

Risk to study nonparticipants: A procedural approach

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Current ethical guidance for research on human subjects is primarily concerned with protecting study participants.* They are, after all, the “human subjects” whose interests are the focus of oversight. But research—whether on human subjects or not—may also strongly affect individuals who are *not* study participants. US law defines study participants as living people about whom data are obtained through intervention or interaction or about whom identifiable private information is collected

(1). Many individuals about whom no data are obtained through intervention, interaction, or other means can be affected by a study.

A complex ethical question therefore arises. What protections are owed to study nonparticipants? Except in the case of fetuses (a relatively complex case in light of their debatable moral status), US law governing all federally funded research does not address risk to nonparticipants (1). Although guidance exists



Research on human subjects can affect people other than the subjects. What protections are owed to study nonparticipants? Image courtesy of Dave Cutler (artist).

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on specific risks—for example, risks from xenotransplantation trials to surrounding individuals and communities and risks from genetic studies to the privacy of relatives—a comprehensive approach or ethical theory is missing. Certainly there is no philosophical foundation that covers highly discrepant risks to third parties from infection, radiation, data exposure, stigmatization, a fully warranted bad name, and so forth. And reasoning in this area pays little attention to relevant normative work on risks to bystanders and collateral damage in tort law, just war theory, and other parallel discussions. Nor, finally, do we even know the scope and intensity of likely nonparticipant effects in typical research practice.

It would be helpful to develop a comprehensive and consistent account of whether and when risks to nonparticipants make research activities illegitimate and which regulatory responses are appropriate. But how to develop such an account? We present one way forward.

Risks to Research Bystanders

Many studies put nonparticipants at risk or otherwise affect them. For example, all studies on pregnant women may affect fetuses (2). Infectious disease

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studies may confer protection (2), or risk (3), onto fetuses, sexual partners, household and community members, and still other people. This impact can be substantial and raise ethical quandaries, as two recent examples illustrate. Participants in ongoing HIV cure-related studies with an interruption of antiretroviral therapy may transmit the virus to fetuses and sexual partners when HIV concentration in body fluids increases after that interruption (4). A report by a US National Institute of Allergy and Infectious Diseases planning committee recently recommended against challenge studies for Zika vaccine candidates in part because such studies would risk transmission to fetuses, sexual partners, and even people bitten by the same mosquitos who bit study participants (5). A scientific study with no human subjects can also put persons at risk of harm. Animal studies that involve transmissible human pathogens place many people at risk of infection and further transmission (6).

Risks to nonparticipants can also compromise their privacy or their social and economic standing. For instance, studies that collect tissue or viral samples from participants for genetic assays thereby often obtain information, including highly personal details, about their relatives or sex partners (<https://matr.vcu.edu>). Even without flagrant violations of privacy, such as Cambridge Analytica's recently revealed abuse of private data (7), studies can use a person's consensual reporting to learn about their online and offline social network, and studies of adherence to medications may track behavior of nonparticipants sharing living quarters (8). Studies of interventions to inform voters

about political candidates may affect election results and candidates' careers (9).

Simply adding nonparticipant risk to the already-crowded agendas of research ethics committees without further guidance is not the right solution (5). Even with instructions, many research ethics committees may lack both the expertise and the resources required for governing this area. In general, these committees are best seen as one (important) element in a broader framework of oversight. This framework should also include self-monitoring by researchers with basic training in research ethics, advice from peers and consultants, and potentially committees with different purposes and compositions (5). To address nonparticipant risk at this point in time—and to gain the knowledge that would facilitate the development of more thorough regulation in the future—we propose the following procedural approach.

A Proposal

In an initial pilot phase over a few years, funders such as the US National Institutes of Health (NIH) would ask all scientific investigators to estimate risks to nonparticipants when applying for funding, and to justify any foreseen risks, in a standardized questionnaire. Online advice would help investigators determine who legally counts as a study participant and who doesn't and provide examples of effects that raise initial concern. The answer to questions regarding nonparticipants may often be "No nonparticipant risks anticipated."

Those investigators who expect nonparticipant risks would be further asked to roughly estimate the size of those risks, as well as determine the mechanism by which the risk emanates from the study. For example, what are the magnitude and probability of harm for any (identifiable) individuals and for society? Is the risk solely due to the study being carried out or merely from the study's publication of stigmatizing or incriminating findings? Would it be caused by potential error, or it is inherent to the design?

