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Minimal or reasonable? Considering the ethical threshold for research risks to nonconsenting bystanders and implications for nonconsenting participants

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Abstract

When research poses risks to non-participant bystanders, it is not always practicable to obtain their consent. One approach to assessing how much research risk may be imposed on nonconsenting bystanders is to examine analogous circumstances, including risk thresholds deemed acceptable for nonconsenting research participants and for nonconsensual risks imposed outside the research setting. For nonconsenting participants, US research regulations typically limit risks to those deemed to be “minimal.” Outside the research context, US tort law tolerates a more flexible “reasonable” risk threshold. This article advances a preliminary case that nonconsenting participants and nonconsenting bystanders exposed to similar research risks may be entitled to the same level of protection, but that risks generated by research may not be special in kind. Thus, limiting research risks to those that are “reasonable,” rather than demanding that they be held to the “minimal” standard, may be the best approach for both nonconsenting participants and nonconsenting bystanders. Further work is needed to establish whether the descriptive standards used to support the analogies relied on here are normatively justifiable, as well as the extent to which the minimal risk standard and the reasonable risk standard would lead to meaningfully different outcomes in practice.

Keywords

bystanders; challenge trial; minimal risk; reasonable risk; research risk; risk thresholds; third parties

1 | INTRODUCTION

US regulations and most ethical guidelines for conducting research with human subjects focus primarily on the rights and welfare of those deemed to be study participants. Research, however, may also pose risks to others.¹ For example, xenotransplantation research risks introducing new pathogens across species barriers, psychiatric washout studies may lead participants to revert to dangerous behavior posing risk to others, and HIV cure studies that require pausing antiretroviral therapy may expose non-participant partners to infection.

Existing approaches to research risk that focus only on study participants leave a potentially substantial gap in oversight that may be appropriately within the purview of review boards intended to promote the ethical conduct of research.²

One of many unanswered questions in this domain centers on how much risk a study may ethically impose on non-participant “bystanders” in the absence of any regulatory requirement to obtain their consent. To begin answering that question, this article considers analogous circumstances occurring both in research and outside it. In particular, lessons can be drawn from regulations governing research conducted without consent from study participants, which is typically limited to “minimal risk.” However, the phenomenon of one party’s behavior generating negative externalities for unconsenting others is not unique to research. The law of tort applies a “reasonableness” standard to such behavior, considering a balance between benefits, risks, costs, and alternatives.

This article examines both the minimal and reasonable risk thresholds as applied to research risks to nonconsenting bystanders (NCBs), defined here to include individuals falling outside the regulatory definition of research participant and who have not been asked to consent to research risk. It concludes that appropriate selection between the candidate thresholds depends on one’s views regarding the moral relevance of two factors: (1) participation versus non-participation in research; and (2) risks generated by research versus some other source.

The goal is to be hypothesis-generating, offering potential standards for risks posed to NCBs and mechanisms for choosing between them based on the *status quo* in and out of research. The article makes a preliminary case that nonconsenting participants and NCBs are sufficiently similar that they may be entitled to the same level of protection. However, it goes on to suggest that risks generated by research may not be special in kind, such that the reasonableness standard is potentially the best choice for both groups. Not only is this an important conclusion with regard to the largely ignored matter of risks to research bystanders, it also challenges the existing regulatory risk threshold applicable to participants themselves.

2 | BACKGROUND

2.1 | Zika virus challenge trial ethics consult

In a 2017 ethics consultation regarding the possibility of conducting Zika virus challenge trials to speed vaccine development (herein “Zika consult”), one of the issues raised was that bystanders—such as the neighbors and partners of trial participants, as well as fetuses in existence or to-be-conceived—might be exposed to the risks of Zika virus due to the research-induced infection of those enrolled. The consult concluded that because bystanders “generally cannot know about, protect themselves from, or consent to risks, risks to them are only reasonable if they can be reduced to *near-zero*.”³ This is a conservative approach, rooted in the uncertain nature of Zika virus and scope of unanswered questions regarding its transmission and impact, which were substantial in early 2017. The consult also emphasized that nonconsensual risks to bystanders may “invite public concern and threaten trust,” thus calling for substantial scrutiny.⁴

The speed with which the consult was conducted, however, precluded development of new ethical frameworks for risks to bystanders more generally.⁵ Thus, the near-zero risk threshold was adopted largely based on a descriptive approach that asked what risks bystanders have previously been exposed to in other types of research (e.g., Phase I and prior challenge trials). Some existing literature regarding research bystanders weighs risk level and the work that can be done by disclosure and consent,⁶ but none directly addresses, contextualizes, or robustly defends what the maximum permissible risk level ought to be for NCBs. In order to do that, it is helpful to draw comparisons to the sorts of risk permitted to direct participants and those permitted outside the research setting.

2.2 | Caveats and scope

A few preliminary caveats are in order. First, this article assumes that there is a threshold beyond which research risks to bystanders become ethically unacceptable; the focus here is on defining that threshold.

