications of the NIH Draft Policy for Data Management and Sharing on Data Derived from Human Participants (As Approved)

The U.S. Department of Health and Human Services ("HHS") Secretary's Advisory Committee on Human Research Protections ("SACHRP") has taken note of the National Institutes of Health ("NIH") Request for Public Comments on a Draft NIH Policy for Data Management and Sharing and Supplemental Draft Guidance (the "Policy"), particularly as it relates to sharing data that are derived from human participants. In this letter, SACHRP seeks to identify the challenges of applying the Policy to such data and proposes guidance to assist the research community in navigating the complexities of data sharing in the context of research involving human participants.

Data-Sharing Provisions in the Draft Policy as Applied to Human Participants

The Draft NIH Policy for Data Management and Sharing and Supplemental Draft Guidance was released in November 2019, as a means to share broadly data from research funded or conducted by NIH and encourage good data management practices. The Policy seeks to encourage the broad sharing of scientific data with the research community and the public.[2] Central to the Policy is a requirement that investigators of all research that generates scientific data and is funded or conducted by NIH prospectively submit a Data Management and Sharing Plan ("Plan") prior to initiating the study.[3] The Plan must describe, in two or fewer pages, how scientific data will be managed, including strategies on how to ensure data security and compliance with privacy protections. Plans must be submitted to the funding NIH Institutes, Centers, and Offices ("ICOs") as part of the funding application process (*e.g.*, as part of Just-in-Time for extramural awards or technical evaluation for contracts).[4] Plans are to be reviewed by appropriate NIH staff and ultimately become a term and condition of the relevant NIH award with which awardees must comply.[5] Failure to comply with a submitted Plan may result in an enforcement action, which can include the imposition of additional special terms and conditions or termination of the award. In addition, failure to comply with the Plan may have an effect on future funding decisions.[6]

NIH states that the Policy was intentionally kept at a high level to allow for flexibility across various scientific domains.[7] In recognition of the generality of the Policy, NIH has also released supplemental draft guidance on (1) allowable costs for data management and sharing and (2) elements of an NIH data management and sharing plan.

With respect to human participants, the Policy recognizes that the sharing of data derived from such individuals should be afforded additional protections, and the sharing of human participants' data **is governed** ~~**should be dictated**~~ by applicable federal, tribal, state, and local laws, regulations, statutes, guidance, and institutional policies, **whose restrictions all investigators must**

[2] 84 Fed. Reg. 60,400 (Nov. 8, 2019).
[3] *Id.*
[4] *Id.*
[5] *Id.* at 60,401.
[6] *Id.* at 60,401.
[7] *Id.* at 60,399.

accommodate in any Plans.[8] Plans must include consideration of these requirements – **which SACHRP recognizes may often be unknown to researchers who are not experts in data privacy law – as the Plan describes ~~when describing~~** proposed approaches to managing and sharing data derived from human participants. Further, the Policy requires that Plans describe the ways in which participants' privacy, rights, and confidentiality will be protected, via de-identification[9] or other means.[10]

The *Federal Register* publication of the Policy is followed by supplemental draft guidance on elements of an NIH data management and sharing plan that outlines additional elements that investigators should consider as they develop their Plans. Under the supplemental draft guidance, investigators are advised to consider, among other things, the rationale for decisions about which data to share, plans for providing appropriate protections of privacy and confidentiality for scientific data derived from human participants, and whether data generated from humans will be available through restricted or through unrestricted access.[11]

Though many experts provided thoughtful input on the Policy, there has been little discussion of the Policy's stance on data derived from human participants. Our intent in this letter is to examine the ways in which the Policy may better protect such data and precautions that SACHRP believes should be implemented to protect the interests of human participants.

Potential Issues Created by the Policy; Recommendations

A. Consent to Data Sharing and Control of Data by Human Participants

As drafted, the Policy includes little to no discussion of informed consent, despite the fact that under the federal Common Rule, the Food and Drug Administration regulations on human subjects research, as well as general common law principles of consent to treatment, the data of human participants are typically collected pursuant to some form of informed consent. Investigators generally should comply with any limitations on future uses and sharing of data derived from human participants that are set forth in the relevant consent document. Though human participants may consent to use and disclosure of their data as part of a clinical trial or other research study, such consents often do not contemplate broad sharing of the collected data with the research community and the public. Moreover, even when the consent does discuss the possibility of future research, the consent document may not define future uses to include sharing the consenting patients' data as

[8] 84 Fed. Reg. 60,401.

[9] For purposes of this document, "de-identification" refers to personal data that have been de-identified under HIPAA standards, and "anonymization" refers to the rendering of personal data, under Common Rule standards, so that the "identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects." "Sensitive data" refers to personal data whose disclosure can reasonably be expected to bring some identifiable ~~reputational~~ injury or harm to the data subject, with degree of data sensitivity increasing as the harm increases in severity.

[10] *Id.*

[11] *Id.* at 60,402.

broadly as is contemplated by the Policy. **SACHRP recommends** that **the Policy ~~should make clear~~ require that investigators ~~should~~ carefully craft consents for subsequent uses of ~~evaluate the underlying consents of~~ data derived from human participants; that investigators using previously-collected data sets pay close attention to any specific data use limitations in the terms and conditions (including consents) under which those data were collected; and that investigators ~~and~~, as part of their Plans, must ensure compliance with any such data use limitations by subsequent data requestors. ~~contained in such consents as part of their Plan.~~ SACHRP further recommends that NIH ~~should~~ consider implementing a means to track such limitations or require downstream users to enter into data use agreements so that subsequent data requesters are made aware of sharing limitations and held accountable for unauthorized future uses of data derived from human participants.**

Further, upon the adopting of the Policy, investigators and institutions will need to undertake the burden of harmonizing existing consent documents and privacy notices to accommodate the type of broad data sharing contemplated by the Policy. For example, if there is an original consent associated with medical treatment, the consent often may not state or indicate that the data collecting during standard of care procedures may be used subsequently in a research study. Also, the Health Insurance Portability and Accountability Act of 1996 ("HIPAA") Privacy Rule requires "covered entities," which include health plans and most U.S. health care providers, to provide individuals a "notice of privacy practices" explaining how such entities may use and disclose individuals' protected health information that are gathered in the course of medical care and health insurance payment. Even though data disclosed pursuant to the Policy may be de-identified and thus no longer subject to HIPAA standards, consideration of medical and research ethics should lead covered entities to inform patients and beneficiaries in these notices that their clinical data may be de-identified or anonymized and re-used for future research, and the privacy notices should describe subsequent data sharing. These disclosures should be made not only in the context of the ~~**broad**~~ data sharing contemplated by the Policy, but also for data sharing pursuant to other contractual obligations, regulatory requirements (*e.g.*, European Medicines Agency Clinical Trial Regulation), publication requirements (*e.g.*, BMJ transparency policy), and institutional commitments. **SACHRP recommends that the Policy ~~should~~ promote transparency in notices of privacy practices and in similar statements of institutional practices regarding subsequent research uses of clinical data, so that patients may be aware of data sharing for future research purposes, even in advance of any participation in a primary research study, as many data used in primary studies are themselves previously gained during delivery of standard of care or previous research. SACHRP further recommends ~~suggests~~ that NIH, in collaboration with the HHS Office for Civil Rights, provide additional guidance in the form of standard text or templates that would assist investigators and institutions in developing updated consent and notice documents that conform to the Policy's expectation for ~~broad~~ data sharing, and that these templates be crafted to respect health literacy limitations that often characterize the public at large.**

The above discussion of informed consent raises the issue of the level of control that human participants have over their data and how to ensure that participants' rights and preferences are protected as their data are being shared downstream. In general, under HIPAA standards as well as under accepted research practices, data subjects do not exercise control over the downstream research uses of any of their de-identified or anonymized data. Further, under HIPAA and under the Common Rule, identifiable data – if they are used under established regulatory pathways such as waiver of authorization and waiver of consent – also are not subject to control of the human sources of those data. Yet the Policy makes no reference to the degree to which human participants may exercise control over their data once such data are made available to the research community or the public under the Policy. Even under existing research practices, there are some circumstances in which such information may be relevant. For example, under the HIPAA Privacy Rule, individuals have the right to revoke authorizations for use or disclosure of their protected health information,[12] and if identifiable research data have been provided to a researcher under an authorization (as opposed to under a waiver of authorization or a limited data set), then the individual may exercise this revocation right. In contrast, the Policy contains no reference to how the revocation would be fully effectuated in regard to those researchers who already have received the data under the Policy. Relatedly, the Policy does not make clear whether and how human participants may access and share their own data with other researchers. **SACHRP recommends that the Policy or its supplemental guidance provide investigators with clearer guidelines on how to make clear to human participants that their rights to maintain any control of their data – whether de-identified or not – once such information has been shared with downstream users are extremely limited. SACHRP further recommends that participants ~~should also~~ be informed of mechanisms through which they may themselves seek to make their data available to third-party researchers.**

B. Efficacy of De-Identification and the Heightened Risk of Re-Identification for Smaller Populations

The Policy relies on de-identification as one of the ways to protect human participants' privacy rights and confidentiality. However, the Policy does not specify a particular standard that should be used to ensure de-identification. Various standards for de-identification exist, and some are more rigorous than others. **SACHRP recommends that the Policy provide minimum standards that investigators should meet or surpass when de-identifying data derived from human participants.** Notwithstanding the above, though de-identification is commonly perceived to be an effective means to protect human participants, certain studies have shown convincingly that other data can be used in conjunction with de-identified data from research studies to re-identify individuals. Increasingly, the protections afforded by removing the eighteen identifying data elements cited in HIPAA[13] have become out of date, as technological advances and the combining of data sets increase the risk of re-identification. For example, commercial interests have increasingly been trying to combine large, de-identified data sets with real-world data collected

[12] 45 C.F.R. § 164.508(b)(5).
[13] *See* 45 C.F.R. § 164.514(b)(2) (describing requirements for de-identification of protected health information).

during the course of ordinary daily activities (*e.g.*, credit card charges, driving habits), which increases the risk of re-identification and misuse of previously de-identified data. **SACHRP recommends that the Policy make note of the potential for re-identification of previously de-identified data and that the Policy direct investigators to consider the risk of re-identification for their particular data sets as they formulate their Plans. SACHRP further recommends that ~~Further,~~ to the extent an investigator's Plan includes putting in place a data use agreement, NIH ~~should~~ require such agreements to include a provision by which the data recipient agrees not to attempt to identify individuals who are subjects of the data.**[14]

Given that technological advances may allow for re-identification of data derived from human participants that have been de-identified, one way to mitigate the risk of re-identification is to exclude certain information from a data set that is made available for broad sharing under the Policy, particularly if such information would not materially contribute to enabling the replication and/or validation of scientific results. **SACHRP recommends that a clearer articulation of standards on how to manage re-identification risks would create a baseline of human participant protections. SACHRP recommends that, at a minimum, the Policy identify common data types that investigators should consider excluding (unless sharing of such information is otherwise explicitly consented to) from a data set, in consideration of re-identification risks.**

Re-identification of data may result in harm to human participants (*e.g.*, discrimination, identity theft, illegal/non-consensual surveillance). However, individuals belonging to smaller populations and minority groups, or "discrete and insular minorities," such as many American Indian and Alaska Native communities, may be more likely to be re-identified and potentially experience greater harm in the event that their data are re-identified. To address the increased risks associated with re-identification of data derived from such closely defined populations, the Policy generally states that investigators should consider including exceptions to sharing certain data in their Plans, especially when working with "small or underserved populations." Recognizing that the data of certain populations warrant extra scrutiny is an important first step, but investigators and the research community more broadly would benefit from additional guidance on when and how to apply such exceptions, to ensure that the sharing of these especially sensitive data is being handled appropriately. For example, individuals belonging to certain closely defined populations, **such as a specific racial, ethnic, religious, national, indigent, or disease-defined community**, might consent to the ~~**broad s**~~sharing of their data as an exercise of their autonomy; however, the Policy does not discuss how investigators should reconcile such consents with the Policy's suggestion that Plans might consider excluding certain information from their data sets to protect these populations. **While sharing of data for additional research uses may often be beneficial, there are circumstances in which the sharing of certain data may increase the risk of harm to human participants, particularly for populations with unique sensitivities, such as those who have historically been the subject of discrimination or lack effective representation in the political**

[14] Note that, as discussed in Section D, Certificate of Confidentiality requirements attach to, and follow, identifiable human data collected in the course of NIH-funded research.

process, or who may suffer dignitary harms as a result of the use of their data for certain types of research projects. SACHRP recommends that the Policy provide additional guidance on how investigators might navigate exceptions to sharing certain data derived from defined, vulnerable ~~small or underserved~~ populations. SACHRP recommends that the Policy give examples of acceptable and prudent limits on data sharing, to signal to investigators the types of data sets and populations that would experience higher risk of harm if re-identification were to occur. SACHRP further recommends that the Policy more clearly articulate that Plans should be carefully crafted to mitigate such risks while preserving the ability for members of these populations to consent to sharing their data.

Genomic data are also particularly susceptible to re-identification – this fact has been recognized in the NIH Genomic Data Sharing Policy, which provides that such data are sufficiently sensitive to warrant obtaining from human participants informed consent explicitly discussing future research use and broad data sharing, even when the data are de-identified to the standard set forth in the HIPAA Privacy Rule. There are some researchers who assert that genomic data cannot be fully de-identified, and the U.S. federal departments and agencies that have adopted the Common Rule have announced an intention to revisit the identifiability of such data as part of the revisions to the Common Rule that took effect in 2019.[15] **SACHRP recommends that the Policy or supplemental guidance explicitly state that in the context of NIH-funded research, and given the purpose of the Policy, the unique nature of genomic data be regarded as precluding de-identification or anonymization as sufficient justification for use or sharing of human participants' genomic data without consent, and that safeguards in addition to de-identification or anonymization should be considered when sharing genomic data under the Policy. Such positions would be consistent with those taken under NIH's own Genomic Data Sharing Policy for NIH-funded research that falls under that policy. Further, SACHRP recommends that consent documents for participants providing genomic data that are to be shared under the Policy include a statement on the unique ability for such data to be re-identified and on any safeguards that might be added to protect the data from re-identification.**

C. Controlled Access to Data Derived from Human Participants

Though the Policy provides researchers the flexibility to specify in their respective Plans when and where the scientific data are to be shared, more specific guidance should be made available to mitigate the possibility of such data being used for malicious intent. Making scientific data broadly available may help achieve legitimate goals, such as enabling the verification of scientific results or facilitating reuse of hard-to-generate data. However, broad data sharing, particularly if such sharing is agnostic as to the recipient of the data, may lead to misuse. For example, broad sharing without any access restrictions may lead to inappropriate targeting of certain populations for political, marketing, or discriminatory purposes. Unrestricted access to data may also affect investigators:

[15] *See* 45 C.F.R. § 46.102(e)(7) (requiring the reexamination of "identifiable private information" and "identifiable biospecimen" within one year of the 2019 revisions to the Common Rule and at least every four years thereafter).

researchers in academic settings may want to avoid secondary use of the data they gathered, for fear of others using the data without providing appropriate attribution, and research sponsors in industry may worry that competitors may use their data as an unfair "leg up" to initiate competing clinical trials at less cost. While some have argued that the automatic issuance of Certificates of Confidentiality for NIH-funded research involving human participants serves sufficiently to safeguard human participant data from inappropriate use,[16] a Certificate of Confidentiality still permits the further disclosure of information for purposes of scientific research conducted in compliance with applicable federal regulations governing the protection of human subjects in research.[17] Thus, for example, genomic information that has been shed of all eighteen HIPAA identifiers could be further shared for research purposes despite the existence of a Certificate of Confidentiality because the sharing of such de-identified genomic information would generally fall outside of the federal Common Rule, which governs the research use only of *identifiable* private information of human subjects.[18] Accordingly, the availability of Certificates of Confidentiality alone is not sufficient to safeguard sensitive data derived from human participants. **SACHRP recommends that sensitive data, particularly those derived from human participants, be more safely shared by encouraging or requiring the implementation of controlled access measures. SACHRP recommends, for example, that NIH consider requiring data requesters to agree to terms and conditions under which the requester must protect data privacy, refrain from attempting to identify individual participants, and not share the data with individuals outside of those who are listed in the data access request. For particularly sensitive data, access could also be controlled by creating a "sandbox" environment in which legitimate requesters may access and manipulate data without obtaining the ability to receive portable copies of the data or to share those data with a third party.**

D. Downstream Sharing and Efficacy of Sanctions

As discussed in various sections above, making data broadly available to the research community and the public may result in downstream uses of the data. Though the Policy recognizes that certain data sets may require limitations on sharing, it is unclear as to whether and how downstream requesters would be held accountable for unauthorized uses of data derived from human participants. Further, the Policy is silent on forms of recourse that human participants can take if downstream requesters use their data in breach of sharing limitations or for malicious purposes. As written, the Policy primarily ensures compliance with Plans by terminating awards or taking non-compliance into consideration when making future funding decisions. Though the loss or diminution of funding may serve as a mild deterrent for data users that depend on NIH awards, the Policy's enforcement provisions have little to no effect on investigators and institutions that operate

