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Symposium on risks to bystanders in clinical research: an introduction

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Medical and scientific studies have obvious effects on two constituencies: study participants, and the patients in need of the novel interventions that may come out of these studies. Research ethics is often cast as a balance between the important interests of these two constituencies. But studies can affect additional people, whom we shall call “bystanders”. This symposium explores how medical and scientific studies ought to treat bystanders.

Examples

Some medical and scientific studies risk, burden, or otherwise affect bystanders:

- Infectious disease studies can place bystanders at risk of acquiring the infection from study participants. Responses to this risk by researchers and the bioethicists advising them vary. To avoid infecting bystanders, all proposals for SARS-CoV-2 vaccine challenge trials require isolating infected participants for many weeks,² and some critics still worry about the remaining, very small chance of secondary transmissions.³ By contrast, ongoing HIV cure-related studies that ask participants to stop antiretroviral therapy place the sexual partners of study participants at elevated risk of HIV infection (from participants’ heightened viremia during the interruption), and some partners may be infected without realizing that they need treatment—a precarious situation.⁴ Yet in these HIV cure-related studies, there is little if any willingness to isolate study participants, for any period.⁵ And multiple COVID studies risk infecting staff or, at one of our universities, may have already infected caused staff to get infected, during study

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²Eyal, N., et al. (2020). Human challenge studies to accelerate coronavirus vaccine licensure. *Journal of Infectious Diseases* 221: 1752–1756; WHO Working Group for Guidance on Human Challenge Studies in COVID-19 (2020). *Key criteria for the ethical acceptability of COVID-19 human challenge studies*. Geneva, WHO.

³Deming, M. E., et al. (2020). Accelerating Development of SARS-CoV-2 Vaccines — The Role for Controlled Human Infection Models. *New England Journal of Medicine*.

⁴Eyal, N., Holtzman, L. G., Deeks, S. (2018). Ethical issues in HIV remission trials. *Curr Opin HIV AIDS*. 13(5). Eyal, N. and S. G. Deeks (2019). Risk to Nonparticipants in HIV Remission Studies with Treatment Interruption: A Symposium. *J Infect Dis* 220(Supplement_1): S1–S4.

operations or perhaps commuting to work on public transportation, yet, perhaps sensibly at this pandemic time, the studies continue nevertheless.⁶

- Studies can expose bystanders to other physical risks. A former colleague runs a study that gives women in developing countries gas ovens to replace smoke-emitting ovens. She shared that the Institutional Review Board (IRB) raised concerns about the risks to the study participants from a potential gas explosion, but never asked about risks to the participants' neighbors and families. Such explosions would affect all.
- Risks to researchers may become a safety concern, especially for student researchers.⁷ A research assistant may be at risk of assault when interviewing participants.⁸ Another research assistant could be traumatized from sitting with participants as they watch a graphic video – while watching the video once will cause only minimal harm to each study participant, watching it repeatedly may cause measurable psychological harm to the assistant.⁹
- Studies can pose informational risks to bystanders. Publication of some studies would unintentionally reveal the stigmatizing genetic makeup of participants' relatives, who are bystanders, unless researchers take the appropriate precautions.¹⁰ Even unpublished data may reveal to the study team that participants' relatives may carry a genetic disorder, raising ethical questions on what to do next, e.g. contacting and potentially startling these bystanders on what may turn out to be nonactionable information or a false positive.¹¹ Discovery of non-genetic information can also put bystanders at risk. When a participant reports partner abuse, should researchers share the participant's report with law authorities? What if the participant reports purely legitimate partner behavior that may nevertheless be subpoenaed by an oppressive government persecuting the partner for political reasons?
- Caretakers of study participants can also become bystanders when helping these participants contribute to research is onerous, or risky. For example, caretakers may need to take participants to multiple study visits, administer additional medications, maintain frequent contact with investigators, and even report on their own levels of distress. Caretakers will typically give no informed consent to this added burden.¹²

⁵Peluso, M. J., et al. (2020). A collaborative, multidisciplinary approach to HIV transmission risk mitigation during analytic treatment interruption. *J Virus Erad* 6(1): 34–37; Eyal, N. and M. Magalhaes (2019). Is it ethical to isolate study participants to prevent HIV transmission during trials with an analytical treatment interruption? *J Infect Dis* 220(Supplement_1): S19–S21.