Second, although the universe of bystanders is potentially vast, as a starting point, this article narrows the analysis to “first-order” bystanders, i.e., those individuals impacted by research risks due to their relation to or interaction with research participants, whether or not the specific bystanders are identifiable in advance. This narrowed approach focuses attention on risks stemming directly from the conduct of a specific protocol, as opposed to risks that may arise as a result of how research findings are interpreted or implemented, or risks that can be traced to research priority setting and resource allocation. Although these issues clearly affect non-participants, they go beyond the types of research risks typically given consideration with regard to research participants themselves.⁷ It is possible that the same or similar principles may apply to all types of research bystanders, but there is also reason to think that the more attenuated the risks to bystanders, the weaker the obligation to protect against them.

Third, the focus is on risk of physical harm to bystanders posed by biomedical research interventions, rather than the potential for economic or dignitary harms, and rather than social/behavioral research. Again, the analysis may ultimately be the same, but for purposes of managing scope, the relevance of these distinctions is not examined here.

Fourth, also for reasons of scope, this article considers only analogies drawn from the US legal context, rather than standards that may apply in other countries or that have been articulated in international guidelines.⁸ Assessing whether the analogies developed here also apply to research conducted abroad will be an important task for future work. It is also true that international contexts may offer additional analogies for ethical consideration.

Finally, this article addresses research risks only to those bystanders who have not been asked to provide individual consent, either because it would be impossible for them to do so (e.g., they cannot be identified or they lack capacity) or because asking them to consent would be impracticable for some reason (e.g., concern for participant privacy or not wanting to give bystanders authority to veto participation by others).⁹ Although I suspect that these conditions will often be met, if there are circumstances in which consent from individual

bystanders *is* possible and practicable, it should likely be obtained—and risks limited to those that would be acceptable for individuals consenting to be research participants.¹⁰

Constraining the analysis in these ways permits attention to foundational principles. Thus, the relevant question can be stated as follows: *How much risk of physical harm can biomedical research ethically impose on nonconsenting bystanders?*

3 | REGULATORY APPROACHES TO NONCONSENSUAL RESEARCH RISK AND THE MINIMAL RISK STANDARD

Although US research regulations fail to address risks to bystanders, they provide a helpful foundation because they do not require participant consent in every case. And if research without participant consent is permissible, then it follows that research without bystander consent can be justified on at least the same criteria. Absent consent in both cases, there is no reason to think bystanders' indirect exposure to research risk should merit *greater* protection, i.e., less risk, than participants' direct exposure.

3.1 | Waiver of consent

When participant consent is unobtainable (for some reason other than refusal after having been asked for consent), it is widely accepted that research may ethically proceed only if the risks are quite low.¹¹ This is reflected in the US regulatory criteria allowing waiver of consent by an Institutional Review Board (IRB),¹² which require as one element that the research pose no more than “minimal risk” to participants.¹³ There is a substantial literature addressing the minimal risk definition, which is not without its critics.¹⁴ For present purposes, however, it is sufficient to note that this term is intended to cover low risks keyed to those occurring in the course of daily life without holding research to an impossible standard of protecting people from risks they can reasonably be expected to bear outside of research. Risks that would be defined as minimal for research participants could also be defined as minimal for bystanders.

The fact of minimal risk alone is insufficient to waive participant consent.¹⁵ The US regulations also require that waiver not adversely affect participant rights or welfare, that it would be impracticable to conduct the research if consent were required, that the participant be provided with additional information later where appropriate, and that the research would be impracticable without retaining identifying information about participants.¹⁶ Critically, however, none of the consent waiver criteria involves a balancing of risks and benefits. In other words, the presence of benefits to participants or society more generally—no matter how high—will not suffice to permit consent waiver for greater than minimal risk research under US regulations.

Although not technically applicable to them, when the regulatory waiver criteria are satisfied for NCBs, the fact of their nonconsent seems unremarkable. After all, they would be at least as well protected as nonconsenting participants despite being a step removed from the research. Thus, it seems that NCBs can be acceptably exposed to minimal risk, assuming the other protections relevant to consent waiver are also in place. But can they be exposed to *more*?

3.2 | Other examples of research permitted without consent

There are several other examples in which US regulations allow research¹⁷ to proceed absent direct, prior consent from participants, which can be examined to assess whether greater risks without consent might be permissible. As described below, however, these examples typically involve either minimal risk, akin to waiver of consent, or delayed and/or substitute consent, which is distinct from the total absence of consent or permission characterizing NCBs.

3.2.1 | Exempt research—The regulations exempt from regulatory compliance—including the typical requirements around informed consent—a number of research activities, such as certain types of educational practices and tests, certain surveys and interviews, and certain research on data and biospecimens collected for other purposes.¹⁸ However, the various exempt categories are viewed as so low risk (either inherently or due to the existence of other protections imposed beyond the research setting) that comprehensive research oversight is unnecessary. Thus, they offer no support for the possibility of exposing NCBs to greater than minimal risk.