[16] *See* 42 U.S.C. § 241(d) (describing the issuance of a certificate of confidentiality to protect individuals who are the subjects of biomedical, behavioral, clinical, or other research funded by the federal government); NIH Notice Number NOT-OD-17-109 (Sept. 7, 2017, eff. Oct. 1, 2017) (announcing updates to the NIH policy for issuing certificates of confidentiality for NIH-funded and -conducted research).
[17] 42 U.S.C. § 241(d)(1)(C)(iv).
[18] *See* 45 C.F.R. § 46.102(e)(5) (defining "identifiable private information" as information for which the identity of the human source is or may readily be ascertained or associated with the information).

independently from NIH funding. **SACHRP believes that the sensitive nature of data derived from human participants necessitates sanctions of sufficient consequence, regardless of whether NIH funding is involved, and SACHRP therefore recommends that NIH articulate stronger measures to deter more effectively any misuse of such data. Suggested enforcement mechanisms may include fines or civil monetary penalties for each instance of non-compliant use or sharing of data derived from human participants. SACHRP recommends that ideally, such measures be applicable to investigators and institutions more universally, without being limited to research being funded by the NIH.**

E. Resolution of Discrepancies Created by Ex-U.S. Standards

The Policy rightly contemplates the applicability of data privacy requirements under federal, tribal, state, and local laws, regulations, statutes, guidance, and institutional policies. However, the Policy remains silent on international requirements that may apply to the use of certain data sets. For example, the General Data Protection Regulation ("GDPR") regulates U.S.-based use and processing of personal data that have been collected in the European Economic Area ("EEA") for research purposes. Under the GDPR, consents for future uses of personal data may be required to have a level of specificity that differs from the broader authorizations that are permitted under HIPAA and its implementing rules and regulations. Even if the Policy does not explicitly acknowledge that Plans should consider privacy requirements that may exist under international law, the GDPR and other international regulations may nonetheless apply to certain U.S.-based research. **GDPR and other national privacy laws often even define such basic privacy terms as "de-identified" or "anonymized" in ways that differ from the U.S. standards with which U.S.-based investigator tend to be most familiar. SACHRP recommends that the NIH bring to researchers' attention the potential applicability of international data privacy standards and provide guidance to clarify discrepancies between U.S. and ex-U.S. requirements on the sharing and maintenance of data derived from human participants.**

Conclusion

As described above, the lack of clarity regarding the Policy's treatment of data derived from human participants provides NIH an opportunity to release additional, acutely needed guidance. Though the intent to create a flexible set of guidelines that applies across scientific disciplines is understandable and laudable, SACHRP recommends that the NIH articulate certain minimum standards and factors designed to protect human participants, in order to direct investigators to tailor data-sharing approaches more carefully to the risks and limitations inherent in their data sets. Additional guidance would provide greater certainty to the research community and give human participants greater confidence in the security and privacy of their personal data.

Attachment B. Issues Surrounding Deceased Donor Intervention Research under 45 CFR part 46 (As Approved)

OHRP has asked SACHRP to consider whether and how certain provisions of the HHS regulations for human subjects research protections apply to research involving interventions conducted on organs from deceased donors19 before they are transplanted into living recipients. Building on the conclusions of the 2017 Consensus Study Report of the National Academy of Medicine (NAM), entitled "Opportunities for Organ Donor Intervention Research: Saving Lives by Improving the Quality and Quantity of Organs for Transplantation" (hereinafter NAM Report)20, SACHRP is asked to form recommendations on the questions below.

In the course of extensive discussions on this topic, issues were raised by ~~**the group**~~ **SACHRP** that are related to but potentially outside the scope of the specific questions, or that expand the context of the questions. These issues are noted both before and at the end of this document.

OHRP has determined that deceased organ donors are not human subjects under the HHS regulations. The NAM report concluded that **recipients of organs**[21] that have been subjected to research interventions, and in whom transplanted organs are now being studied for their function, efficacy, and safety, should be treated as research subjects. While the NAM Report addressed numerous issues affecting deceased donor intervention research (DDIR), the specific charge to SACHRP addresses only certain questions and recommendations affecting human subjects research protections under HHS jurisdiction. Specifically, when individuals are identified as needing an organ transplant, a two-part conversation process begins. The precise contours of this process vary across transplant centers, but are generally similar in intent. The first part of the two-part conversation begins when a patient and health care provider discuss whether the patient should become a transplant candidate. This first conversation usually includes some standardized education about transplantation and the candidate role. Discussion about transplant continues periodically with the health care team throughout the time during which the patient waits for an organ offer. That waiting time can vary from days to years.

In the first conversation, individuals are told about the process of organ transplantation, including the clinical risks. Individuals are also told about the potential availability of organs that may carry a risk of infection (formerly categorized as "increased risk" organs), and organs that may have a lower likelihood of functioning well or may have a shorter lifespan than most (called "non-

[19] Note such interventions extend to those on: (1) deceased donors after declaration of death and before organ procurement; and (2) organs after they have been procured from a deceased donor.

[20] National Academies of Sciences, Engineering, and Medicine, ***Opportunities for Organ Donor Intervention Research: Saving Lives by Improving the Quality and Quantity of Organs for Transplantation***. Washington, DC: The National Academies Press (2017) (available at https://doi.org/10.17226/24884).

[21] Note "organs" refers here to vascularized human organs (regulated by HRSA and the OPTN) in accordance with the definition of organ set forth in 42 CFR 121.2, and not to human tissues or human cells, or cellular and tissue-based products (HCT/Ps) (regulated by the FDA).

standard" or "marginal" organs). Potential recipients may decide at any time that they do not wish to receive offers of such organs. They are also free to change their minds at any time. During this first conversation, individuals could also be told about the potential availability of DDIR organs, given general information about DDIR and what participating in DDIR would entail for organ recipients, and perhaps could also be told about current IRB-approved research interventions on such organs. Individuals could decide that they do not want to receive offers of DDIR organs, but could change their minds at any time while awaiting transplant.

Transplantation does not occur until after the second step, which is the organ offer call. This conversation takes place immediately before the transplant, when a suitable organ is offered to a potential recipient and that individual decides whether or not to accept that organ. This second step is the only opportunity to obtain informed consent for a research intervention, as consent has traditionally been interpreted. In most situations, there will be only 30 minutes to an hour for the transplant surgeon, the facility and the potential recipient to determine, respectively, that an offered organ is clinically appropriate, surgical resources are available, and the organ is acceptable.

SACHRP has been advised that the request from OHRP has been prompted by the understanding that there is a lack of professional consensus in the community, and a lack of standardized practice, with respect to the application of the HHS regulations for human subjects research protections to research involving deceased donor organs that have been or will be manipulated and subsequently implanted in living human recipients. The diversity of practice probably arises from differing perspectives in the research, transplant, and ethics communities about how the requirements of the HHS protection of human subjects regulations apply to such research, the overlap between clinical practice and research, and the complex and novel ethical and practical considerations inherent in this unique context.

In January of 2019, OHRP requested that SACHRP explore this issue by responding to ten specific questions. The expectation is that SACHRP's recommendations will inform HHS action, including issuance of guidance concerning the proper application of the HHS regulations for human subjects research protections to DDIR and whether a Secretarial waiver22 of certain regulatory requirements may be necessary with respect to such research.

A. The Unique Context of DDIR

In the process of learning about the ethical, regulatory, and practical challenges posed by this unique research context and responding to these ten questions, SACHRP has considered and discussed how the system and circumstances of organ transplantation affect a wide range of issues posed both by 45 CFR 46.116 and by the ethical bedrock on which the Common Rule is based.

[22] For research subject to the codified Common Rule, 101(i) permits a department or agency head to waive the applicability of some or all of the provisions to specific research activities or classes of research activities otherwise subject to the specific requirements for IRB review and research informed consent. Any waiver must ensure that the alternative procedures to be followed are consistent with the principles of the Belmont Report.

Research involving manipulation of donor organs and their subsequent use in transplant recipients has several unusual structural characteristics. These include:

- The research involves two interventions (manipulation of the donor organ and transplant) that are separated in space and time, meaning that the primary research team may not be involved in the intervention on the living human participant. As a corollary, the individuals with whom the participant/transplant recipient interacts may only be involved in the research to the extent that it offers a clinical alternative to the patient.
- The lack of well-defined sites: while the deceased donor intervention may take place at a small number of institutions, transplant of the manipulated organ may occur at any of the over 250 transplant hospitals in the United States;
- A recipient's decision to accept a manipulated organ must be made under severe time constraints. There are parallels for this kind of decision-making in other research settings, but in those settings the constraints are usually dictated by a patient's clinical circumstances (e.g., research involving individuals with an acute MI or stroke). In DDIR the constraints arise from the limited window of viability for the donor organ.
- Although time constraints limit both the ability to convey sufficient information and sufficient opportunity to discuss and consider research participation, individuals on the transplant waiting list are a well-defined population who typically have frequent interactions with the healthcare delivery system. These circumstances provide other opportunities to support informed decision-making, opportunities that are absent in other clinical circumstances in which some IRBs have approved time-constrained research decision-making.
- The choice facing the potential participant in DDIR is unusually stark. Whatever the research-related risk, saying "no" to an organ offer generally means returning to an unstable and typically worsening clinical situation with no certainty of when another offer will be made. This decision stands in contrast to other time-constrained decisions, where the potential participant may generally choose between a research intervention and standard-of-care treatment, both of which are available at the time of the decision.
- The reality of the decision facing a potential participant (not whether or not to participate in research versus receiving standard-of-care treatment, but whether or not to receive a potentially life-saving organ by becoming a research subject) carries a heightened ethical obligation to make the decision-making process as clear and straightforward as possible for the potential recipient/participant.
- Individual research proposals cannot be considered outside the context of the organ transplant system as a whole. Donated organs are a scarce resource, and approving a particular research study may mean that organs are not available for other research, or, if DDIR becomes more common, for transplant as unmanipulated organs. Further, manipulation of donors has an impact on organs that are not the focus of the research: so-called "off target" organs. DDIR thus may also implicate a broader group of potential recipients who will be human subjects, but are not the primary subjects of the research.
- The structural reality that DDIR must be managed as a scarce resource for the public good also has ethical implications. Ethical review in this setting must go beyond balancing risks of harm and potential benefits for individual participants and focus on the benefits to society from the production of generalizable knowledge, thus expanding consideration of individual DDIR studies to include their impact on the organ transplantation landscape as a whole.

We first respond to the ten questions, and then offer recommendations based on our responses.

B. Responses to Questions

IRB Approval and Informed Consent when transplant candidates are considered human subjects for DDIR:

Question 1. If the two-part process proposed by the NAM for seeking informed consent from transplant candidates offered organs as part of DDIR studies were implemented, would the information provided to a transplant candidate in the second part of such a process (at the time a specific organ that was subject to a research intervention is offered) substantially differ from, or be significantly more time-consuming to share than, the information routinely provided to a transplant candidate when offered an organ as part of clinical practice? Does this change if the organs are coming from high-risk donors?

Discussion:

SACHRP has been provided with information from representatives from HRSA as well as external consultants at numerous meetings of the Committee and of the SACHRP subcommittees from June 2019 through March 2020. Notable points included the following: while currently there are only a limited number of IRB-approved studies relating to deceased donor organs that will be transplanted into living human recipients, the expectation is that the number of such studies will increase significantly over time. In addition, there was discussion that the length of time a harvested organ remains viable differs depending on the organ (e.g., heart, lung or kidney). Finally, both the gravity of the situation facing individuals on transplant waiting lists and the time constraints mean that the decision-making process (often conducted by telephone) that takes place when a DDIR organ is being offered could be less than optimal.

SACHRP discussed whether the first step in the NAM-described two-part process could include a discussion of currently approved IRB protocols that could be applicable to that individual, as well as a general discussion of what types of future intervention research might be approved. However, transplant representatives noted that the initial conversation could take place years before the actual transplant and that new protocols could be approved in the interim period. SACHRP discussed the desirability of a communication system such as a single website that could provide prospective transplant recipients with information on IRB-approved protocols. Representatives of the transplant community were divided as to the practicality of creating and effectively maintaining such a resource. Even were such a central resource available, SACHRP had concerns about placing the obligation to be informed on potential research participants, who might not be in a position to keep up with ongoing research, and even if they were vigilant, might not have learned about or be able to recall particulars if offered an organ from any specific study. Thus, the first step in the NAM process could provide potential recipients/participants with education about DDIR in general, but could not reliably provide relevant information about particular research in advance of the organ offer itself.

While clinical consent to receive an organ from a high risk donor provides many parallels to DDIR, differences between what has been deemed adequate for clinical as compared to research consent led SACHRP to conclude that research consent in this context would be expected to require more time and discussion than has usually been allotted for clinical consent.

Question 2. Should an IRB's approval of DDIR be affected by circumstances specific to organ transplantation, including the following factors: (i) the time period available to a transplant candidate to accept or reject an organ offer; (ii) whether a transplant candidate is likely to die without a transplant or alternative treatments exist (e.g., dialysis for patients with end stage renal disease); (iii) the likelihood that transplant candidates will receive other organ offers, including offers of organs not subject to the same interventions; and (iv) the fact that any organ offered for transplantation, whether subject to a research intervention or not, must be individually accepted by a transplant candidate? Please explain.

Discussion:

SACHRP considers that an IRB's approval of deceased donor intervention research (DDIR) will be affected as follows:

(i) the time period available to a transplant candidate to accept or reject an organ offer:

Yes, because this will affect the informed consent content and process.

(ii) whether a transplant candidate is likely to die without a transplant or alternative treatments exist (e.g., dialysis for patients with end stage renal disease):

IRBs routinely approve research in which the prospective participants have no standard of care options and may be facing death. The likelihood of death should not affect the IRB's approval of the research, except in so far as it may compromise an individual's decision-making at the time consent is sought. Individuals on the transplant list are at risk of death from their underlying condition; the offer of a research organ may provide an early opportunity for intervention, and refusal should not change their priority on the transplant list. Thus, a refusal of a DDIR organ does not change an individual's risk of death from where it stood before the research offer, and it should not be considered a risk of the research (unlike any risk of death that may arise from the research intervention on the organ). That being said, there is never a guarantee of an organ offer, and the IRB must acknowledge that a prospective participant's decisions will be significantly affected by the choice between acceptance of an immediate and potentially life-saving offer and deciding to continue to wait. This is particularly true because for many DDIR protocols, the risks of harm from participation, although greater than minimal, may well be lower than the risks of death or increased disability arising from waiting longer for a standard organ.

(iii) the likelihood that transplant candidates will receive other organ offers, including offers of organs not subject to the same interventions:

This could affect an individual's decision whether to accept a DDIR organ. It is an important aspect

of consideration of alternatives to participating in research. However, it is not clear how the availability or unavailability of other organs should affect the IRB's approval determination. Certainly, individuals who are unlikely to timely receive another organ offer will be motivated to accept a research organ. As in (ii), this should not affect the IRB's approval of the research but will need to be considered in the process of obtaining informed consent.

Should DDIR become more common, it is also possible that approval of a research study could affect the supply of unmanipulated organs. That is, growth in approved DDIR could decrease the general availability of standard, unmanipulated organs, thus decreasing the likelihood that anyone on the transplant list would be offered a non-research organ. The potential for such an impact must be evaluated by the IRB or a committee charged with scientific review in the context of organ transplantation.

(iv) the fact that any organ offered for transplantation, whether subject to a research intervention or not, must be individually accepted by a transplant candidate:

It is not clear what this question is intended to mean, nor why this circumstance should be regarded as specific to organ transplantation. Clinical consent (i.e., individual acceptance) is required for any surgical intervention unless there are circumstances that make it impractical or impossible, and affirmative research consent is required before a participant receives a research intervention – a requirement that is subject to even more restrictive constraints than apply to clinical consent. The challenge to IRB approval of DDIR arises from the particular context of this organ offer process, rather than from the requirement that an offer be accepted or declined.

Question 3. How practicable would it be for investigators to implement the two-step consent process proposed by the NAM? Specifically, is the second step of the proposed consent process feasible to implement given that it would occur at the time the organ is being offered to the transplant candidate?

Discussion:

The step one discussion of DDIR is practicable by any standard, because it can feasibly be added to existing general education about transplantation. This general education discussion, which begins when potential transplant recipients are in the process of committing to wait for an organ, already includes education about organs that, for various reasons, might be less desirable than standard organs (they might pose a risk of infecting the recipient, or might be expected not to last as long as a standard organ, or might not be as likely to be successfully transplanted). Potential recipients are educated generally about the reasons an organ might be designated as nonstandard and are told that they can choose not to receive some or all such offers but may change their decisions at any time. Similarly, general education about DDIR organs and about being a research subject in DDIR could easily be provided during the step one discussion, and that information could be revisited and updated during clinical visits while the potential recipient is waiting for an organ offer.

