SACHRP Charge

Consideration of Risks to Non-subjects 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, while regulations allow the IRB to consider benefits to both subjects and society, they only require the IRB to consider risks to subjects. The regulatory structure does not require that the IRB consider risks to researchers, the larger study team, and other personnel at research facilities that interact with research subjects who are infected with a transmissible agent. 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.

The regulations already acknowledge that research can lead to harms beyond those to the research subjects. This reality is explicitly addressed in the requirement to report unanticipated problems, which may involve risks to subjects *or others.*

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 subject(s), 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 may be less prepared to consistently deal with these broader classes of risk.

Commented [DB1]: One commenter asks if we have evidence of this beyond our own experiences? If not, how should we soften this statement?

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 refer to these non-subjects as bystanders, which we define as individuals who are exposed to research-related risks even though they themselves are not human research subjects.

Even when there are known possible risks to bystanders, IRBs may not 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.

When an IRB does evaluate risks to bystanders, limiting the review to those risks that are reasonably foreseeable rather than considering any conceivable risk may serve as a useful limitation for IRBs. This is also consistent with the regulatory requirement that subjects be informed of the reasonably foreseeable risks and discomforts associated with the research.

Other factors include 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) and therefore cannot take self-protective measures.

Other non-subjects with exposure to research risk

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 sometimes 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. This document will not include members of the research team as non-subjects exposed to risk.

Regulatory Parameters:

The criteria for IRB approval of research at 45 CFR 46.111(a) limits the scope of IRB review to risks to research subjects.

"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..."

The regulatory structure does not require that the IRB from consider any risks to researchers, the larger study team, and other personnel at research facilities that interact with research subjects who are infected with a transmissible agent. This is the case even in research where such risks to bystanders are reasonably foreseeable.

While changes to research ordinarily require prospective review and approval by the IRB, 45 CFR 46.108(a)(3) allows an exception when changes are related to risks to subjects:

> "(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."**

As with the regulatory criteria for approval of research by the IRB, the regulations related to changes to approved research make no mention of risks to non-subjects.

The only instance where the regulations refer to risks to non-subjects is in the context of unanticipated problems. 45 CFR 46.108(a)(4) requires IRBs to have a procedure that requires reporting of unanticipated problems involving risks to subjects or others:

> "(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..."

In this case, the regulations require IRBs to have a policy for reporting these issues to the IRB. However, the regulations provide no additional direction to the IRB for the review of unanticipated problems or the resulting risks to others. 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 subjects. However, this review is not a regulatory requirement.

Ethical Parameters:

While it is true that IRBs are governed by, and held accountable to, regulations that are written to primarily address the involvement of individual research subjects, the regulatory framework reflects the ethical principles described in the Belmont Report. In the Belmont Report, it is acknowledged that research risks "may affect the individual subjects, the families of the individual subjects, and society at large."

It has been argued that IRBs should be charged with overseeing bystander risk because they are the lone body with an explicit direction to broadly consider the ethical acceptability of proposed research and specifically assess risk and benefit in research.[1] As stated in the Belmont Report,

[1] Kimmelman J. Why IRBs should protect bystanders in human research. Bioethics. 2020;00:1– 4. https://doi.org/10.1111/bioe.12812

"Risks and benefits of research may affect the individual subjects, the families of the individual subjects, and society at large."

Therefore, it may be reasonable for IRBs to consider risks to bystanders in some scenarios. The challenge will be in setting the bar for engagement by the IRB on bystander issues. Otherwise, there is a potential for unwanted mission creep that may occur.

Concerns over IRB mission creep

Within the research community IRBs are viewed as the group that is responsible for ensuring that research is ethical, and this often leads to IRBs being tasked as the gatekeepers for all issues related to research ethics. IRBs frequently become indirectly responsible for a variety of issues that are tangential to the regulations that govern IRBs, including financial conflict of interest, HIPAA, and institutional requirements for training on research ethics.

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 be given a broad mandate to actively seek out potential by-stander risk issues in all proposals.

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]

Some research networks (e.g., HIV Prevention Trials Network) also utilize community advisory boards (CABs) as a component of the protocol development process. CAB review often considers the community impact aspect of proposed research, and CABs work in collaboration with the sponsor and local investigators to address potential concerns prior to study implementation.

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

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.

Points to Consider:

In the following Points to Consider, scenarios are provided where an IRB may consider if there are risks to bystanders that should be formally addressed. As mentioned earlier, for the purposes of this document bystanders are defined as individuals who are exposed to research-related risks even though they themselves are not human research subjects. 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 effects of applying knowledge gained in the research that IRBs are prohibited from considering in their assessment of research.

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. 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.

[3] Ad citation to HFL paper minimal or reasonable

Subjects in studies of investigational products with known pregnancy risks may choose to not use protocol-mandated contraception and/or not inform sexual partners about their participation in research and 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 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 a additional safety monitoring of subjects while there is the high potential for transmission.

Subjects participating in a study of public behaviors contribute to data collection using a wearable sensor / recording technology that may capture images and sound from bystanders without their consent. Although some of this information may be considered publicly available, bystanders may object to having audio and video of themselves captured for research purposes. Depending on the nature of the research, it is also conceivable that the recorded information could place the bystanders at risk of criminal or civil liability or be damaging to their financial standing, employability, educational advancement, or reputation. To mitigate these risks, IRBs may consider data security measures, the ability to deidentify recordings, and approaches to data collection that minimize exposure of bystanders. (Open to other suggestions for how IRBs might address)

Community risks, including those related to racial or ethnic groups. Higher household densities in some communities might elevate bystander risk, for example. (No suggestions for an actual scenario or for how IRBs would assess/address)

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.

Conclusion:

To be written as content comes together.

Notes from previous discussion: