SACHRP Charge

Consideration of Risks to By-standers 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.

By-standers 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, by-standers, indirect participants and collateral participants. In this document we will generally refer to these non-subjects as by-standers. Such individuals are considered by-standers because there is no direct intervention to, or research interaction with, these individuals.[1]

[1] Kimmelman

Even when there are known possible risks to by-standers, 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 by-standers. 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 by-standers is greater than minimal risk and consideration that by-standers may include those who are aware (*e.g.*, caregivers of research subjects) and can take self-protective measures vs by-standers 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 by-standers, 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 By-standers 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 by-standers that should be formally addressed and scenarios where the IRB need not concern themselves with risks to by-standers.

Points to Consider:

In the following Points to Consider, SACHRP provides scenarios where an IRB may consider if there are risks to by-standers 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-

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

range 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 by-stander 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 by-stander risk issues in all proposals.

Review by other Oversight Bodies

In cases where risks to by-standers are addressed by separate oversight bodies, IRBs should utilize the results of those reviews rather than conducting a separate review of possible risks to by-standers. 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 By-standers

Subjects in psychiatric washout studies may engage in dangerous behaviors that place by-standers at risk.[3] Examples of by-standers 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 by-stander 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 by-stander, 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 by-standers 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 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

[3] Ad citation to HFL paper minimal or reasonable

of infection. IRBs should consider whether the protocol includes adequate provisions for limiting the opportunity of exposing by-standers. Provisions could include quarantine of research subjects, community consultation, or a additional safety monitoring of subjects while there is the high potential for transmission.

Research Scenarios where IRBs Should Not Consider Risks to By-standers

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 by-standers in the course of routine review of research. The consideration of research risks to by-standers 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.