When any organ is offered, including any nonstandard organ, information about that specific organ

is provided in the step two organ offer discussion. This second step, which occurs at the time of organ offer, is severely time constrained and made under circumstances that could be construed as unduly influential, or even coercive, because the possibly life-saving clinical offer of an organ is contingent on agreement to participate in research.23 Further, this step is likely to be conducted over the telephone by a transplant coordinator who is not an investigator on the DDIR protocol, raising additional barriers to provision of sufficient "opportunity to discuss and consider" participation. For all these reasons, it would be difficult for this step alone to meet traditional ethical and regulatory requirements for information, comprehension and voluntariness, but consent regulations require that, absent regulatorily specified exceptional circumstances, potential participants be informed of the particulars of a specific research protocol at the time they must decide whether or not to participate. Thus, it is this problematic second step in the process described in the NAM report that must satisfy the regulatory requirements for consent. ~~**Practicability is therefore not an issue for investigators in implementing the two-step process described in the NAM report, but**~~ **It may be practicable for clinicians or investigators to have the conversation that constitutes the second step in the NAM process, but** the IRB ~~**faces**~~ **will face** real difficulty in determining that ~~**step two of the two-step process**~~ **this conversation,** while adequate for clinical consent, ~~**conforms with**~~ **fulfills the** ~~**usual interpretation of the**~~ regulatory **requirements for *research* informed consent as usually interpreted.**

Question 4. Would the two-step process, taken as a whole, satisfy the regulatory criteria for informed consent? If not, what would need to be included, and what circumstances would make regulatory **compliance challenging?**

Discussion:

Based upon the information provided to SACHRP, it is unlikely that the two-step consent process as a whole could meet the requirements for research informed consent, except in unusual circumstances when the first conversation takes place at a time when the research intervention is known and it is clear that a specific organ would be offered to a specific recipient. The step one process could include considerable information about what it means to be a research subject, how that differs from receiving treatment, and what accepting a DDIR organ means for recipients (including mandatory use of clinical data for research purposes, the possibility that recipients might be asked to consider agreeing to additional data-gathering interventions solely for research purposes, the DDIR currently underway, and a general description of the kinds of DDIR that could begin in the future and potentially be the source of offered organs). Nonetheless, as noted in Question 3, step two is fundamental to the DDIR informed consent process and presents challenges to the usual interpretation of the consent regulations.

Waiver or Alteration of Informed Consent when transplant candidates are considered human subjects for DDIR:

[23] Note that it is the circumstances, not the consent form or process, that are coercive/unduly influential.

Question 5. Should an IRB's consideration of waiver of informed consent in DDIR be affected by the circumstances specific to organ transplantation, including the factors listed in question #2?

Discussion:

In order for an IRB to grant a waiver or alteration of any or all of the elements of informed consent, the IRB must find the following:

(i) The research involves no more than minimal risk to the subjects; (ii) The research could not practicably be carried out without the requested waiver or alteration; (iii) If the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format; (iv) The waiver or alteration will not adversely affect the rights and welfare of the subjects; and (v) Whenever appropriate, the subjects or legally authorized representatives will be provided with additional pertinent information after participation.

The question asks whether the factors listed in question number 2 will affect the IRB's consideration of waiver or alteration of informed consent. Those factors are:

(i) the time period available to a transplant candidate to accept or reject an organ offer; (ii) whether a transplant candidate is likely to die without a transplant or alternative treatments exist (e.g., dialysis for patients with end stage renal disease); (iii) the likelihood that transplant candidates will receive other organ offers, including offers of organs not subject to the same interventions; and (iv) the fact that any organ offered for transplantation, whether subject to a research intervention or not, must be individually accepted by a transplant candidate?

If the research is minimal risk research, meaning that: "the probability and magnitude of physical or psychological harm anticipated in the **research** are not greater in and of themselves than those **ordinarily encountered in daily life**, or in routine medical, dental, or psychological examinations," then the factors noted above should not affect the decision to waive or alter research informed consent.

Question 6. How should an IRB determine whether waiver or alteration of informed consent will not adversely affect the rights and welfare of transplant recipients?

Discussion:

IRBs routinely approve waivers and alterations of informed consent and make determinations that a waiver will not adversely affect the rights and welfare of participants. As in all research, the answer is dependent upon the context. If the research is truly minimal risk research, then the IRB would be expected to use its usual criteria and processes to determine that the rights and welfare of transplant recipients are not adversely affected.

Question 7. If it is not practicable to get consent for a study that is not greater than minimal risk, is it permissible to waive consent under 45 CFR 46.116(e) or (f)?

Discussion:

If the research is minimal risk research, the IRB finds that it is not practicable to obtain consent, and the research meets the other criteria for waiver or alteration, then a waiver or alteration of consent would be appropriate**. In determining whether it is practicable to obtain consent, IRBs often base their decision on the availability of potential participants and the opportunity to have an interaction with a clinician or investigator. In the context of DDIR, there *must* be such an interaction to document clinical consent, and this necessary interaction might suggest that it *is* practicable to get consent and that a waiver is therefore inappropriate. HAlthought typically a circumstance in which there is an opportunity for interaction would not meet the impracticability component of the waiver provisions, DDIR presents unique circumstances in which consent *is not* practicable despite the opportunity for interaction, as argued in SACHRP's response to questions 3,4, and 8. This concern is the basis for the recommendation that a Secretarial waiver be required. If such a waiver is required for research that presents greater than minimal risk because obtaining adequate consent is generally not practicable, that same reasoning should justify the determination that it is not practicable to obtain consent when the research presents no greater than minimal risk. ~~There is nothing obviously different about DDIR that would affect application of the waiver criteria. The question assumes that it is not practicable to obtain consent, and issues of practicability are central to SACHRP's recommendation, below, that a Secretarial Waiver is required to conduct DDIR in situations where the research presents greater than minimal risk. Thus, IRBs are likely to find that consent as required in §116 is not practicable and that it is permissible to waive consent if the other criteria for waiver are satisfied.~~**

Department or Agency Waivers of Regulatory Requirements:

Question 8. Is a Secretarial waiver necessary or appropriate for any DDIR? If so, please describe the scope of such a waiver, including which regulatory requirements should be waived, and whether the waiver should include alternate procedures to be followed for the conduct of the research. Would such waiver be necessary or appropriate if informed consent were required for all DDIR (i.e., if an IRB determined that the current regulatory requirements would not allow informed consent to be waived or altered for such research)?

Discussion:

SACHRP believes that a Secretarial waiver is both necessary and appropriate for research on deceased donor organs where those organs will be transplanted into living individuals, because the step one consent conversation is not sufficient to meet the regulatory requirements for research informed consent and the step two consent conversation is likely to be time-constrained and raise other issues of understanding and voluntariness. In particular, it may not be possible to satisfy the regulatory criteria that: (1) key information and all basic elements be conveyed in a way that facilitates understanding (.116(a)5 and (b)), and (2) participants have sufficient opportunity to discuss and consider participation in the research in circumstances that minimize the possibility of

coercion or undue influence (.116(a)(2)).

The NAM Report described the two-step consent process from an ethically informed perspective, but without the regulatory perspective that SACHRP necessarily brings. From a regulatory perspective, only step two of the process constitutes a regulatory opportunity to consent (see Question 3). The first step is essentially general education about and a decision whether to receive an offer of a manipulated organ. The second step is consent to participate in a specific DDIR protocol as a research subject. In this context, SACHRP does not have concerns about the step one conversation, in which the recipient is introduced to the idea and implications of receiving an organ on which there has been a research intervention.

Since the particular research is not likely to be known at the time of the step one discussion, the step two discussion needs to satisfy all of the elements of consent. In other words, the discussion at the time of organ offer constitutes the research consent, from the perspective of the usual interpretation of the regulations. Accordingly, since the step two process alone is unlikely to be consistent with this usual interpretation, the Secretary could waive the requirement at 45 CFR 46.116(a)(2) that: "An investigator shall seek informed consent only under circumstances that provide the prospective subject or the legally authorized representative sufficient opportunity to discuss and consider whether or not to participate and that minimize the possibility of coercion or undue influence" and also the required elements of consent at 45 CFR 46.116(b). Provision of such a waiver would be conditioned on satisfying 45 CFR 46.116(a)(5)(i), the requirement for a concise and focused presentation of key information, which would be presented as part of the step two discussion, and on the preparation of a complete consent form, satisfying 45 CFR 46.116(b), which would be made available to the transplant recipient after the step two discussion but as soon as possible, and no later than upon arrival at the transplant center.

In the few cases where the details of specific research are known before the organ offer, and there is thus an opportunity to discuss these with potential participants, a Secretarial waiver of the same provisions described above could be conditioned on the same requirements for presenting key information during step two, but also on satisfying the 45 CFR 46.116(b) required elements of consent as part of the step one process.

Question 9. The NAM report recommended three independent but affiliated and cooperative structures. One is a single IRB, which could be a central IRB or an IRB of record, with enough scientific, ethical, and regulatory expertise to address organ donor intervention research. A second recommended central structure is the Donor Research Oversight Committee (D-ROC). A third recommended structure consists of one or more data and safety monitoring boards with the appropriate expertise to oversee the conduct of DDIR. Does SACHRP believe these structures would help improve the quality of the system of human research protection programs for DDIR?

Discussion:

SACHRP agrees that these three entities -- the single IRB, the D-ROC, and the DSMB(s) -- would help improve the quality of the system of human research protection programs for DDIR. In

particular, the D-ROC would be an appropriate group to assess the impact of DDIR on the availability of unmanipulated organs. It is also worth noting that, unless and until the number of DDIR studies increases greatly, a single standing DSMB might be well-positioned to assist in assessing the progress and effects of DDIR on transplantation overall.

SACHRP regards a single, central IRB with a national scope as an important source of standardization and consistency in DDIR, but notes that in order adequately to protect patient-subjects who are transplant recipients, the single IRB must be well-equipped for broad and comparative consideration of ethical and regulatory issues as well as transplantation science. (For instance, it will be important for the single IRB to distinguish between minimal risk as a regulatory criterion and a clinical determination that the risk posed by a particular DDIR protocol presents minimal incremental risk in the context of the risks posed by transplantation of standard organs.) The single IRB may also be best positioned to incorporate the perspectives of transplant recipients and experienced research subjects into its protocol reviews on an ongoing basis. Lastly, DDIR is likely to constitute only a small proportion of the reviews of conducted by an existing IRB. A single IRB will be necessary to ensure consistent interpretation of risk and benefit in this unique circumstance, and to promote a single understanding of the ethical requirements for such research in both the research and transplant recipient communities.

While SACHRP strongly supports the establishment of these entities, the committee also recognizes that developing a single, national IRB as well as the D-ROC and DSMB, will take time and resources. The committee also notes that most, if not all, DDIR protocols will require single IRB review under the Common Rule. Accordingly, until such time as these entities are established, all of the recommendations in this report should apply to the single reviewing IRB, regardless of its location. Importantly, all DDIR research should go through the national or other single IRB, regardless of whether or not it is deemed to be minimal risk. The decision not to require establishment of central oversight and management acknowledges the importance of this research, but should not be interpreted as lessening the need to establish these entities, which should be proceed as quickly as possible.

Question 10. Should these structures of IRB oversight also address research in which transplant recipients receive non-targeted organs (organs from donors that were subject to research interventions that were targeted only toward other organs in the same donor prior to procurement)?

Discussion:

Yes. SACHRP would very much welcome more information about non-targeted organs in order to improve our understanding of the issue of consent in this context, but in general non-targeted organs appear to raise essentially the same issues as targeted organs. Whether non-targeted organs are affected by research interventions on targeted organs seems highly context-specific, but in many cases, the only interventions on a research participant will be (1) the receipt of a manipulated organ; (2) additional sample and data collection. Given that the risks associated with (1) are the major risks of the protocol, and that recipients of non-targeted organs would be exposed to these same risks, it

would be consistent to consider them research participants except in circumstances in which the intervention is known not to affect the non-targeted organ.

C. Recommendations

(1) The three independent, affiliated, centralized, and cooperative structures recommended in the NAM report – the single IRB, the D-ROC, and either a standing DSMB or a study-specific DSMB for each protocol – should be created. A single national IRB to review all DDIR protocols will promote completeness, consistency, and regulatory compliance, and maximize attention to respect for persons, beneficence, and justice in DDIR under the unique constraints of organ transplantation.

Until such time as these entities are established, the following recommendations should be implemented by the single IRB for each DDIR protocol wherever possible. Some recommendations (e.g., the development of standardized educational information about DDIR and the creation of a website and hotline for protocol-specific information) may be implemented centrally by the appropriate entities. Finally, SACHRP trusts it is clear that, although these recommendations focus almost exclusively on the consent form and process in DDIR, any IRB reviewing a DDIR protocol must determine its compliance with all of the regulatory criteria for approval of research.

(2) Secretarial Waiver Required:

While SACHRP recognizes that, in practice, some IRBs approve individual protocols that recognize consent discussions conducted under extreme time constraints to be compliant with the regulations, SACHRP does NOT equate DDIR decision-making with that more general context. Instead, our goals are (1) to standardize decision-making policy and practice in an important developing research area that has the unique features we have described and (2) to do so in a manner that maximizes autonomy and reasoned decision-making for an identified cohort of potential patient-subjects. (It is our hope that some of our recommendations may be adaptable to the broader context of time-constrained decision-making in general, but that is not our goal here.)

SACHRP believes it will be difficult to find that DDIR presents no more than minimal risk to participating organ recipients but recognizes that this determination ~~will~~ should be made by the IRB on a study-by-study basis. Except in the rare case where the IRB determines that the research presents no greater than minimal risk and subsequently waives the requirement to obtain informed consent, the time constraints of the organ offer call require the following conditions to be deemed ~~In order to consider the highly time-constrained organ offer call~~ adequate in terms of both regulatory compliance and ethics:

(a) A Secretarial waiver of 45 CFR 46.116(a)(2) and (b) at the time of the organ offer consent process is necessary.

(b) **45 CFR 46.116(a)(5)(i) is NOT waived. Because of the time constraints, the development of a clear and robust key information summary that satisfies 45 CFR 46.116(a)(5)(i) is essential ~~and must be addressed as described in (6) below,~~**

(c) Most importantly, this key information summary must be used during the organ offer call. Conveying key information about the DDIR study is central to the consent process during that call. For each DDIR protocol, a telephone consent script based on the key information summary must be prepared for use at the time of organ offer. This oral version of the key information summary can convey a minimally acceptable amount of meaningful information that can fit the time constraints of the call. An opportunity to ask questions must also be included (and may be answered, at least in part, by using the key information summary and other parts of the complete consent form as a reference- see (D), below). The research consent process during the organ offer call should adhere to the model provided in 46.117(b)(2) for witnessed oral presentation of key information. Training in use of the consent scripts and provision of access to further resources to respond to potential recipients' questions must be mandatory and completed before any organ is offered from the relevant protocol.

(d) ~~**For each DDIR protocol, complete**~~ A **complete** ~~**consent**~~ **information form that fully satisfies 45 CFR 46.116 must be prepared by study PIs and approved by the single IRB for use by the transplant center during the organ offer call (step two of the two-part process described in the NAM report) and to provide to the recipient after arrival at the transplant center. Recipients should review and sign the** ~~**complete information consent**~~ **form to attest to its receipt and presentation at the first practical opportunity, but are *not* required to do so before surgery. The Secretarial Waiver** ~~**deseribed above**~~ **is required in recognition that the decision to accept an organ must be made at the time of the organ offer call.** ~~**Because of the time constraints on that call, the development of a clear and robust key information summary that satisfies 45 CFR 46.116(a)(5)(i) is essential.**~~

(e) **AND the following recommendations must be implemented and followed as conditions of the waiver.**

The recommendations that follow are both independent recommendations and requirements for use of the Secretarial waiver.

(3) In the initial education session and subsequent clinical interactions before receiving an organ offer (collectively step one of the two-part process described in the NAS report), potential transplant recipients are told about high risk or non-standard organs and about why it is reasonable to offer such organs. Potential recipients consider whether they would be willing to receive offers of such organs and are free to decide that they do not wish to be offered non-standard organs. While they wait for an organ offer, the health care team may seek to persuade them of the benefits of accepting a non-standard organ, and they may change their minds and agree to accept an offer of a non-standard organ at any time, but they may also decide to persist in waiting for a standard organ. Similarly, potential recipients should be told about DDIR organs, given standardized general education about DDIR, about how acceptance of a DDIR organ would make a recipient a research subject and what that would mean in this context, examples of some current trials, and a brief explanation of what will happen when offered such an organ. Potential transplant recipients should be afforded the opportunity to state that they do not wish to receive offers of DDIR organs; they

should be informed that they may change their minds at any time, and they should be offered the opportunity to do so at any time while awaiting an organ offer. The team may seek to persuade them of the benefits of considering an offer of a DDIR organ, but potential recipients remain free either to refuse to be offered a DDIR organ or to agree to consider such an offer.

(4) Standardized education about DDIR for potential transplant recipients should be approved by the single IRB that has been established to review DDIR at a national level.

(5) Standardized education about DDIR for transplant teams, especially for transplant surgeons, coordinators, and any other personnel likely to interact with recipients offered DDIR organs, should be approved by the single IRB and made mandatory for personnel at all transplant centers likely to be provided with a DDIR organ.

~~(6) For each DDIR protocol, complete consent forms that fully satisfy 45 CFR 46.116 must be prepared by study PIs and approved by the single IRB for use by the transplant center during the organ offer call (step two of the two-part process described in the NAM report) and to provide to the recipient after arrival at the transplant center. Recipients should review and sign the complete consent form to attest to its receipt and presentation, but are not required to do so before surgery. The Secretarial Waiver described above is required in recognition that the decision to accept an organ must be made at the time of the organ offer call. Because of the time constraints on that call, the development of a clear and robust key information summary that satisfies 45 CFR 46.116(a)(5)(i) is essential.~~

~~(7) Most importantly, this key information summary must be used during the organ offer call. Conveying key information about the DDIR study is central to the consent process during that call. For each DDIR protocol, a telephone consent script based on the key information summary must be prepared for use at the time of organ offer. This oral version of the key information summary can convey a minimally acceptable amount of meaningful information that can fit the time constraints of the call. An opportunity to ask questions must also be included (and may be answered, at least in part, by using the key information summary and other parts of the complete consent form as a reference). The research consent process during the organ offer call should adhere to the model provided in 46.117(b)(2) for witnessed oral presentation of key information. Training in use of the consent scripts and provision of access to further resources to respond to potential recipients' questions must be mandatory and completed before any organ is offered from the relevant protocol.~~

(6) The following additional resources must be developed and periodically updated so that potential recipients who choose to do so can stay apprised of current DDIR protocols and so that any potential recipient may ask questions of personnel knowledgeable about particular DDIR protocols:

- A website, designed with the principles of accessibility and health literacy, that provides a synopsis of approved and active DDIR protocols
- A telephone hotline, accessible at all hours, that can answer potential participant questions about particular protocols in the context of an organ offer. Such a resource could help to ameliorate the problem that the transplant team offering a DDIR organ might know only the broadest details of the particular protocol applicable to that organ, and thus might not be able to answer specific questions.

(7) Additional protections similar to those offered by the emergency exception to informed consent – for instance, consultation with the community of potential transplant recipients about particular DDIR protocols before they are implemented – may be considered and encouraged or required by the single IRB, as may other means of sharing experiences in effectively implementing the requirements of the Secretarial waiver.

Justification for Secretarial Waiver

SACHRP believes that the above recommendations are consistent with the principles of the Belmont Report.

Respect for Persons and Beneficence:

SACHRP is confident that an ethically appropriate balance of respecting and supporting autonomous decision-making and maximizing the potential for transplant recipients to benefit from what is learned through DDIR is achieved by:

a) the oral provision of key information during the organ offer call to potential transplant recipients about the particular DDIR protocol that has manipulated the organ being offered, which is

b) preceded by required information about DDIR in general and the implications of receiving a DDIR organ and being a DDIR subject, by the opportunity to opt out of DDIR organ offers, and by periodic opportunities to learn about ongoing DDIR studies, and which is

c) followed by provision of a consent form that fulfills all the requirements of 45 CFR 46.116.

Although in most instances there will be insufficient time during the organ offer call to consider and discuss all of the elements of consent enumerated in 45 CFR 46.116(b), there will be enough time to briefly consider and discuss key information as provided in 45 CFR 46.116(a)(5), thereby providing potential transplant recipients with a minimally sufficient opportunity to decide whether to accept a DDIR organ, and thus enroll in the relevant research, without jeopardizing that recipient's potential

to benefit from receipt of the offered organ and still preserving the organ's availability to benefit another potential recipient should the first offer be refused. SACHRP's conditions for the Secretarial waiver are therefore consistent with respect for persons and beneficence.

Justice:

SACHRP heard presentations from the transplant community suggesting that the decentralized management and oversight of the organ transplant process is a barrier to successful and equitable implementation of DDIR. In particular, transplant centers and organ procurement organizations may have concerns that DDIR could pose unacceptable ethical, reputational, and compliance risks, with the result that many are currently reluctant to participate in such research.

The unwillingness of the community to broadly embrace DDIR has several consequences. First, it makes this research more difficult to do, delaying much needed innovation that could expand the pool of useable organs. Second, trials that are conducted may be less generalizable, given the systematically limited pool of participants. Finally, selective participation raises concerns about justice. Should DDIR validate an intervention that improves organ viability or increases the pool of useable organs, all individuals needing organ transplant will benefit, but the burden of the research would be borne by recipients at the relatively small number of sites that take the institutional risk to conduct such research.

It is SACHRP's hope that our recommendations will help allay some of the concerns about the ethics and compliance aspects of this research. As with all research, each protocol must be reviewed for ethics and participant protections, but the Committee believes that there is nothing inherently unethical about DDIR as a whole. In addition, central oversight and management of the organ transplant enterprise would ensure fair distribution of research burdens and generalizable results and would help assuage concerns about individual institutional exposure24.

For these reasons, satisfying the conditions of the Secretarial waiver as set forth in our recommendations constitute alternative procedures that are consistent with the principles of the Belmont Report.

D. Additional Considerations

FDA-Regulated DDIR:

SACHRP has also considered that a Secretarial waiver will only apply to HHS-funded research and not to FDA-regulated DDIR, although many, if not most, DDIR protocols will seek to develop

[24] SACHRP considered requiring the establishment of a single, national IRB for DDIR as a condition of the waiver, and the committee still feels that such an approach is the best way to ensure participant protections and justice. The committee chose not to require such an IRB as a necessary condition in recognition of practical issues in its implementation, but this decision is not meant to communicate that this recommendation of the NAM report is optional or not of critical importance.

FDA-approved interventions to extend or improve the viability of transplantable organs. Unlike the Common Rule, the FDA regulations do not allow for a Secretarial waiver of any of their provisions, instead providing two existing exceptions to the requirements for informed consent: 21 CFR 50.23 provides for research consent when an individual is unable to give consent, time is not sufficient to obtain consent from their legally authorized representative, and participation in research offers the best clinical choice in a life-threatening situation; 21 CFR 50.24 provides for planned emergency research in a population of interest. In this latter circumstance, the ability to obtain voluntary informed consent is constrained by the situation but that constraint is anticipated as part of the research design.

SACHRP does not believe that DDIR fits the intent of 21 CFR 50.24, because the potential subjects of DDIR do not lack decision-making capacity and do not meet the specified criteria in 21 CFR 50.24(a)(1), and completely forgoing all individual consent discussion is neither contemplated nor justifiable in DDIR. The FDA crafted specific exceptions to the general informed consent requirements because the Agency believed that those general requirements were not satisfied in the two situations described at 21 CFR 50.23 and 50.24, and SACHRP has recommended that a Secretarial Waiver is necessary to satisfy those same general provisions. Accordingly, it is likely that the FDA will find that rulemaking is necessary to conduct DDIR in a manner that is compliant with its regulations. In order to avoid further delays and barriers to the conduct of this important research, SACHRP recommends that the FDA signal its use of enforcement discretion in this area pending final rulemaking, as it did during the rulemaking to allow waivers of informed consent.

Conclusion

SACHRP commends the transplant community for its diligence and conscientiousness in ensuring that transplant recipients are adequately protected when receiving an organ on which a research intervention has been conducted, and for the significant progress that has been made in setting the stage for implementing the NAM recommendations and our follow-up recommendations contained herein. DDIR raises important issues at the complicated intersection of clinical and research consent, and addressing these issues productively could significantly improve the organ transplantation landscape. We also believe that this effort could serve as a model or starting point for considering other research contexts that present challenges in learning healthcare systems and similar settings.

SACHRP is ready to assist HRSA and the transplant community in further developing and implementing our recommendations to satisfy regulatory requirements and to protect the rights and welfare of transplant recipients considering offers of DDIR organs.

Attachment C(1). Interpretation of *Public Health Authority* and *Public Health Surveillance Activities*, 46.102(k), 46.102(l)(2): Showing Revisions

Introduction

OHRP is frequently asked to respond to questions from the research community regarding the interpretation and application of 45 CFR 46.102(k) and (l)(2). While OHRP and other HHS agencies have already considered these questions, OHRP asks SACHRP to independently deliberate the questions below and come to its own objective recommendations. OHRP would be interested in SACHRP's views even if additional rulemaking were necessary to clarify or modify aspects of the regulations.

The regulatory text is as follows:

> 45 CFR 46.102(k)
>
> Public health authority means an agency or authority of the United States, a state, a territory, a political subdivision of a state or territory, an Indian tribe, or a foreign government, or a person or entity acting under a grant of authority from or contract with such public agency, including the employees or agents of such public agency or its contractors or persons or entities to whom it has granted authority, that is responsible for public health matters as part of its official mandate.
>
> 45 CFR 46.102(l)(2)
>
> Public health surveillance activities, including the collection and testing of information or biospecimens, conducted, supported, requested, ordered, required, or authorized by a public health authority. Such activities are limited to those necessary to allow a public health authority to identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance (including trends, signals, risk factors, patterns in diseases, or increases in injuries from using consumer products). Such activities include those associated with providing timely situational awareness and priority setting during the course of an event or crisis that threatens public health (including natural or man-made disasters).

In the pre-2018 version of the Common Rule, there were a number of categories of exempt research, which were presented at 45 CFR 46.101(b)(1) through (b)(6). Of note, these are human subjects research, but research that is exempt from the requirements of the Common Rule. In the revised Common Rule, known as the 2018 Requirements, those exemptions were modified extensively and were moved to 45 CFR 46.104. In addition, the definition of research was modified at 45 CFR 46.102(l) to include four activities which "are deemed not to be research." These four activities are commonly referred to as "exclusions," although that term was not carried over from the NPRM and the Federal Register announcement (Vol. 82, No. 12 /Thursday, January 19, 2017, page 7149) into the 2018 Requirements. There is some conceptual uncertainty as to whether the

four exclusions are not research or alternatively are research that does not require compliance with the 2018 Requirements, similar to the exemptions at 45 CFR 46.104, but in the end that distinction does not have practical implications and does not need to be resolved in order to apply the exclusions.

~~SACHRP Opening Comments~~

~~The Common Rule serves two distinct purposes. First, it articulates application of broad ethical principles and sets expectations about how we should treat one another. This purpose is what we usually debate, e.g., how to balance the needs of society and the individual where the regulations are not directive. But it is also a practical tool to further social utility. It provides an expectation of what the research enterprise must do to maintain public trust to further the social goal of scientific progress. The purposes of the FDA regulations are different: their social utility is not broad scientific progress, but sustaining trust to allow the collection of data to ensure that medical practices are safe and effective.~~
~~Seen from this perspective, the exclusion to the Common Rule for Public Health Surveillance Activities (PHSAs) is more than a simple technical exclusion. Instead, it is a recognition that the goal of PHSAs is not to support scientific progress, but rather to support the more immediate goal of maintaining public health. Indirectly, scientific progress may ultimately support public health, but only in a general way the details of which cannot be predicted. In the same way that a particular activity can be either research or quality improvement depending on its purpose, a particular activity can be either research or a public health surveillance activity.~~
~~Confusion with the wording of the regulations arises because we are committed to scientific progress as a way to improve population health. Thus, descriptions of public health surveillance activities as "activities… to allow a public health authority to identify, monitor, assess or investigate… conditions of public health importance" could be broadly applied to almost any clinical research conducted by the National Institutes of Health. However, to do so confuses direct support of maintaining public health with our aspirational expectations for scientific progress.~~

~~Therefore, SACHRP believes~~

Introduction

In this recommendation, SACHRP first answers OHRP's questions 1 through 8, then provides brief commentary on the draft OHRP guidance "SACHRP Commentary on OHRP draft guidance "Activities Deemed Not to Be Research: Public Health Surveillance 2018 Requirements," and third provides an algorithm to apply the exclusion.

SACHRP Opening Comments

~~Finally, SACHRP notes that if a proposed activity does not meet the exclusion provided by 45 CFR 46.102(l)(2), and it meets the definition of research, then the practical effect is that IRB review will be required unless the activity meets one of the exemptions under 45 CFR 46.104. In many cases, if the activity is research, it will be minimal risk (if it has appropriate~~

~~**protections for confidentiality) and may also qualify for a waiver of consent under 45 CFR 46.116(f).**~~

SACHRP also notes that just because an agency is designated as a public health agency, that does not mean that every activity conducted by the agency is a public health activity, or a public health surveillance activity, or that every department in the agency is conducting public health activities. For instance, NIH performs some public health activities, but much of the work NIH does is not a public health activity.

Third, SACHRP wants to clarify that "grant of authority" as used in 45 CFR 46.102(k) is not synonymous with the term "grant," as used to indicate a decision by an agency such as NIH to support a study. This is clear in the OHRP draft guidance, "Activities Deemed Not to Be Research: Public Health Surveillance 2018 Requirements," which says,

> **Public health surveillance activities that are *supported* by a public health authority (*e.g., through a grant or cooperative agreement*), or that are requested, ordered, required, or authorized by a public health authority, also may be eligible for consideration under this provision, even if they are carried out by an entity that is not a public health authority (e.g., academic institutions, health care organizations, nonprofit entities). (emphasis added)**

Therefore, for the purposes of this recommendation the term "grant of authority" references to the definition of "public health authority" in 45 CFR 46.102(k). In contrast, the term "grant" references the situation where a public agency (e.g., NIH) is providing support to a public health authority, and thus references the term "supported" as used in the public health surveillance exclusion at 45 CFR 46.102(l)(2), which says,

> **Public health surveillance activities, including the collection and testing of information or biospecimens, conducted, *supported*, requested, ordered, required, or authorized by a public health authority. (emphasis added)**

CDC uses a type of financial assistance mechanism similar to a grant, called a cooperative agreement, that is a type of federal support. When distinguishing a grant of authority from the federal funding mechanisms, a cooperative agreement references "support" as well.

SACHRP Responses

OHRP Question 1. What entities should be considered to meet the Common Rule definition of a 'public health authority'? Note that this definition is largely the same as the HIPAA definition, so please consider past applications of this definition in the HIPAA context as well.

(a) If a Federal agency that is a public health authority engages in a partnership with a private institution to conduct public health surveillance activities, should (or might) the institution be considered to be a 'public health authority' in this context? Please consider providing an explanation as to why or why not the institution should (or might) be considered to be a "public

health authority."

The HIPAA definition is below for convenience.

> 45 CFR 164.501
>
> Public health authority means an agency or authority of the United States, a State, a territory, a political subdivision of a State or territory, or an Indian tribe, or a person or entity acting under a grant of authority from or contract with such public agency, including the employees or agents of such public agency or its contractors or persons or entities to whom it has granted authority, that is responsible for public health matters as part of its official mandate.

SACHRP answer to Question 1

SACHRP supports the harmonization of definitions across HHS, FDA and OCR, as evidenced by the creation of the standing SACHRP Subcommittee on Harmonization. Therefore, SACHRP encourages reliance on past applications of this definition of a "public health authority" in the HIPAA context.

The Committee does note one significant difference between the definitions; the Common Rule definition includes an agency or authority of "a foreign government" as well as US agencies and authorities, whereas the HIPAA definition is limited to US agencies and authorities. SACHRP believes that the extension of this exclusion to a foreign government should be interpreted as narrowly as possible, with the only use being the use of US federal funds to conduct public health surveillance activities in the foreign government's country only. It should not be used to allow a foreign government to conduct public health surveillance activities in the United States or in a country other than that of the foreign government.

The definition appears to be quite broad. A plain reading of the regulation indicates that a person or entity acting under a grant of authority from, or contract with, such public agency is also a public health authority. Therefore, institutions or private companies could meet the definition.

SACHRP answer to Question 1(a)

If a Federal agency that is a public health authority engages in a partnership with a private institution to conduct public health surveillance activities, the private institution should not be considered to be a 'public health authority' solely based on the partnership. The plain reading of the definition is that a public health authority must be an agency or authority of the US or a foreign government. A private institution does not meet that definition per se. However, if the partnership involves a "grant of authority from or contract with such public agency," then the private institution is a public health authority by the definition.

SACHRP recommends that the grant of authority be interpreted narrowly when a private institution is designated to become a public health authority. The grant of authority or contract should be clearly limited to a defined public health surveillance activity. It should not be allowed to extend to

other projects or other activities and still be considered to fall under the exclusion. Furthermore, as noted in the preamble to the 2018 Requirements, "subsequent research using information collected during a public health surveillance activity, for instance, genetic analysis of biospecimens, would not be removed from the definition" of research. (FR Vol. 82, No. 12, Thursday, January 19, 2017, p. 7176.)

Also, SACHRP notes that the preamble describes certain research activities that do not fall under the exclusion. As noted in the preamble:

> "This clarification of current interpretation would not remove the following activities from the definition of "research": exploratory studies designed to better understand risk factors for chronic diseases, including genetic predisposition, for chronic diseases; exploratory studies designed to elucidate the relationships between biomarkers of exposure and biomarkers of disease; and exploratory studies of potential relationships between behavioral factors (e.g., diet) and indicators of environmental exposures. These types of activities would be considered research because they would not be conducted solely for the purposes described in §__.102(l)(2), and thus would be covered by the Common Rule if they involved human subjects, even if conducted by a federal agency with a public health mandate. Again, they might fall within an exemption, depending on how they are carried out." (FR Vol. 82, No. 12, Thursday, January 19, 2017, p. 7176)

Finally, SACHRP recommends the grant of authority should be clearly documented in a legal document, which can take several forms, such as an MOU, contract, purchase order or letter. It should clearly cite to a federal or state law or regulation. Both the Office of Civil Rights (OCR) and the Centers for Disease Control (CDC) has given examples of such grants.