⁶Email correspondence with Howard Kipen and Reynold Panettieri, 14 September 2020.

⁷Canadian Institutes of Health Research. (2014). *Tri-council policy statement: Ethical conduct for research involving humans* (TCPS2 2014 ed.): Interagency Secretariat on Research Ethics.

⁸Naufel, K.Z. and D.R. Beike (2013). The ethical treatment of research assistants: are we forsaking safety for science? *Journal of Research Practice* 9(2), Article M11.

⁹Naufel, K.Z. (2017). Do no harm (unless it's to a research assistant?). *APS Observer*. 30(4).

¹⁰Virginia Commonwealth University. Mid-Atlantic twin registry 2017 [updated April 24, 2017. Available from: <https://matr.vcu.edu> accessed March 16, 2018.

¹¹Francis, L.P. (2014). Genomic knowledge sharing: A review of the ethical and legal issues. *Applied & Translational Genomics*. 3(4): 111–115.

When human bystanders are heavily affected, burdened or placed at risk, should they not receive the same standard protections that participants receive? In the US, the strict legal answer is No. The US Department of Health and Human Services defines a human subject as “a living individual about whom an investigator... obtains (1) Data through intervention or interaction with the individual, or (2) Identifiable private information.”¹³ This definition enables study risks and burdens to befall non-subjects in two ways. First, risks and burdens can accrue to a person on whom data is collected (intentionally or not) through channels other than intervention or interaction, e.g. through public and non-identifying records.¹⁴ Second, risks and burdens can accrue to a person on whom data is not collected.¹⁵ The same US law provides protections from the effects of research, but only for research “involving human subjects.”¹⁶ While that language is strictly-speaking open to the interpretation that in human subjects’ research, IRBs should protect bystanders as well, the US Food and Drug Administration’s (FDA) definition of an IRB may rule that out: “The primary purpose of [IRB] review is to assure the protection of the rights and welfare of the human subjects.”¹⁷ The US FDA law, at least, does not demand protection of bystanders, and may even open the possibility that protecting them constitutes overreach.

It follows that the IRB that puzzled our researcher colleague by failing to consider risks from a study-borne gas explosion to neighbors (while inquiring about the risks to the participant) was acting precisely in line with US law. Perhaps inappropriately, US IRBs are currently legally authorized to protect participants, and, with few exceptions,¹⁸ not other people at risk.

¹²Lingler, J., Parker, L., DeKosky, S., & Schulz, R. (2006). Caregivers as Subjects of Clinical Drug Trials: A Review of Human Subjects Protection Practices in Published Studies of Alzheimer’s Disease Pharmacotherapies. *IRB: Ethics & Human Research*, 28(3), 11–18.

¹³US 45 CFR § 46.102 (f), PROTECTION OF HUMAN SUBJECTS Subpart A—Basic HHS Policy for Protection of Human Research Subjects. Definitions.

¹⁴The same law clarifies: “Intervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject’s environment that are performed for research purposes.” Hence, the said “interventions” do not cover all medical interventions that put people in harm’s way, just interventions to collect data (Ibid.).