Applicants would also be prompted to offer a plan for mitigating any risks to nonparticipants and a justification for any anticipated remaining risks. For example, applicants could lay out protections offered to nonparticipants—such as HIV pre-exposure prophylaxis for stable sexual partners in studies that involve antiretroviral treatment interruption (4). Applicants could also explain why they view remaining risks to nonparticipants as irrelevant, minor, or irreducible at a reasonable cost, short of fundamental changes to a highly valuable research strategy. They could state whether assent or informed consent will be sought from nonparticipants at risk and whether compensation is planned for nonparticipants who are harmed by a study or a finding. Or they could use any of a number of answers offered in a related, brief tutorial. This questionnaire on nonparticipant risk would become a standard, compact element in grant applications—akin to when researchers provide descriptions of the pain vertebrate animals are likely to experience as part of a given laboratory study—as they do in current NIH grant proposals.

During the initial pilot phase for the questionnaire on nonparticipant risk, applicants' risk assessments and justifications, along with some other information about the proposed studies, will be noted and collected for study with candidate investigators' authorization. These assessments will not, however, affect the evaluation of their grant proposals. NIH or another suitable funding agency would then seek applications for one working group (or several) that would use the data collected to develop draft guidelines for investigators and grant reviewers on what's acceptable and unacceptable in terms of risk to nonparticipants. Insights from other areas of ethics, research ethics, and biolaw would help the funded working group advance our understanding of when risks to nonparticipants are acceptable and assess the plausibility of applicants' justifications of anticipated risks. The draft guidelines should use external data on harms to nonparticipants to assess whether applicants' estimates systematically under- or over-report important effects.

Important Caveats

Although the working group should remain open to the possibility of exposing the failure of retaining this self-regulation approach, it should likewise be alert to overemphasis on speculative or relatively trivial burdens on nonparticipants and to any curbs on academic freedom. To that end, the working group should keep track of the added administrative burden imposed by any proposed addition to the grant application process and of any potentially stifling effects on proposing new studies.

And it makes sense to set limits here. In a recent editorial, bioethicists declared that it is "important to protect all research by-standers because they may be unable to protect themselves; obtaining their consent might be impossible in some cases and problematic in others" (5). We believe that it would be a mistake to protect bystanders from all risks of research; principles are needed to distinguish when such protection is required. Surely a study that risks decreasing the incomes of some manufacturers and clinicians by showing that a drug is ineffective can be perfectly ethical. Generally, academic freedom permits the pursuit of knowledge on many occasions

that that knowledge affects some people adversely, including, in some studies, affecting bystanders (10). Distinguishing between harms coming from study conduct (e.g., infection) and ones coming from study findings (e.g. lower revenue for manufacturers of drugs found ineffective) is helpful (10). But it, too, fails to capture the full picture. The publication of confidential personal information should typically remain forbidden; and some argue that certain "dual-use" research that could enable, for example, biological weapons should also remain unpublished in order to protect bystanders.

For many of the more minor harms to nonparticipants, self-regulation should play a large part of the solution finally adopted. Many investigators will be first to acknowledge a moral responsibility not to impose serious, unjustified risks on nonparticipants. The current proposal seeks to routinize, systematize, and operationalize that acknowledgement and to offer a menu of potential responses that would help most investigators achieve what they want to achieve anyhow—namely, socially responsible science. This proposal is primarily seeking to make investigators more mindful of potential risks and suggest how to plan studies accordingly. Far from a rigid, fine-grained system of regulations, the resulting guidelines may be as simple as a checklist. That may turn out to be sufficient to create occasion for contemplation of serious adverse effects, their justification, and their possible mitigation.

The proposed reform may even stimulate useful new science. Any attempt to define the likely effects on nonparticipants would encourage investigators to view their interventions from a broader societal perspective. This added step to research planning could highlight important knowledge gaps that further investigation could explore.

It might seem as though, absent a comprehensive theory and policy, it is premature to burden investigators with additional deliberation, writing, and data collection. But the proposed reform is likely to facilitate the emergence of such a comprehensive theory and policy and to make science richer, more responsible, and even more worthy of broad societal support.

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