In the preamble to the Privacy Rule, OCR said:

> In some circumstances, a person or entity acting on behalf of a government agency may make a request for disclosure of protected health information under these subsections. For example, public health agencies may contract with a nonprofit agency to collect and analyze certain data. In such cases, the covered entity is required to verify the requestor's identity and authority through examination of reasonable documentation that the requestor is acting on behalf of the government agency. Reasonable evidence includes a written request provided on agency letterhead that describes the legal authority for requesting the release and states that the person or entity is acting under the agency's authority, or other documentation, including a contract, a memorandum of understanding, or purchase order that confirms that the requestor is acting on behalf of the government agency. 65 FR 82462, 82547 (Dec. 28, 2000).

CDC has also addressed this issue in its guidance entitled "HIPAA Privacy Rule and Public Health: CDC Guidance (April 11, 2003)," which says:

> Public health agencies often conduct their authorized public health activities with other entities by using different mechanisms (e.g., contracts and memoranda or letters of agreement). These other entities are public health authorities under the Privacy Rule with

respect to the activities they conduct under a grant of authority from such a public health agency. A covered entity may disclose PHI to public health authorities and to these designated entities pursuant to the public health provisions of the Privacy Rule. https://www.cdc.gov/mmwr/preview/mmwrhtml/m2e411a1.htm.

For transparency, the grant of authority should be publicly available and easy for the public to locate, as public health surveillance activities involve issues of privacy.

OHRP Question 2. How should the exclusion operate when the public health surveillance activities will be wholly carried out by an entity outside of the Federal, State, or local government? Consider whether there is a distinction if the activities are carried out by a contractor (in which activities are directed by the awarding governmental agency through the terms of the contract, and will provide data back to the awarding agency) versus a grantee (in which activities are proposed by the grantee and are not directed by the awarding governmental agency, and which may or may not result in data being provided back to the awarding agency) versus through a public-private partnership that does not involve an award of funds. Please specifically consider the following language of the exclusion in these contexts: "The activity must be limited to that necessary to allow a public health authority to identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance…" (emphasis added).

SACHRP answer to Question 2

~~**This answer is based on the assumption that a "grant of authority" and a "grant" are synonymous.**~~

First, we note that a plain reading of the regulation is that the definition of a public health authority includes "a person or entity acting under a grant of authority from or contract with such public agency." Therefore, it appears that a person or private entity becomes a public health authority when such a grant of authority or contract is in place. ~~**Therefore, one might argue that**~~ **Thus,** a government agency or authority can designate a person or private entity to perform all of the functions of the agency or authority, even if that person or private entity does not provide the information back to the agency, because the person or private entity becomes a public health authority. ~~**However, SACHRP recommends that this provision be interpreted narrowly, and that sufficient data should be provided back to the public health agency or authority so that the agency or authority itself can "**~~

Question 2 also asks whether there should be distinctions when the public health surveillance activities are wholly carried out by an entity outside of the Federal, State, or local government, in particular a contractor versus a grantee versus a public-private partnership that does not involve an award of funds. There are distinctions between contractors and grantees that receive support, in that contractors are obligated to fulfill the terms of the contract, which in the case of public health surveillance activities could include a wide variety of responsibilities and requirements. Recipients of grants (support) for public health surveillance activities are not required to satisfy contractual terms, but are required to meet

the regulatory conditions for receiving the grant, and thus generally involve more latitude. It is difficult to make an assessment of public-private partnerships in a similar fashion, as such partnerships can vary greatly in structure and details. Many will include a contract between the public and private participants, but that is not a legal requirement. OHPR also asks that SACHRP consider these legal mechanisms in light of the regulatory requirement that the activity "must be limited to that necessary to allow a public health authority to identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance…" Clearly, the Federal, State, or local government has more ability to ensure the activity is limited to that necessary when a contract is in place, as requirements can be included as terms of the contract.

OHRP also asks "how *should* the exclusion operate?" (emphasis added.) SACHRP believes that to the extent possible, mechanisms should be in place to help ensure that the activity is limited to that necessary to identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance~~…" Such sufficient data may include raw data, or it may include reports or summaries.~~ . **However, these mechanisms will vary depending on the legal nature of the relationship.**

~~**Question 2 also asks whether there should be distinctions when activities are carried out by a contractor versus a grantee versus a public-private partnership that does not involve an award of funds. SACHRP recommends that this provision be interpreted narrowly, and we do not believe there should be distinctions between these arrangements, and that under each of these arrangements sufficient data should be provided back to public health agency or authority to allow the public health agency or authority to "identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance…"**~~

OHRP Question 3. What types of activities should be considered to be "public health surveillance activities" for purposes of this exclusion? Note that this term is used in the Common Rule but is not defined in the Common Rule. Please consider developing a rubric for analyzing planned activities, including specific rationale as to why certain types of activities should or should not be considered to be "public health surveillance." For example, should the purpose of the surveillance activity be solely to inform the decisions or actions that must be made by a public health authority, or to apply study findings to public health practice? Should activities that do not meet this exclusion include disseminating findings to stimulate public health action by others, but not informing the public health authority of actions that it would take to improve public health?

(a) Please also consider developing illustrative case studies that describe the creation of a repository as the primary study, as well as a repository embedded within a trial. For example, consider whether establishment of a repository containing individually identifiable private information or individually identifiable biospecimens could fall within this exclusion, and what other facts would need to be known in order to address this question. For example, is it relevant if the planned uses of the repository information:

- Are unknown?
- Would only constitute non-exempt human subjects research?
- Would only constitute public surveillance activities (PSA) that would also meet the conditions of the exclusion?
- Would require an additional assessment to determine whether they met all the conditions of the exclusion?

SACHRP answer to Question 3

Both the exclusion itself and the preamble include activities that should be considered "public health surveillance activities." The exclusion says that such activities are:

- Those necessary to allow a public health authority to identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance (including trends, signals, risk factors, patterns in diseases, or increases in injuries from using consumer products); and
- Those associated with providing timely situational awareness and priority setting during the course of an event or crisis that threatens public health (including natural or man-made disasters).

The preamble says that such activities include:

- Collecting, analyzing, and using data to target public health and disease prevention;
- Surveillance uses data from a variety of sources, including mandatory reporting of certain conditions, routine monitoring, vital records, medical billing records, and public health investigations.
- Safety and injury surveillance activities designed to enable a public health authority to identify, monitor, assess, and investigate potential safety signals for a specific product or class of products (for example, the surveillance activities of the FDA's Adverse Event Reporting System (FAERS), the Vaccine Adverse Event Reporting System (VAERS), Manufacturer and User Facility Device Experience database, the Medical Product Safety Network, and the Sentinel Initiative);
- Surveillance activities designed to enable a public health authority to identify unexpected changes in the incidence or prevalence of a certain disease in a defined geographic region where specific public health concerns have been raised (*e.g.,* the U.S. influenza surveillance system…;
- Surveillance activities designed to enable a public health authority to identify the prevalence of known risk factors associated with a health problem in the context of a domestic or international public health emergency;
- Surveillance activities designed to enable a public health authority to identify the prevalence of known risk factors associated with a health problem in the context of a domestic or international public health emergency; and,
- Surveillance activities designed to enable a public health authority to detect the onset of disease outbreaks or provide timely situational awareness during the course of an event or crisis that threatens the public health, such as a natural or man-made disaster, and Surveillance activities designed to enable a public health authority to identify the prevalence of a condition of public health importance, known risk factors associated with a condition of public health

importance, or behaviors or medical practices related to prevalence of a known condition of public health importance (*e.g.,* surveillance of the prevalence of: tobacco use, exposure to secondhand smoke, lung cancer, or use of smoking cessation treatments).

~~**SACHRP does not have any suggested additions to this list. [if we do, add here]**~~

SACHRP suggests the following additions to this list. Public Health Surveillance activities may be categorized as either passive or active. Passive surveillance systems involve the routine submission of data into data repositories that are used for ongoing analysis and assessment of public health issues. These systems rely upon awareness of the existence of these systems, and the initiative of individuals to file appropriate reports. Examples include FAERS and VAERS (maintained by the FDA), which are used to monitor the safety of licensed drugs and vaccines, respectively. Another example is the notifiable disease reporting system, which is used to track trends in the number of cases of certain infectious diseases (maintained by the CDC). Passive surveillance systems are typically conducted indefinitely. In contrast, active surveillance systems are typically fit for purpose activities that involve the active solicitation of reports by those conducting the surveillance activities. These are generally more labor-intensive, shorter in duration, and may be used for a range of activities, from disease detection to assessing the impact of public health policy. Examples include the Active Bacterial Core System (CDC), used to characterize vaccine effectiveness, the Gonococcal Isolate Surveillance Project (CDC), used to monitor trends in antimicrobial susceptibility of Neisseria gonorrhea isolates and inform treatment recommendations, and the National Immunization Survey, used to characterize the susceptibility of the population to vaccine-preventable diseases, and to inform policy.

The preamble also provides a list of research activities that do *not* fall under the exclusion, because they would not be conducted solely for the purposes described in §.102(l)(2). These are:

- exploratory studies designed to better understand risk factors for chronic diseases, including genetic predisposition, for chronic diseases;
- exploratory studies designed to elucidate the relationships between biomarkers of exposure and biomarkers of disease; and
- exploratory studies of potential relationships between behavioral factors (*e.g.,* diet) and indicators of environmental exposures.

SACHRP does not have any suggested additions to this list.

OHRP question 3 also asks,

> **For example, should the purpose of the surveillance activity be solely to inform the decisions or actions that must be made by a public health authority, or to apply study findings to public health practice? Should activities that do not meet this exclusion include disseminating findings to stimulate public health action by others, but not informing the public health authority of actions that it would take to improve public**

health?

SACHRP recommends that the definition of public health surveillance activity be narrowly interpreted, and therefore should not include study findings to public health practice or disseminating findings to stimulate public health action by others (for instance, to wear masks during the COVID-19 pandemic. While these practices should not be considered public health surveillance activities, they may or may not meet the definition of research. That is a separate analysis.

SACHRP answer to Question 3(a)

Question 3(a) asks whether establishment of a repository containing individually identifiable private information or individually identifiable biospecimens could fall within this exclusion, and asks SACHRP to consider two scenarios, the creation of a repository as the primary study, as well as the creation of a repository embedded within a trial.

Regarding the creation of a repository as the primary study, SACHPR believes that it if the use of the data or samples from the repository is clearly going to be for a public health surveillance activity or activities, then that use of the repository would qualify for the exclusion.

Question 3a asks whether it is relevant if the planned uses of the repository information:

- Are unknown?
- Would only constitute non-exempt human subjects research?
- Would only constitute public surveillance activities that would also meet the conditions of the exclusion?
- Would require an additional assessment to determine whether they met all the conditions of the exclusion?

SACHRP believes that the exclusion should be applied narrowly, and that in order to this exclusion to apply to the creation of a repository, there would have to be adequate description of the project to allow an application of the public health surveillance activities. If the uses were unknown, or would constitute non-exempt research, then the exclusion should not apply. If the planned uses only constitute public health surveillance activities, the exclusion should apply. As noted previously, any secondary uses of the data or samples would need to be analyzed to determine whether they meet the definition of a public health surveillance activity.

Regarding the creation of a repository embedded within a trial, and whether it might qualify for the exclusion, SACHRP notes that OHRP addressed this issue in the OHRP draft guidance "Activities Deemed Not to Be Research: Public Health Surveillance 2018 Requirements." The draft guidance says "If an activity is composed of multiple components, some of which are not public health surveillance, OHRP's view is that only those components that serve to enable a public health authority to carry out one or more public health surveillance objectives should be considered potentially eligible for the public health surveillance activity exclusion under 45 CFR 46.102(l)(2)."

SACHRP agrees with this position, which effectively allows public health surveillance activities that are part of a project that also has research activities to be carved out from application of the Common Rule. Therefore, if a repository is embedded in a clinical trial, and the use of the data or samples from the repository is clearly going to be public health surveillance activities, then those uses of the repository qualify for the exclusion. SACHRP also notes that this is a distinct approach from the traditional approach to the issue of exempt activities that are embedded within a trial, which has been that if any part of a project qualifies as research, then the exempt parts must also receive IRB review. SACHRP recommends that this distinction is clearly highlighted in any guidance on this issue.

OHRP Question 4. The regulatory language of the exclusion provides that "[t]he activity must be conducted, supported, requested, ordered, required, or authorized by a public health authority." What do each of these actions entail, and how do they differ? Please consider developing suggested examples illustrating each of these scenarios.

SACHRP answer to Question 4

- "Conducted" means the activity is performed by the public health authority.
- "Supported" means that the public health authority provides funding or other resources, but a different entity is involved in conducting the activity.
- "Requested" means that the public health authority has asked a different entity to conduct the activity, but the entity can decline to do so without consequence
- "Ordered" means that the public health authority has the legal authority to require the entity to conduct the activity.
- "Required" is ~~**synonymous with "ordered."**~~ **substantively similar to "ordered," but might take a different form. For instance, the requirement might be included in the charter of an organization.**
- "Authorized by" means that that public health authority has given permission for the entity to conduct the activity.

SACHRP notes that "supported" and "requested" could potentially allow for more flexibility than the other terms. We believe that these terms should be interpreted narrowly.

OHRP Question 5. While this exclusion clearly may apply in the context of a public health emergency, it is not limited to the emergency context. What are the pros and cons involved in broad application of this exclusion? Please consider outlining such considerations from the perspective of a government agency acting as a public health authority, a non-governmental institution conducting a public health surveillance activity, and the individuals whose data and biospecimens will be used in the public health surveillance activity.

SACHRP answer to Question 5

A ~~**pro**~~ **positive** of allowing a broad application or interpretation of this exclusion is that it provides

Public Health Authorities, both public and private, with more flexibility in the conduct of public health surveillance activities, and can reduce administrative burden and the need to consider whether informed consent **meeting human subject protection regulations is** necessary. ~~The con~~ **A negative** is that a broad application may harm public trust if it is applied to activities for which IRB review and **informed** consent **meeting human subject protection regulations** would otherwise be required. The use of the exclusion should be transparent and used with a narrow application outside of a public health emergency. During a public health emergency, a broader application may be appropriate in order to allow Public Health Authorities to take appropriate and timely action to accomplish public health surveillance activities that are pressing and of wide concern.

OHRP Question 6. What entity or involved individual may or should decide whether a planned activity meets the requirements of this exclusion? Are there any recommended considerations involved with this decision, and do they differ depending on what entity or individual might be making this decision?

SACHRP answer to Question 6

SACHRP recommends that ~~**someone other than the principal investigator determine**~~ **determinations** that ~~**the requirements for**~~ **an activity meet**s the exclusion ~~**are metas**~~ **a** public health surveillance ~~**activities often involve many institutions and may involve gathering information outside of institutional settings, so this may not be a practical approach. It will be more practical for an agency official to make the decision. However, such decisions should**~~ **activity** be clearly documented and readily available to the public to ensure transparency~~**and they should be narrowly applied. Also, transparency will be increased by providing**~~**Providing** the criteria or rationale for the ~~**decision**~~ **determination,** rather than just the final ~~**decision**~~ d**etermination** itself ~~**SACHRP**~~, **will** also ~~**recommends tha**~~ **aid transparency. Public health surveillance activities often involve many institutions and may involve gathering information outside of institutional settings, and in such cases it will likely be most practical for the agency to make the determination. When this occurs, involved** institutions **should h**ave a mechanism to review the decision and confirm agreement with the decision**, particularly if some activities in a project may not meet the exclusion. In cases where the activity is limited to one or more institutions, it may be appropriate to have an institutional mechanism for making the determination, similar to exempt determinations. This could entities such as an IRB administrator, a research office, or an institutional official. In any case, the determination should not be made by the party or parties who are offered the grant or contract to do the public health surveillance activities.**

OHRP Question 7. Should documentation be recommended or required regarding each of the decision points involved with this exclusion? If so, please consider providing specific suggestions as to documentation and how entities or individuals should accomplish this.

SACHRP answer to Question 7

Yes. SACHRP believes that documentation of the decision that an activity is a public health

surveillance activity should be documented with specific reference to how it meets 45 CFR 46.102(l). This documentation should be publicly available, and easily accessible.

OHRP Question 8. This exclusion will not apply to activities dually regulated by FDA and OHRP. Are there any useful recommendations for involved institutions and individuals in such circumstances? (If not, feel free not to further consider this point.)