¹⁵Interestingly, the 2012 Ottawa Statement on the Ethical Design and Conduct of Cluster Randomized Trials (CRTs) defines study subjects (in CRTs) in a way that may initially seem to make all people affected by CRTs (and whom US law CFR46 would sometimes regard as mere bystanders) into subjects: “A research participant can be identified as an individual whose interests may be affected as a result of study interventions or data collection procedures.” The Ottawa Statement proceeds to clarify: “That is, an individual (1) who is the intended recipient of an experimental (or control) intervention; or (2) who is the direct target of an experimental (or control) manipulation of his/her environment; or (3) with whom an investigator interacts for the purpose of collecting data about that individual; or (4) about whom an investigator obtains identifiable private information for the purpose of collecting data about that individual. Unless one or more of these criteria is met, an individual is not a research participant” (and see similar clarifications in McRae, A.D., Weijer, C., Binik, A., White A., Grimshaw, J.M., Boruch, R.,... Taljaard, M. (2011). Who is the research subject in cluster randomized trials in health research? *Trials* 12(183) doi: 10.1186/1745–6215-12–183). However, a lab worker who gets infected would not count as a participant because she does not meet conditions (1)–(4). So the clarification shows that the Ottawa statement also fails to count all affected parties as subjects, and thus fails to support typical subject protections and rights for at least some whom US law could consider mere bystanders, ineligible for human subject protection.

¹⁶US Code of Federal Regulations, Title 45—Public Welfare, Subtitle A—Department of Health and Human Services, Subchapter A—General Administration, Part 46—Protection of Human Subjects, § 46.101 (a). Likewise, § 46.111 and § 46.120 condition approval on the benefits to the subject and to society alike, but when it comes to risk, solely on risks to the subject herself, and their minimization. §45CFR46.111(2) even adds “The IRB should not consider possible long range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.” That sentence may even forbid IRBs from heeding risks of potential abuse of published study findings, e.g. the development of biological warfare that would affect non-subjects. While IRB practice may be very different, the strict letter of this law affords little if any protection to bystanders.

¹⁷US Code of Federal Regulations, Title 21—Food and Drugs, Chapter I—Food and Drug Administration, Department of Health and Human Services, Subchapter A—General, Part 56 -- Institutional Review Boards§ 56.102(g).

¹⁸One exception to the general non-protection of bystanders concerns fetuses: §§ 46.203–4. Another small exception is that prompt reporting to IRBs or other relevant agencies is required midway through a study if there turn out to be *un*anticipated risks to subjects “or others” (§ 46.103(5)).

Ethical questions

Is the US legal landscape the way it should be? What protections would be appropriate for bystanders and what other legal rights should bystanders have (e.g., to consent, ancillary care, sharing of research results, and other alleged rights of study participants)? How much priority should researchers place on protecting bystanders when those protections conflict with participant protection, or with generating novel interventions for patients everywhere? Operationally, who should protect bystanders and guard their rights—IRBs? Other special committees? Investigators? Funders? Insurers? Governments? Finally, what can the appropriate standard for bystander protection teach us about the appropriate standard for participant protection?

Two groups of background inquiries may help delineate the obligations concerning research bystanders. First, do studies affect bystanders differently than they affect participants—potentially calling for different responses? For example:

- When bystanders who are affected by studies, are they typically affected more positively or negatively than these studies' participants, and to what degree? An influential document in research ethics states that "Human participants are unique among the many parties involved in research, because they bear the primary risks of the research."¹⁹ HIV cure-related studies with an interruption of antiretroviral therapy may constitute an exception. The least manageable risks of these studies may befall partners to unstable sexual relationships when they remain unaware that they were infected. Although these studies may put participants at serious risk as well, bystanders not participants may be said to bear the most serious study risks.
- Are bystanders affected as much as participants only *ex post* (that is, as eventually impacted by study interventions)? Or also *ex ante* (that is, in the prospects that they face before these interventions commence)? When a study with long antiretroviral interruption commences, partners to unstable sexual relationships remain unidentified, keeping the risk of infection to any (as yet, potential) partner low. How much does that excuse harm that may later ensue to such a sexual partner?
- Are all effects on bystanders mere side effects of these studies' intended effects (and therefore, on some ethical theories, command lower priority than the latter)? Alec Walen's contribution to this symposium argues that (usually) that is the case. For example, an HIV-cure related study with an interruption to antiretroviral protection may risk participants' sexual partners, but only downstream from the study's intended effect on the participant. Perhaps contrary to Walen's view, there are other cases, where risk to bystanders seems to be a means to achieving the study aim. A researcher may do something to a bystander only in order to check how that would affect the bystander's spouse, and by