SACHRP answer to Question 8

SACHRP does not agree that it is universally true that "this exclusion will not apply to activities dually regulated by FDA and OHRP." For instance, if a public health authority used HHS funding to conduct or support a surveillance program that involved return of COVID-19 test results to subjects, it seems that the project would meet the exclusion at 45 CFR 46.102(l)(2) and simultaneously require FDA review under 21 CFR 812 as an investigational diagnostic device.

FDA does conduct some public health surveillance activities such as the Sentinel project, and ~~as~~ **the FAERS and VEARS reporting systems. As** an HHS agency, FDA can utilize the exclusion for the public health surveillance activities that FDA itself conducts or supports. However, the FDA drug, **biologic** and device regulations do not include this exclusion at this time, and any clinical investigation of FDA regulated medical products must follow those regulations, even if there are aspects of public health surveillance activities included in the project.

We note that CLIA is also not subject to the exclusion, and CLIA must be separately followed when it is applicable.

SACHRP Commentary on OHRP draft guidance "Activities Deemed Not to Be Research: Public Health Surveillance 2018 Requirements"

SACHRP has reviewed the OHRP draft guidance, and in general agrees with the draft guidance as written. SACHRP believes that several of the points bear repeating in this recommendation.

The draft guidance notes, "This explicit exclusion of public health surveillance activities from the definition of research does not mean that other public health activities that do not constitute public health surveillance activities, as described in 45 CFR 46.102(l)(2), are necessarily research subject to 45 CFR part 46."

Also, the draft guidance states, "Research activities that do not constitute public health surveillance, such as a secondary research analysis of data for some other scientific purpose using information collected as part of a public health surveillance activity, can be carried out in tandem with a public health surveillance activity. In such a circumstance, the non-public health surveillance activity (in the example above, the secondary research analysis) should be reviewed to determine whether the 2018 requirements apply."

Algorithm:

SACHRP has developed the following algorithm to help with the analysis of projects.

Is the project conducted, supported, requested, ordered, required, or authorized by a public health authority?

- If yes, proceed to question xxx
- If no, it does not meet the exclusion

Does the project involve public health surveillance activities, including the collection and testing of information or biospecimens?

- If yes, proceed to question xx
- If no, it does not meet the exclusion.

Does the project involve only public health surveillance activities?

- If yes, proceed to question xx
- If no, the parts of the project that are not public health surveillance activities must be assessed separately to determine whether they are research, meet another exclusion, meet an exemption, or require IRB review.

Are the public health surveillance activities limited to those necessary to allow a public health authority to identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance (including trends, signals, risk factors, patterns in diseases, or increases in injuries from using consumer products)? Such activities include those associated with providing timely situational awareness and priority setting during the course of an event or crisis that threatens public health (including natural or man-made disasters).

The OHRP draft guidance "Activities Deemed Not to Be Research: Public Health Surveillance 2018 Requirements" contains the following definitions of terms:

- ✓ *Identify* generally refers to activities that are undertaken to detect potential signals, onsets of disease outbreaks, or conditions of public health importance that had not previously been recognized.
- ✓ *Monitor* generally refers to activities that are undertaken to maintain situational awareness of an identified signal, outbreak, or condition, in order to detect changes that warrant further public health action.
- ✓ *Assess* generally refers to activities that are undertaken to evaluate the characteristics of a signal, outbreak, or condition, including its magnitude, prevalence or incidence, and the context in which a signal, outbreak, or condition occurs or has been detected, in order to inform public health action.
- ✓ *Investigate* generally refers to the range of activities that are undertaken in response to an identified or perceived threat to public health, to determine the magnitude of the problem, identify cases, or determine the cause, and to inform appropriate control measures. The problem under investigation might be a signal, an outbreak, or any other occurrence that warrants action.
- ✓ *Provide situational awareness* refers to assembling the critical information that is needed to respond to a disease outbreak or other public health emergency.

- ✓ *Potential public health signals, onsets of disease outbreaks, and conditions of public health importance* generally include conditions affecting health and safety, such as infectious and chronic diseases, injury, including those related to medical products, and mental health.

- If yes, the exclusion is met

If no, it does not meet the exclusion.

~~Relevant OCR guidance on definition of PHA:~~

~~1) This is OCR's guidance from 2003 titled "DISCLOSURES FOR PUBLIC HEALTH ACTIVITIES" attached or found at https://www.hhs.gov/hipaa/for-professionals/special-topics/public-health/index.html~~

~~2) CDC published a report on HIPAA, where box #4 may provide a few specific examples https://www.cdc.gov/mmwr/preview/mmwrhtml/m2e411a1.htm~~

~~3) This might describe more specific example of how PHA is extended https://www.cdc.gov/nhsn/hipaa/index.html~~

~~4) Decision Tool to inform Disclosures for Emergency Preparedness - A Decision Tool: Is the Recipient a Public Health Authority (PHA)? It nicely lays out the definition of the PHA from HIPAA.~~

~~https://www.hhs.gov/hipaa/for-professionals/special-topics/emergency-preparedness/is-recipient-public-health-authority/index.html~~

Attachment C(2) Interpretation of *Public Health Authority* and *Public Health Surveillance Activities*, 46.102(k), 46.102(l)(2): With Revisions Accepted

Introduction

OHRP is frequently asked to respond to questions from the research community regarding the interpretation and application of 45 CFR 46.102(k) and (l)(2). While OHRP and other HHS agencies have already considered these questions, OHRP asks SACHRP to independently deliberate the questions below and come to its own objective recommendations. OHRP would be interested in SACHRP's views even if additional rulemaking were necessary to clarify or modify aspects of the regulations.

The regulatory text is as follows:

> 45 CFR 46.102(k)
>
> Public health authority means an agency or authority of the United States, a state, a territory, a political subdivision of a state or territory, an Indian tribe, or a foreign government, or a person or entity acting under a grant of authority from or contract with such public agency, including the employees or agents of such public agency or its contractors or persons or entities to whom it has granted authority, that is responsible for public health matters as part of its official mandate.
>
> 45 CFR 46.102(l)(2)
>
> Public health surveillance activities, including the collection and testing of information or biospecimens, conducted, supported, requested, ordered, required, or authorized by a public health authority. Such activities are limited to those necessary to allow a public health authority to identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance (including trends, signals, risk factors, patterns in diseases, or increases in injuries from using consumer products). Such activities include those associated with providing timely situational awareness and priority setting during the course of an event or crisis that threatens public health (including natural or man-made disasters).

In the pre-2018 version of the Common Rule, there were a number of categories of exempt research, which were presented at 45 CFR 46.101(b)(1) through (b)(6). Of note, these are human subjects research, but research that is exempt from the requirements of the Common Rule. In the revised Common Rule, known as the 2018 Requirements, those exemptions were modified extensively and were moved to 45 CFR 46.104. In addition, the definition of research was modified at 45 CFR 46.102(l) to include four activities which "are deemed not to be research." These four activities are commonly referred to as "exclusions," although that term was not carried over from the NPRM and the Federal Register announcement (Vol. 82, No. 12 /Thursday, January 19, 2017, page 7149) into the 2018 Requirements. There is some conceptual uncertainty as to whether the

four exclusions are not research or alternatively are research that does not require compliance with the 2018 Requirements, similar to the exemptions at 45 CFR 46.104, but in the end that distinction does not have practical implications and does not need to be resolved in order to apply the exclusions.

Introduction

In this recommendation, SACHRP first answers OHRP's questions 1 through 8, then provides brief commentary on the draft OHRP guidance "SACHRP Commentary on OHRP draft guidance "Activities Deemed Not to Be Research: Public Health Surveillance 2018 Requirements," and third provides an algorithm to apply the exclusion.

SACHRP Opening Comments

SACHRP notes that if a proposed activity does not meet the exclusion provided by 45 CFR 46.102(l)(2), and it meets the definition of research, then the practical effect is that IRB review will be required unless the activity meets one of the exemptions under 45 CFR 46.104. In many cases, if the activity is research, it will be minimal risk (if it has appropriate protections for confidentiality) and may also qualify for a waiver of consent under 45 CFR 46.116(f).

SACHRP also notes that just because an agency is designated as a public health agency, that does not mean that every activity conducted by the agency is a public health activity, or a public health surveillance activity, or that every department in the agency is conducting public health activities. For instance, NIH performs some public health activities, but much of the work NIH does is not a public health activity.

Third, SACHRP wants to clarify that "grant of authority" as used in 45 CFR 46.102(k) is not synonymous with the term "grant," as used to indicate a decision by an agency such as NIH to support a study. This is clear in the OHRP draft guidance, "Activities Deemed Not to Be Research: Public Health Surveillance 2018 Requirements," which says,

> Public health surveillance activities that are *supported* by a public health authority (*e.g., through a grant or cooperative agreement*), or that are requested, ordered, required, or authorized by a public health authority, also may be eligible for consideration under this provision, even if they are carried out by an entity that is not a public health authority (e.g., academic institutions, health care organizations, nonprofit entities). (emphasis added)

Therefore, for the purposes of this recommendation the term "grant of authority" references to the definition of "public health authority" in 45 CFR 46.102(k). In contrast, the term "grant" references the situation where a public agency (e.g., NIH) is providing support to a public health authority, and thus references the term "supported" as used in the public health surveillance exclusion at 45 CFR 46.102(l)(2), which says,

> Public health surveillance activities, including the collection and testing of information or biospecimens, conducted, *supported*, requested, ordered, required, or authorized by a public

health authority. (emphasis added)

CDC uses a type of financial assistance mechanism similar to a grant, called a cooperative agreement, that is a type of federal support. When distinguishing a grant of authority from the federal funding mechanisms, a cooperative agreement references "support" as well.

SACHRP Responses

OHRP Question 1. What entities should be considered to meet the Common Rule definition of a 'public health authority'? Note that this definition is largely the same as the HIPAA definition, so please consider past applications of this definition in the HIPAA context as well.

(a) If a Federal agency that is a public health authority engages in a partnership with a private institution to conduct public health surveillance activities, should (or might) the institution be considered to be a 'public health authority' in this context? Please consider providing an explanation as to why or why not the institution should (or might) be considered to be a "public health authority."

The HIPAA definition is below for convenience.

> 45 CFR 164.501
>
> Public health authority means an agency or authority of the United States, a State, a territory, a political subdivision of a State or territory, or an Indian tribe, or a person or entity acting under a grant of authority from or contract with such public agency, including the employees or agents of such public agency or its contractors or persons or entities to whom it has granted authority, that is responsible for public health matters as part of its official mandate.

SACHRP answer to Question 1

SACHRP supports the harmonization of definitions across HHS, FDA and OCR, as evidenced by the creation of the standing SACHRP Subcommittee on Harmonization. Therefore, SACHRP encourages reliance on past applications of this definition of a "public health authority" in the HIPAA context.

The Committee does note one significant difference between the definitions; the Common Rule definition includes an agency or authority of "a foreign government" as well as US agencies and authorities, whereas the HIPAA definition is limited to US agencies and authorities. SACHRP believes that the extension of this exclusion to a foreign government should be interpreted as narrowly as possible, with the only use being the use of US federal funds to conduct public health surveillance activities in the foreign government's country only. It should not be used to allow a foreign government to conduct public health surveillance activities in the United States or in a country other than that of the foreign government.

The definition appears to be quite broad. A plain reading of the regulation indicates that a person or

entity acting under a grant of authority from, or contract with, such public agency is also a public health authority. Therefore, institutions or private companies could meet the definition.

SACHRP answer to Question 1(a)

If a Federal agency that is a public health authority engages in a partnership with a private institution to conduct public health surveillance activities, the private institution should not be considered to be a 'public health authority' solely based on the partnership. The plain reading of the definition is that a public health authority must be an agency or authority of the US or a foreign government. A private institution does not meet that definition per se. However, if the partnership involves a "grant of authority from or contract with such public agency," then the private institution is a public health authority by the definition.

SACHRP recommends that the grant of authority be interpreted narrowly when a private institution is designated to become a public health authority. The grant of authority or contract should be clearly limited to a defined public health surveillance activity. It should not be allowed to extend to other projects or other activities and still be considered to fall under the exclusion. Furthermore, as noted in the preamble to the 2018 Requirements, "subsequent research using information collected during a public health surveillance activity, for instance, genetic analysis of biospecimens, would not be removed from the definition" of research. (FR Vol. 82, No. 12, Thursday, January 19, 2017, p. 7176.)

Also, SACHRP notes that the preamble describes certain research activities that do not fall under the exclusion. As noted in the preamble:

> "This clarification of current interpretation would not remove the following activities from the definition of "research": exploratory studies designed to better understand risk factors for chronic diseases, including genetic predisposition, for chronic diseases; exploratory studies designed to elucidate the relationships between biomarkers of exposure and biomarkers of disease; and exploratory studies of potential relationships between behavioral factors (e.g., diet) and indicators of environmental exposures. These types of activities would be considered research because they would not be conducted solely for the purposes described in §__.102(l)(2), and thus would be covered by the Common Rule if they involved human subjects, even if conducted by a federal agency with a public health mandate. Again, they might fall within an exemption, depending on how they are carried out." (FR Vol. 82, No. 12, Thursday, January 19, 2017, p. 7176)

Finally, SACHRP recommends the grant of authority should be clearly documented in a legal document, which can take several forms, such as an MOU, contract, purchase order or letter. It should clearly cite to a federal or state law or regulation. Both the Office of Civil Rights (OCR) and the Centers for Disease Control (CDC) has given examples of such grants.

In the preamble to the Privacy Rule, OCR said:

> In some circumstances, a person or entity acting on behalf of a government agency may make a request for disclosure of protected health information under these subsections. For

> example, public health agencies may contract with a nonprofit agency to collect and analyze certain data. In such cases, the covered entity is required to verify the requestor's identity and authority through examination of reasonable documentation that the requestor is acting on behalf of the government agency. Reasonable evidence includes a written request provided on agency letterhead that describes the legal authority for requesting the release and states that the person or entity is acting under the agency's authority, or other documentation, including a contract, a memorandum of understanding, or purchase order that confirms that the requestor is acting on behalf of the government agency. 65 FR 82462, 82547 (Dec. 28, 2000).

CDC has also addressed this issue in its guidance entitled "HIPAA Privacy Rule and Public Health: CDC Guidance (April 11, 2003)," which says:

> Public health agencies often conduct their authorized public health activities with other entities by using different mechanisms (e.g., contracts and memoranda or letters of agreement). These other entities are public health authorities under the Privacy Rule with respect to the activities they conduct under a grant of authority from such a public health agency. A covered entity may disclose PHI to public health authorities and to these designated entities pursuant to the public health provisions of the Privacy Rule. https://www.cdc.gov/mmwr/preview/mmwrhtml/m2e411a1.htm.

For transparency, the grant of authority should be publicly available and easy for the public to locate, as public health surveillance activities involve issues of privacy.

OHRP Question 2. How should the exclusion operate when the public health surveillance activities will be wholly carried out by an entity outside of the Federal, State, or local government? Consider whether there is a distinction if the activities are carried out by a contractor (in which activities are directed by the awarding governmental agency through the terms of the contract, and will provide data back to the awarding agency) versus a grantee (in which activities are proposed by the grantee and are not directed by the awarding governmental agency, and which may or may not result in data being provided back to the awarding agency) versus through a public-private partnership that does not involve an award of funds. Please specifically consider the following language of the exclusion in these contexts: "The activity must be limited to that necessary to allow a public health authority to identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance…" (emphasis added).

SACHRP answer to Question 2

First, we note that a plain reading of the regulation is that the definition of a public health authority includes "a person or entity acting under a grant of authority from or contract with such public agency." Therefore, it appears that a person or private entity becomes a public health authority when such a grant of authority or contract is in place. Thus, a government agency or authority can designate a person or private entity to perform all of the functions of the agency or authority, even if that person or private entity does not provide the information back to the agency, because the person

or private entity becomes a public health authority.

Question 2 also asks whether there should be distinctions when the public health surveillance activities are wholly carried out by an entity outside of the Federal, State, or local government, in particular a contractor versus a grantee versus a public-private partnership that does not involve an award of funds. There are distinctions between contractors and grantees that receive support, in that contractors are obligated to fulfill the terms of the contract, which in the case of public health surveillance activities could include a wide variety of responsibilities and requirements. Recipients of grants (support) for public health surveillance activities are not required to satisfy contractual terms, but are required to meet the regulatory conditions for receiving the grant, and thus generally involve more latitude. It is difficult to make an assessment of public-private partnerships in a similar fashion, as such partnerships can vary greatly in structure and details. Many will include a contract between the public and private participants, but that is not a legal requirement. OHPR also asks that SACHRP consider these legal mechanisms in light of the regulatory requirement that the activity "must be limited to that necessary to allow a public health authority to identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance…" Clearly, the Federal, State, or local government has more ability to ensure the activity is limited to that necessary when a contract is in place, as requirements can be included as terms of the contract.

OHRP also asks "how *should* the exclusion operate?" (emphasis added.) SACHRP believes that to the extent possible, mechanisms should be in place to help ensure that the activity is limited to that necessary to identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance. However, these mechanisms will vary depending on the legal nature of the relationship.

OHRP Question 3. What types of activities should be considered to be "public health surveillance activities" for purposes of this exclusion? Note that this term is used in the Common Rule but is not defined in the Common Rule. Please consider developing a rubric for analyzing planned activities, including specific rationale as to why certain types of activities should or should not be considered to be "public health surveillance." For example, should the purpose of the surveillance activity be solely to inform the decisions or actions that must be made by a public health authority, or to apply study findings to public health practice? Should activities that do not meet this exclusion include disseminating findings to stimulate public health action by others, but not informing the public health authority of actions that it would take to improve public health?

(a) Please also consider developing illustrative case studies that describe the creation of a repository as the primary study, as well as a repository embedded within a trial. For example, consider whether establishment of a repository containing individually identifiable private information or individually identifiable biospecimens could fall within this exclusion, and what other facts would need to be known in order to address this question. For example, is it relevant if the planned uses of the repository information:

- Are unknown?
- Would only constitute non-exempt human subjects research?
- Would only constitute public surveillance activities that would also meet the conditions of the exclusion?
- Would require an additional assessment to determine whether they met all the conditions of the exclusion?

SACHRP answer to Question 3

Both the exclusion itself and the preamble include activities that should be considered "public health surveillance activities." The exclusion says that such activities are:

- Those necessary to allow a public health authority to identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance (including trends, signals, risk factors, patterns in diseases, or increases in injuries from using consumer products); and
- Those associated with providing timely situational awareness and priority setting during the course of an event or crisis that threatens public health (including natural or man-made disasters).

The preamble says that such activities include:

- Collecting, analyzing, and using data to target public health and disease prevention;
- Surveillance uses data from a variety of sources, including mandatory reporting of certain conditions, routine monitoring, vital records, medical billing records, and public health investigations.
- Safety and injury surveillance activities designed to enable a public health authority to identify, monitor, assess, and investigate potential safety signals for a specific product or class of products (for example, the surveillance activities of the FDA's Adverse Event Reporting System, the Vaccine Adverse Event Reporting System, Manufacturer and User Facility Device Experience database, the Medical Product Safety Network, and the Sentinel Initiative);
- Surveillance activities designed to enable a public health authority to identify unexpected changes in the incidence or prevalence of a certain disease in a defined geographic region where specific public health concerns have been raised (*e.g.,* the U.S. influenza surveillance system…;
- Surveillance activities designed to enable a public health authority to identify the prevalence of known risk factors associated with a health problem in the context of a domestic or international public health emergency;
- Surveillance activities designed to enable a public health authority to identify the prevalence of known risk factors associated with a health problem in the context of a domestic or international public health emergency; and,
- Surveillance activities designed to enable a public health authority to detect the onset of disease outbreaks or provide timely situational awareness during the course of an event or crisis that threatens the public health, such as a natural or man-made disaster, and Surveillance activities designed to enable a public health authority to identify the prevalence of a condition of public health importance, known risk factors associated with a condition of public health importance, or behaviors or medical practices related to prevalence of a known condition of

public health importance (*e.g.,* surveillance of the prevalence of: tobacco use, exposure to secondhand smoke, lung cancer, or use of smoking cessation treatments).

SACHRP suggests the following additions to this list. Public Health Surveillance activities may be categorized as either passive or active. Passive surveillance systems involve the routine submission of data into data repositories that are used for ongoing analysis and assessment of public health issues. These systems rely upon awareness of the existence of these systems, and the initiative of individuals to file appropriate reports. Examples include FAERS and VAERS (maintained by the FDA), which are used to monitor the safety of licensed drugs and vaccines, respectively. Another example is the notifiable disease reporting system, which is used to track trends in the number of cases of certain infectious diseases (maintained by the CDC). Passive surveillance systems are typically conducted indefinitely. In contrast, active surveillance systems are typically fit for purpose activities that involve the active solicitation of reports by those conducting the surveillance activities. These are generally more labor-intensive, shorter in duration, and may be used for a range of activities, from disease detection to assessing the impact of public health policy. Examples include the Active Bacterial Core System (CDC), used to characterize vaccine effectiveness, the Gonococcal Isolate Surveillance Project (CDC), used to monitor trends in antimicrobial susceptibility of Neisseria gonorrhea isolates and inform treatment recommendations, and the National Immunization Survey, used to characterize the susceptibility of the population to vaccine-preventable diseases, and to inform policy.

The preamble also provides a list of research activities that do *not* fall under the exclusion, because they would not be conducted solely for the purposes described in §.102(l)(2). These are:

- exploratory studies designed to better understand risk factors for chronic diseases, including genetic predisposition, for chronic diseases;
- exploratory studies designed to elucidate the relationships between biomarkers of exposure and biomarkers of disease; and
- exploratory studies of potential relationships between behavioral factors (*e.g.,* diet) and indicators of environmental exposures.

SACHRP does not have any suggested additions to this list.

OHRP question 3 also asks,

> For example, should the purpose of the surveillance activity be solely to inform the decisions or actions that must be made by a public health authority, or to apply study findings to public health practice? Should activities that do not meet this exclusion include disseminating findings to stimulate public health action by others, but not informing the public health authority of actions that it would take to improve public health?

SACHRP recommends that the definition of public health surveillance activity be narrowly interpreted, and therefore should not include study findings to public health practice or disseminating findings to stimulate public health action by others (for instance, to wear masks

during the COVID-19 pandemic. While these practices should not be considered public health surveillance activities, they may or may not meet the definition of research. That is a separate analysis.

SACHRP answer to Question 3(a)

Question 3(a) asks whether establishment of a repository containing individually identifiable private information or individually identifiable biospecimens could fall within this exclusion, and asks SACHRP to consider two scenarios, the creation of a repository as the primary study, as well as the creation of a repository embedded within a trial.

Regarding the creation of a repository as the primary study, SACHPR believes that it if the use of the data or samples from the repository is clearly going to be for a public health surveillance activity or activities, then that use of the repository would qualify for the exclusion.

Question 3a asks whether it is relevant if the planned uses of the repository information:

- Are unknown?
- Would only constitute non-exempt human subjects research?
- Would only constitute public surveillance activities that would also meet the conditions of the exclusion?
- Would require an additional assessment to determine whether they met all the conditions of the exclusion?

SACHRP believes that the exclusion should be applied narrowly, and that in order to this exclusion to apply to the creation of a repository, there would have to be adequate description of the project to allow an application of the public health surveillance activities. If the uses were unknown, or would constitute non-exempt research, then the exclusion should not apply. If the planned uses only constitute public health surveillance activities, the exclusion should apply. As noted previously, any secondary uses of the data or samples would need to be analyzed to determine whether they meet the definition of a public health surveillance activity.

Regarding the creation of a repository embedded within a trial, and whether it might qualify for the exclusion, SACHRP notes that OHRP addressed this issue in the OHRP draft guidance "Activities Deemed Not to Be Research: Public Health Surveillance 2018 Requirements." The draft guidance says "If an activity is composed of multiple components, some of which are not public health surveillance, OHRP's view is that only those components that serve to enable a public health authority to carry out one or more public health surveillance objectives should be considered potentially eligible for the public health surveillance activity exclusion under 45 CFR 46.102(l)(2)."

SACHRP agrees with this position, which effectively allows public health surveillance activities that are part of a project that also has research activities to be carved out from application of the Common Rule. Therefore, if a repository is embedded in a clinical trial, and the use of the data or samples from the repository is clearly going to be public health surveillance activities, then those uses of the repository qualify for the exclusion. SACHRP also notes that this is a distinct approach

from the traditional approach to the issue of exempt activities that are embedded within a trial, which has been that if any part of a project qualifies as research, then the exempt parts must also receive IRB review. SACHRP recommends that this distinction is clearly highlighted in any guidance on this issue.

OHRP Question 4. The regulatory language of the exclusion provides that "[t]he activity must be conducted, supported, requested, ordered, required, or authorized by a public health authority." What do each of these actions entail, and how do they differ? Please consider developing suggested examples illustrating each of these scenarios.

SACHRP answer to Question 4

- "Conducted" means the activity is performed by the public health authority.
- "Supported" means that the public health authority provides funding or other resources, but a different entity is involved in conducting the activity.
- "Requested" means that the public health authority has asked a different entity to conduct the activity, but the entity can decline to do so without consequence
- "Ordered" means that the public health authority has the legal authority to require the entity to conduct the activity.
- "Required" is substantively similar to "ordered," but might take a different form. For instance, the requirement might be included in the charter of an organization.
- "Authorized by" means that that public health authority has given permission for the entity to conduct the activity.

SACHRP notes that "supported" and "requested" could potentially allow for more flexibility than the other terms. We believe that these terms should be interpreted narrowly.

OHRP Question 5. While this exclusion clearly may apply in the context of a public health emergency, it is not limited to the emergency context. What are the pros and cons involved in broad application of this exclusion? Please consider outlining such considerations from the perspective of a government agency acting as a public health authority, a non-governmental institution conducting a public health surveillance activity, and the individuals whose data and biospecimens will be used in the public health surveillance activity.

SACHRP answer to Question 5

A positive of allowing a broad application or interpretation of this exclusion is that it provides Public Health Authorities, both public and private, with more flexibility in the conduct of public health surveillance activities, and can reduce administrative burden and the need to consider whether informed consent meeting human subject protection regulations is necessary. A negative is that a broad application may harm public trust if it is applied to activities for which IRB review and informed consent meeting human subject protection regulations would otherwise be required. The use of the exclusion should be transparent and used with a narrow application outside of a public health emergency. During a public health emergency, a broader application may be appropriate in

order to allow Public Health Authorities to take appropriate and timely action to accomplish public health surveillance activities that are pressing and of wide concern.

OHRP Question 6. What entity or involved individual may or should decide whether a planned activity meets the requirements of this exclusion? Are there any recommended considerations involved with this decision, and do they differ depending on what entity or individual might be making this decision?

SACHRP answer to Question 6

SACHRP recommends that determinations that an activity meets the exclusion as a public health surveillance activity be clearly documented and readily available to the public to ensure transparency. Providing the criteria or rationale for the determination, rather than just the final determination itself, will also aid transparency. Public health surveillance activities often involve many institutions and may involve gathering information outside of institutional settings, and in such cases it will likely be most practical for the agency to make the determination. When this occurs, involved institutions should have a mechanism to review the decision and confirm agreement with the decision, particularly if some activities in a project may not meet the exclusion. In cases where the activity is limited to one or more institutions, it may be appropriate to have an institutional mechanism for making the determination, similar to exempt determinations. This could entities such as an IRB administrator, a research office, or an institutional official. In any case, the determination should not be made by the party or parties who are offered the grant or contract to do the public health surveillance activities.

OHRP Question 7. Should documentation be recommended or required regarding each of the decision points involved with this exclusion? If so, please consider providing specific suggestions as to documentation and how entities or individuals should accomplish this.

SACHRP answer to Question 7

Yes. SACHRP believes that documentation of the decision that an activity is a public health surveillance activity should be documented with specific reference to how it meets 45 CFR 46.102(l). This documentation should be publicly available, and easily accessible.

OHRP Question 8. This exclusion will not apply to activities dually regulated by FDA and OHRP. Are there any useful recommendations for involved institutions and individuals in such circumstances? (If not, feel free not to further consider this point.)

SACHRP answer to Question 8

SACHRP does not agree that it is universally true that "this exclusion will not apply to activities dually regulated by FDA and OHRP." For instance, if a public health authority used HHS funding to conduct or support a surveillance program that involved return of COVID-19 test results to subjects, it seems that the project would meet the exclusion at 45 CFR 46.102(l)(2) and simultaneously require FDA review under 21 CFR 812 as an investigational diagnostic device.

FDA does conduct some public health surveillance activities such as the Sentinel project, and the FAERS and VEARS reporting systems. As an HHS agency, FDA can utilize the exclusion for the public health surveillance activities that FDA itself conducts or supports. However, the FDA drug, biologic and device regulations do not include this exclusion at this time, and any clinical investigation of FDA regulated medical products must follow those regulations, even if there are aspects of public health surveillance activities included in the project.

We note that CLIA is also not subject to the exclusion, and CLIA must be separately followed when it is applicable.

SACHRP Commentary on OHRP draft guidance "Activities Deemed Not to Be Research: Public Health Surveillance 2018 Requirements"

SACHRP has reviewed the OHRP draft guidance, and in general agrees with the draft guidance as written. SACHRP believes that several of the points bear repeating in this recommendation.

The draft guidance notes, "This explicit exclusion of public health surveillance activities from the definition of research does not mean that other public health activities that do not constitute public health surveillance activities, as described in 45 CFR 46.102(l)(2), are necessarily research subject to 45 CFR part 46."

Also, the draft guidance states, "Research activities that do not constitute public health surveillance, such as a secondary research analysis of data for some other scientific purpose using information collected as part of a public health surveillance activity, can be carried out in tandem with a public health surveillance activity. In such a circumstance, the non-public health surveillance activity (in the example above, the secondary research analysis) should be reviewed to determine whether the 2018 requirements apply."

Algorithm:

SACHRP has developed the following algorithm to help with the analysis of projects.

Is the project conducted, supported, requested, ordered, required, or authorized by a public health authority?

- If yes, proceed to question xxx
- If no, it does not meet the exclusion

Does the project involve public health surveillance activities, including the collection and testing of information or biospecimens?

- If yes, proceed to question xx
- If no, it does not meet the exclusion.

Does the project involve only public health surveillance activities?

- If yes, proceed to question xx
- If no, the parts of the project that are not public health surveillance activities must be assessed separately to determine whether they are research, meet another exclusion, meet an exemption, or require IRB review.

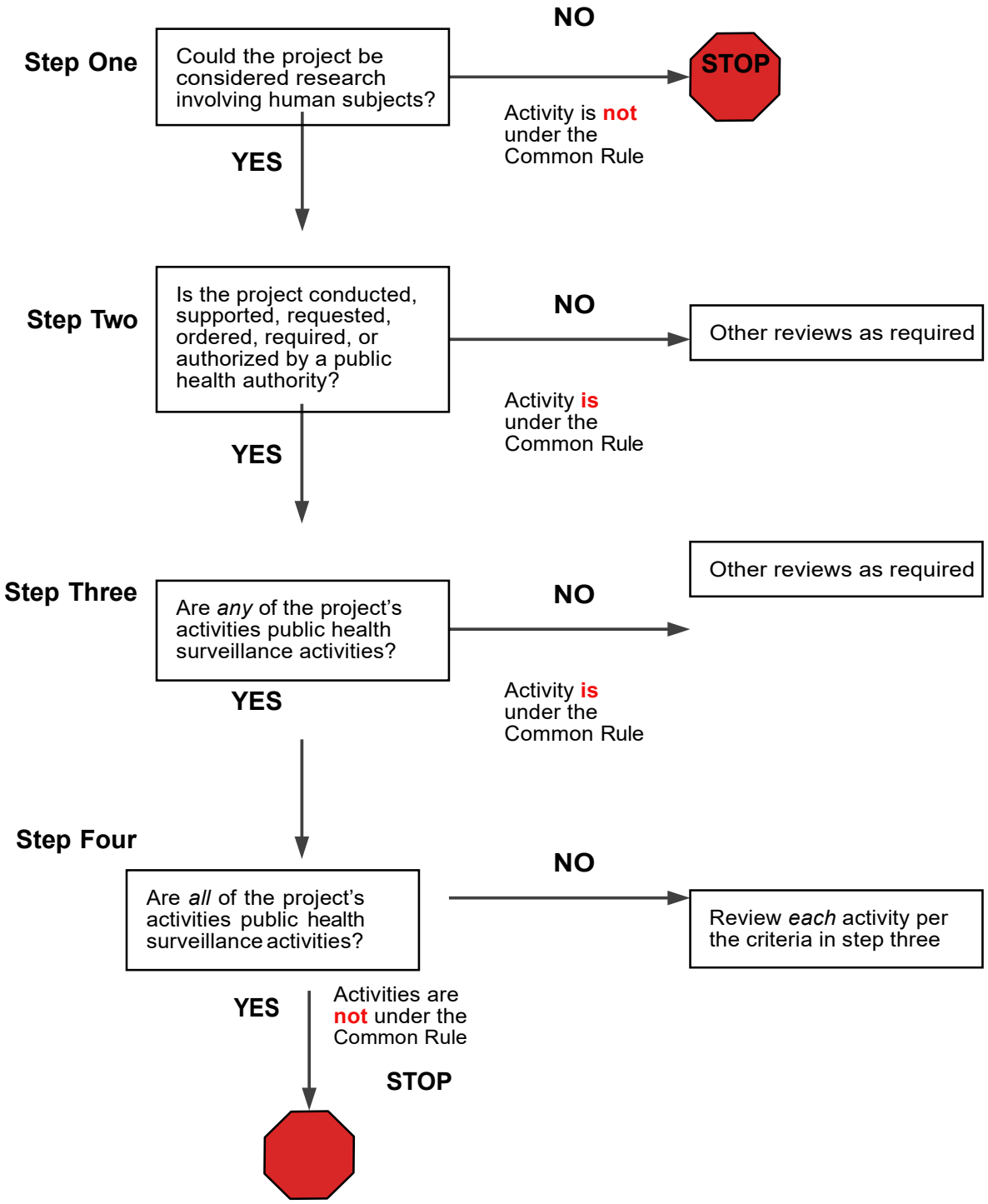
Are the public health surveillance activities limited to those necessary to allow a public health authority to identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance (including trends, signals, risk factors, patterns in diseases, or increases in injuries from using consumer products)? Such activities include those associated with providing timely situational awareness and priority setting during the course of an event or crisis that threatens public health (including natural or man-made disasters).