¹⁹Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, Social Sciences and Humanities Research Council of Canada. (2014). Tri-Council Policy Statement (TCPS2): Ethical Conduct for Research Involving Humans, p. 16.

gathering data only on that spouse, who is therefore the study's participant. A hypothetical case in point: Researchers wish to check if long wait times for elective orthopedic surgery suppress patients' spouses' salaries (e.g. by forcing the spouses to put in extra domestic work that interferes with their work for pay). To gauge the impact of these wait times on spouses' salaries, investigators obtain consent from the spouses to randomize these orthopedic patients to get the surgery either a few weeks or a few months from when the initial diagnosis was made. There is no deceit, but researchers do not seek the patients' consent for the surgery assignment date. The research team then asks the patients' spouses to complete a survey about their salaries and domestic work before and after the surgery. The research team then compares the spouses' reported salaries (and domestic workload) in different periods and checks if differences are more extreme for spouses of orthopedic patients who waited for longer. Here, researchers gather data only on the spouses, who therefore are the only study subjects; the orthopedic patients are bystanders. But a means to conducting the study is these orthopedic patients' surgery deferrals. Indeed, the main medical effect befalls these bystanders, not the study subjects. Walen might respond that it is precisely for these reasons that, intuitively, this study is not ethically conducted.

Perhaps however we do need to settle these general questions. A second group of questions that may help delineate obligations toward bystanders demarcates different ways in which a particular study might impact them. These questions arise regardless of how study impacts on these two constituencies compare in general. For example:

- In a particular study, who is most affected? Who is most affected as a means to the study's ends?
- In a particular study, is a given risk that someone will be harmed scattered evenly across a large and relatively unidentifiable population, or concentrated in a specific small sub-population that is easily identifiable in advance?²⁰ For example, seasonal flu is so infectious that in a seasonal flu challenge study whose participants sleep at home and go to work regularly, even if safety instructions are followed, it remains likely that some person will get the flu from a study participant. Yet the identity of the person who acquires this typically-moderate condition is highly unclear in advance. On the other hand, in a seasonal flu challenge study that isolates study participants while they are infectious, their young children may miss their parents whilst away, and experience anything from very mild to severe psychological distress; the potential victims are identifiable, but fewer.²¹
- In a particular study, are bystanders put at risk by study conduct, by the study publication, or by both? For example, do risks to privacy or to social standing

²⁰Ibid: 488, Battin, M.P., van der Heide, A., Ganzini, L., van der Wal, G. & Onwuteaka-Philipsen, B.D. (2007). Legal physician-assisted dying in Oregon and the Netherlands: evidence concerning the impact on patients in "vulnerable" groups. *J Med Ethics*. 33(10):591–7, pp. 594–597.

²¹We thank Yonatan Grad, who helped us improve this example.

come from study interaction and data collection and storage, or from study dissemination? This may matter because publications may be protected by freedom of expression.²²

- In a particular study, are bystanders put at risk by researchers' direct moral failure (e.g. when sloppy research practices release germs near the lab)? Or are they affected only by other parties' moral failures (e.g. when terrorists manage to hack into a study's reasonably protected and encrypted dataset and use its findings to produce and employ biological weapons)? Are they affected by their own failure (staff infection in one of our institution may have resulted from failure to wear a mask on the train journey to the study).²³ Can bystanders be at risk absent moral failure on anyone's part (e.g. when researchers are extremely careful yet germs escape and affect third parties)?
- In a particular study, are bystanders affected in ways that they usually have a right not to be affected? For instance, a study may destroy a non-participating pharma executive's career by carelessly stating publicly that the reason why her spouse was recruited for an HIV Pre-Exposure Prophylaxis study is that she, the executive, had been reported by the spouse to have HIV, a stigmatizing condition. This is something that the researchers are independently forbidden from doing.²⁴ Another study may destroy the non-participating pharma executive's career by showing that her company's drug does not work. This is something that is not independently forbidden. Accordingly, the first study commits an ethical breach and the latter does not.
- Does a particular study put only a few bystanders at risk, or many?²⁵ Other things being equal, the latter raises the likelihood that someone will be harmed.
- In a particular study, are any bystanders already physically and/or socially "vulnerable",²⁶ such that study risks would augment underlying risks to them?

What's coming

The symposium opens with two articles on actual cases. The first, by bioethicists Seema Shah, Franklin Miller, and Holly Fernandez Lynch, describes a Zika virus human challenge study proposal that they had criticized, partly to protect bystanders' health, in a report for the US National Institute of Allergy and Infectious Diseases and Walter Reed Army Institute of Research, which they had authored with others. The report added that if Zika challenge studies later move forward, community engagement would be necessary. In the current symposium, Shah, Miller, and Fernandez Lynch expound the importance of community engagement and how it can mitigate or justify bystander risk.

²²Hausman, D.M. (2007). Third-party risks in research: should IRBs address them? *IRB*. 29(3):1–5.

²³Email correspondence with Howard Kipen and Reynold Panettieri, 14 September 2020.

²⁴Compare: Bärnighausen, T. (2019). Sex partners as bystanders in HIV prevention trials: Two test cases for research ethics. *Clin Trials* 16(5): 455–457.

²⁵Kimmelman, J. (2007). *Missing the Forest: Further Thoughts on the Ethics of Bystander Risk in Medical Research*. Cambridge Quarterly of Healthcare Ethics, 16, 483–490, p. 488.

²⁶Kimmelman (2007): 488.

Historian Susan Reverby examines two pivotal ethics transgressions in human subject research, the Tuskegee-Public Health Service syphilis study in the US, and the Public Health Service sexually-transmitted disease studies in Guatemala. She considers the difference between victims and potential bystanders of these two studies – spouses and children who were later discovered to have syphilis – and what is owed to them, e.g. in terms of apology, financial compensation, and recognition, given that some infections were not proven to be study-borne.

The next group of articles assesses philosophically the moral claims that bystanders have against researchers to not be harmed by their study. First, Alec Walen argues that bystanders' claims differ somewhat from those of study participants because only participants are used as means to conducting the study. Although either group can be placed at risk, only risk to participants is causally upstream from achieving whatever good would justify that risk. Helen Frowe argues that the correct threshold of permissible risk for research bystanders depends in part on whether the prospective scientific gains of the trial may benefit these bystanders, and that bystanders' typical lack of consent to net harms need not pose a moral problem. Matthew Hanser takes it as a given that any risk to bystanders must figure into the decision-making of researchers. Sometimes, that risk is clearly impermissible. Whether bystanders' consent to that risk to them is required will depend among other things on precisely how bystanders are put at risk. Gerard Vong and Meira Levinson ask what should happen when the risk to bystanders cannot be eliminated, just displaced to other people, including study participants.

Legal thinker Holly Fernandez Lynch proposes, perhaps contrarily to some of these philosophers, that the maximal-risk threshold for bystanders who cannot consent should be lower than the one for participants. The former, she argues, cannot consent to risks, so those risks are especially inopportune. She tolerates, however, bystander risks that remain greater than "minimal" (the risk threshold in US law when participants cannot consent). Instead, she proposes keeping risks to bystanders "reasonable" (the risk threshold that US tort law applies to non-research activities).

Ethicists Jonathan Kimmelman and Daniel Wikler debate a question of implementation. Kimmelman argues that research ethics guidelines and regulations should formally protect bystanders. Wikler argues that the IRB system is unsuited to protecting them.

Nir Eyal ends the symposium with the suggestion that thinking about protecting bystanders can challenge thinking about protecting participants. Specifically, the appropriate standard for bystander protection questions any upper limits on the risks that research may legitimately visit upon participants.

Human subject protection is only one part of research ethics. Another major part is the protection of any human bystanders. The contributions to this symposium attest to the many ethical questions that remain open about protecting that constituency.

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