The OHRP draft guidance "Activities Deemed Not to Be Research: Public Health Surveillance 2018 Requirements" contains the following definitions of terms:

- ✓ *Identify* generally refers to activities that are undertaken to detect potential signals, onsets of disease outbreaks, or conditions of public health importance that had not previously been recognized.
- ✓ *Monitor* generally refers to activities that are undertaken to maintain situational awareness of an identified signal, outbreak, or condition, in order to detect changes that warrant further public health action.
- ✓ *Assess* generally refers to activities that are undertaken to evaluate the characteristics of a signal, outbreak, or condition, including its magnitude, prevalence or incidence, and the context in which a signal, outbreak, or condition occurs or has been detected, in order to inform public health action.
- ✓ *Investigate* generally refers to the range of activities that are undertaken in response to an identified or perceived threat to public health, to determine the magnitude of the problem, identify cases, or determine the cause, and to inform appropriate control measures. The problem under investigation might be a signal, an outbreak, or any other occurrence that warrants action.
- ✓ *Provide situational awareness* refers to assembling the critical information that is needed to respond to a disease outbreak or other public health emergency.
- ✓ *Potential public health signals, onsets of disease outbreaks, and conditions of public health importance* generally include conditions affecting health and safety, such as infectious and chronic diseases, injury, including those related to medical products, and mental health.

- If yes, the exclusion is met
- If no, it does not meet the exclusion.

Attachment C(3). Public Health Surveillance Activities: Complete Decision Tree



Attachment D. Consideration of the Role of Justice as an Ethical Principle in 45 CFR Part 46

Background

The Belmont Report embraces Justice as one of its three principles, and recognizes the major role of injustice in the development of research ethics:

> Questions of justice have long been associated with social practices such as punishment, taxation and political representation. Until recently these questions have not generally been associated with scientific research. However, they are foreshadowed even in the earliest reflections on the ethics of research involving human subjects. For example, during the 19th and early 20th centuries the burdens of serving as research subjects fell largely upon poor ward patients, while the benefits of improved medical care flowed primarily to private patients. Subsequently, the exploitation of unwilling prisoners as research subjects in Nazi concentration camps was condemned as a particularly flagrant injustice. In this country, in the 1940's, the Tuskegee syphilis study used disadvantaged, rural black men to study the untreated course of a disease that is by no means confined to that population. These subjects were deprived of demonstrably effective treatment in order not to interrupt the project, long after such treatment became generally available.

These examples, particularly Nuremberg and Tuskegee, were the events that drove adoption of regulatory protections; absent issues of Justice, oversight had been entrusted to professional norms. Yet despite its recognition of the historical importance of these events, Belmont arguably avoids the underlying issue, suggesting Nazi victims were used for research because they were "unwilling prisoners" (*i.e.,* a population of convenience) and that rural black men were simply "disadvantaged." It may be more accurate to suggest that the reason why individuals were held in concentration camps, or were disadvantaged in the rural South, was also the reason these individuals were deemed suitable for research that was grossly unethical: the perception that such individuals belonged to populations that were intrinsically less deserving of the protections society affords its members, *i.e.,* racism. The Belmont report ends with the admonition:

> One special instance of injustice results from the involvement of vulnerable subjects. Certain groups, such as racial minorities, the economically disadvantaged, the very sick, and the institutionalized may continually be sought as research subjects, owing to their ready availability in settings where research is conducted. Given their dependent status and their frequently compromised capacity for free consent, they should be protected against the danger of being involved in research solely for administrative convenience, or because they are easy to manipulate as a result of their illness or socioeconomic condition.

Some of these populations are sought as research subjects because of their aforementioned "availability in settings where research is conducted," but others are populations of moral, rather than administrative, convenience, in the sense that moral codes based on common humanity have

historically not been applied equally to all groups.

Regulatory Language

The Common Rule empowers the IRB to address issues of injustice in several ways. First, the criterion at §46.111(a)(3) states that research is only approvable if:

> Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted. The IRB should be particularly cognizant of the special problems of research that involves a category of subjects who are vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons.

Second, §46.111 closes with:

> (b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

It is worth noting that the eight criteria under §111(a) are preceded by the the description: "In order to approve research covered by this policy the IRB shall determine that all of the following requirements are satisfied:"

Placing §111(b) outside this qualifier implies that the *research* must meet the §111(a) criteria, and that the "additional safeguards" are, at least potentially, outside the scope of the research itself. This construction leaves IRBs with ambiguity as to their role in upholding the rights of socalled "vulnerable" populations.

The Common Rule also addresses potential injustice through its requirements for IRB membership at §107(a):

> Each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB shall be sufficiently qualified through the experience and expertise of its members (professional competence), and the **diversity of its members, including race, gender, and cultural backgrounds** and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. The IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments (including policies and resources) and regulations, applicable law, and standards of professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas. **If an IRB regularly reviews research that involves a category of subjects that is vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons, consideration**

shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with these categories of subjects.

Thus, the regulation embraces two structural approaches to address potential injustice: (1) representation, *i.e.,* diversity of membership; and (2) expertise and experience.

Charge to SACHRP

The committee is asked to consider whether additional interpretation or guidance is required to adequately ensure that research involving disadvantaged populations is ethical. In particular:

1. §46.111(a)(3) requires the IRB to take into account "the setting in which the research will be conducted." For much biomedical research, particularly research with the potential for direct benefit to participants (*i.e,* studying potentially therapeutic interventions) the setting in which research is conducted is the healthcare delivery system. There is ample data demonstrating that the current healthcare delivery system has structural inequities related to race, income and socioeconomic status. What is the role of the IRB in ensuring that research conducted in this setting appropriately protects the rights and welfare of research participants? In particular, how can research be conducted so that it does not implicitly inherit the injustices of the healthcare delivery system (*e.g.,* restricting participation to individuals who are insured and able to afford copays)?

2. §46.111(b) asks the IRB to ensure that "additional safeguards" are in place to protect research subjects "vulnerable to coercion or undue influence." What measures constitute adequate safeguards in these circumstances, and how should their adequacy be assessed? Should the requirement for such safeguards be limited to those "vulnerable to coercion or undue influence" (*i.e.,* populations with diminished autonomy), or are there concerns of social justice that should lead to a more expansive interpretation of vulnerability to exploitation?

3. §46.107(a) requires that the IRB "consider inclusion" of individuals who are "knowledgeable about and experienced in working with" disadvantaged populations if it regularly reviews research involving such groups. This language is often interpreted to apply when research targets a specific group, but given the diversity of the U.S. population, should the language be interpreted more broadly to require that inclusion of such members be the rule, rather than the exception? And, given the awareness of ubiquitous structural racism, is it sufficient to rely on expertise and experience rather than representation to "promote respect for (the IRBs) advice and counsel?"

4. Is there any additional guidance, training, or resources that can be helpful to IRBs in raising awareness of and responding to ethical issues involving disadvantaged populations in research?

Attachment E: Consideration of Risks to Bystanders Posed by the Research Setting

Introduction

The nature of risks posed by research in the setting of a potentially lethal infectious agent such as SARS-CoV-2 are incompletely addressed in existing regulation and guidance. Specifically, regulation only requires the IRB to consider risks to subjects, but treating research participants who are infected with a transmissible agent carries risks to researchers, the larger study team, and other personnel at the research facility. Narrowly interpreted, the criteria for approval of research do not ask the IRB to assess such risks in evaluating a protocol, yet such risks are clearly real and are risks of the research. Similarly, researchers are permitted to make changes to a study without prior IRB approval **if** there are immediate hazards to participants, but no similar provision exists to allow mitigation of risks to others. While it is unlikely that an IRB would approve a study that was designed in such a way that risks to the study team and others were not addressed, researchers don't currently have the authority under the regulations to modify ongoing studies without prior approval in such circumstances. In the case of COVID-19, strict compliance with this requirement for prior review could expose researchers and others to significant unnecessary risks.

While COVID-19 makes it urgent that this issue be addressed, the regulations already acknowledge that research can lead to harms beyond those to the research subjects. This reality is explicitly addressed in the definition of unanticipated problems, and IRBs have traditionally felt it within their remit to address such problems when they were reported, even if the harms did not directly involve research participants.

The issue of risks to others is well-defined in the context of COVID-19, but pandemic risks are a subset of a broader set of risks to others that are outside the regulatory authority of the IRB as currently defined. Recent advances in genomics and "big data" raise the possibility that research procedures (*e.g.,* full genome sequencing) may have create risk to individuals other than the participant, including family, community and racial/ethnic group. Similarly, tools for genetic manipulation like CRISPR can have unintended consequences beyond the somatic genome and potentially affect future generations. While IRBs are used to addressing the "bystander risks" of vaccines and vectors, they are less prepared to consistently deal with these broader classes of risk.

Bystanders with Exposure to Research Risk

Non-subjects who are exposed to research risk will vary depending on the nature of the research. They have been identified in the literature as third parties, bystanders, indirect participants and collateral participants. In this document we will generally refer to these non-subjects as bystanders. Such individuals are considered bystanders because there is no direct intervention to, or research interaction with, these individuals.[1]

[1] Kimmelman

Even when there are known possible risks to bystanders, IRBs do not often address them in a systematic manner due to the lack of clear regulatory authority for IRBs to require the minimization of risks to bystanders. 45 CFR 46.108(a)(4)(i) requires IRBs to maintain procedures for reporting "unanticipated problems involving risks to subjects *or others.*" However, the regulations are silent with respect to how IRBs should evaluate unanticipated problems.

Other factors include the whether the risk to bystanders is greater than minimal risk and consideration that bystanders may include those who are aware (*e.g.,* caregivers of research subjects) and can take self-protective measures vs bystanders who are not aware (*e.g.,* sexual partner of subject taking an investigational product that is contraindicated in pregnancy) who may not be aware and therefore cannot take self-protective measures.

In addition to bystanders, it should be acknowledged that there will be research in which subjects are asked to provide data or information about others and in some instances the nature of the information provided may make it possible to identify these other individuals. These individuals are referred to as "secondary subjects" because they may be identifiable – and therefore meet the definition of a human subject – even though they are not considered primary subjects, have not given their consent to participate, and may not be aware that researchers are obtaining information about them. This document will not address the concept of "secondary subjects" as non-subjects exposed to risk.

Finally, members of the research team form a category of non-subjects. Research on certain topics or conducted with certain populations may necessarily expose researchers to risk. Examples range from research on illegal/illicit behaviors or among high-risk populations to research involving highly infectious agents. However, once can presume that research staff choose to work in these situations, do so with an understanding of the work-related risks and can take self-protective measures. As noted earlier, it is unlikely that an IRB would approve research where known risks to researchers were not actively monitored and managed. This document will not include members of the research team as non-subjects exposed to risk.

Relevant Regulatory and Guidance Language

45 CFR 46.108(a) In order to fulfill the requirements of this policy each IRB shall:

- (3) Establish and follow written procedures for: (iii) Ensuring prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that investigators will conduct the research activity in accordance with the terms of the IRB approval until any proposed changes have been reviewed and approved by the IRB, **except when necessary to eliminate apparent immediate hazards to the subject.**
- (4) Establish and follow written procedures for ensuring prompt reporting to the IRB; appropriate institutional officials; the department or agency head; and the Office for Human Research Protections, HHS, or any successor office, or the equivalent office within the appropriate Federal department or agency of (i) Any unanticipated problems involving **risks**

to subjects or others or any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB...

45 CFR 46.111(a) In order to approve research covered by this policy the IRB shall determine that all of the following requirements are satisfied:

- (1) Risks to **subjects** are minimized...
- (2) Risks to **subjects** are reasonable in relation to anticipated benefits...

Other Oversight Mechanisms

While IRBs are the best-known mechanism for ensuring subject safety, they are not the only body that assesses risks related to human subjects research. Certain types of research proposals must be reviewed and approved by specialized review committees even when there is IRB oversight.

Many research institutions utilize a radiation safety committee to review uses of radioactive materials and radiation-producing devices, including research uses. Institutions that conduct research with recombinant or synthetic nucleic acid molecules and other hazardous biological agents establish institutional biosafety committees (IBCs) to ensure that the biological aspects of the research are conducted in a safe manner by assessing worker safety, public health, agricultural and environmental protection. At the federal level, the NIH established the Recombinant DNA Advisory Committee (RAC) in 1974 to review the scientific, safety, and ethical issues related to basic and clinical research involving recombinant or synthetic nucleic acid molecules. [2]

In each of these examples, the review committees do consider risks beyond those to individual research subjects. However, these specialized reviews only apply to a small percentage of clinical research.

Recommendation

SACHRP recommends that bystanders in research be defined as individuals who are exposed to research-related risks even though they themselves are not human research subjects.

In the following Points to Consider, SACHRP provides scenarios both where an IRB may consider if there are risks to bystanders that should be formally addressed and scenarios where the IRB need not concern themselves with risks to bystanders.

Points to Consider

In the following Points to Consider, SACHRP provides scenarios where an IRB may consider if there are risks to bystanders that should be formally addressed. While the criteria for approval at 45 CFR 46.111 require the minimization of risks for research subjects, they do not prohibit the IRB from considering risks to others, and risks to others are separable from the possible long-range

[2] https://osp.od.nih.gov/biotechnology/recombinant-dna-advisory-committee/

effects of applying knowledge gained in the research that IRBs are prohibited from considering in their assessment of research.

SACHRP is cognizant of the concern that addressing bystander risks is extra-regulatory and could lead to IRBs assuming a role that was not intended in the U.S. regulatory framework. This type of mission creep is discouraged, and IRBs should not view these Points to Consider as an invitation to actively seek out potential bystander risk issues in all proposals.

Review by Other Oversight Bodies

In cases where risks to bystanders are addressed by separate oversight bodies, IRBs should utilize the results of those reviews rather than conducting a separate review of possible risks to bystanders. In these cases the IRB should focus its attention of the criteria for approval at 45 CFR 46.111 as they apply to the subjects of the research.

Research Scenarios where IRBs Might Consider Risks to Bystanders

Subjects in psychiatric washout studies may engage in dangerous behaviors that place bystanders at risk.[3] Examples of bystanders may include caregivers and other family members or personal relations of the research subject as well as members of the general public. In this scenario an IRB may consider if either of these bystander populations are placed at heightened risk because of the research. An IRB may determine that caregivers/family members be informed of subject's participation the possible impact on the bystander, but also determine that members of the general public need not be accounted for by the IRB, because the risk is minimal in that it is commensurate with everyday life where there will be multiple members of the public with mental health issues who are not accessing treatment or adhering to prescribed treatment regimens.

Subjects in HIV prevention or HIV cure research may decide to engage in high-risk sexual behavior due to therapeutic misconception or research-induced disinhibition. As a result, sexual partners may be exposed to a greater risk of infection as a result of the subject's high-risk behaviors. In this scenario, the IRB may consider these risks and determine that the research informed consent process and protocol-required counseling of subjects about risk-taking behaviors sufficiently mitigates risk to bystanders or that these messages should be enhanced. The IRB may also consider that sexual partners are also free to implement their own risk reduction measures, without regard to the subject's participation in the research.

Subjects in studies of investigational products with known pregnancy risks may simultaneously choose to not use protocol-mandated contraception and not tell inform sexual partners about their participation in research and/or the related risks to pregnancy. In this scenario the IRB may determine that the language in the consent form and the consent process is sufficient. If the risks are great enough the IRB

[3] Ad citation to HFL paper minimal or reasonable

may consider more stringent requirements for subjects with partners of child-bearing potential.

Subjects participating in a challenge trial of a highly infectious disease without a proven effective treatment may be expose family members and members of the general public to an increased risk of infection. IRBs should consider whether the protocol includes adequate provisions for limiting the opportunity of exposing bystanders. Provisions could include quarantine of research subjects, community consultation, or an additional safety monitoring of subjects while there is the high potential for transmission.

Research Scenarios where IRBs Should Not Consider Risks to Bystanders

The regulations already prohibit IRBs from considering "the possible long-range effects of applying knowledge gained in the research (e.g., the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility." (45 CFR 46.111(a)(2)) The risks that this regulation addresses clearly includes people beyond the research subjects.

IRBs should not attempt to identify risks to bystanders in the course of routine review of research. The consideration of research risks to bystanders should be managed on a case-by-case basis when there is no additional oversight by another entity, such as an institutional biosafety committee.

IRBs should not be concerned about research-related risks to bystanders when the risk is not directly related to the research intervention. In a scenario where research subjects are required to travel long distances for extended periods of time in order to access the research, the IRB should not consider the impact of the displacement on the subject's family as a research risk.

Other examples?

Conclusion

To be written once the final direction of the document is determined.