3.2.2. | Emergency research—The regulations do permit research posing greater than minimal risk to proceed without prospective consent from participants in certain emergency settings in which consent is not possible.¹⁹ However, there are a number of requirements that distinguish this scenario from that typically facing NCBs, including that participants face an immediately life-threatening situation, available treatments are unproven or unsatisfactory, and participation offers the prospect of direct benefit.

Consent waiver for emergency research is also disanalogous to the circumstances surrounding NCBs for another important reason, which is that research participants, or their legally authorized representatives (LARs), must be informed of their inclusion in the research at the earliest possible opportunity and given an opportunity to discontinue participation if not already complete.²⁰ This might be viewed as a delayed consent requirement, with a preserved right of withdrawal. NCBs, however, may be completely powerless to discontinue their exposure to research risks, if they are even aware of them.

3.2.3 | Research with incompetent participants—Greater than minimal risk is also permitted for research involving incompetent adults, despite the fact that they cannot consent to research participation themselves. In these contexts, however, the regulations require that consent be obtained from the participant's LAR,²¹ or waived under the criteria described above. Although there is no explicit regulatory risk threshold applicable to research in this population, LARs have a responsibility to protect participant interests, which likely precludes substantial risk not justified by the prospect of direct benefit. Ultimately this example is also distinct from the case at hand for NCBs, who may be perfectly competent to consent to research risks and for whom no one would be consenting on their behalf.

For similar reasons, any analogy that might be drawn between NCBs and research with children also fails. The pediatric research regulations permit children to be included in research without their direct consent, including for greater than minimal risk research, depending on potential benefits.²² However, they demand permission from the parent(s) of

pediatric participants (or some suitable advocate), and encourage seeking assent from older children when possible.²³ In contrast, there is no authorized guardian providing permission on behalf of NCBs in the conditions under consideration here.

3.2.4 | Research with fetuses—US regulations directly address risks to nonconsenting individuals incidentally affected by research participation in one circumstance—namely, the fetus in research involving pregnant women.

Certain research involving pregnant women is limited to minimal risk,²⁴ and another category involves research with the prospect of direct benefit solely to the fetus.²⁵ Neither scenario adds much to the analysis regarding NCBs, given the default already established above of a minimal risk threshold, and the fact that the exclusive derivation of direct benefit from research (i.e., skipping over participants) would be exceptional for bystanders.

In contrast, when research is done with the prospect of direct benefit solely to the pregnant woman, the fetus begins to look more like a true NCB. Here, the regulations demand consent only from the pregnant woman as the research participant, and that consent is not clearly intended to serve also on behalf of the fetus, given the potential conflict between their interests. Risks to the fetus in these scenarios are permitted to be greater than minimal so long as they are caused only by interventions or procedures holding the prospect of direct benefit for the pregnant woman.²⁶

Despite certain similarities to research risks to NCBs, this approach cannot support a broad conclusion that the prospect of direct benefit to research participants can override the interests of others, who may be exposed to greater than minimal risk without their consent. This is because the relationship between a pregnant woman and her fetus is unique, characterized by complete physical dependence and unilateral control. At least for a significant portion of the gestational period, the pregnant woman bears a constitutionally protected right to terminate the life of the fetus, and potentially to engage in behaviors that expose the fetus to substantial risk.²⁷ Importantly, there are no similar circumstances in which research participants and bystanders stand in this sort of relationship to one another.

3.2.5 | Agency waiver—Finally, there is one other circumstance in the US regulations that would permit research participants to be exposed to greater than minimal risk without their consent. Department or agency heads are granted plenary authority to waive regulatory requirements that would otherwise be applicable for specific research activities or classes of research activities, provided that alternative procedures are used consistent with the Belmont principles.²⁸ It is also required that the public be notified of proposed waivers and provided the opportunity to comment. This means that it is possible under the regulations for consent to be waived, in whole or in part, even when the usual standards for consent waiver, including minimal risk, cannot be satisfied.

This is a rarely exercised regulatory authority, used only four times since 1982, including to permit a Medicaid demonstration project conducted by the government, to broadly permit emergency research under FDA regulations as described above (despite inability to satisfy Common Rule consent waiver standards), and to permit certain epidemiologic research on

prisoners that does not exceed minimal risk.²⁹ Given that this waiver authority is truly exceptional, and that there is no evidence that it would be granted for a complete waiver of consent for research involving greater than minimal risk of physical harm, it does not offer strong support for deviation from the minimal risk threshold for NCBs. Nonetheless, it does seem to reflect an opening for the reasonable risk threshold described in section 5.

4. | IS MINIMAL RISK THE RIGHT STANDARD FOR NONCONSENSUAL RESEARCH RISKS TO BYSTANDERS?

This review of the US regulations suggests that, at the very least, it may be justifiable to impose minimal research risks on NCBs, as a matter of consistency. But since there are no regulatory analogies that would support imposing greater than minimal risks on NCBs (Table 1), must such research be blocked? In other words, should risks to NCBs be bound by the same parameters as risks to nonconsenting participants?

As a preliminary matter, note that the practical impact of this question depends on what counts as minimal risk, which under the US regulations is determined by comparison to the probability and magnitude of harm or discomfort ordinarily encountered in daily life or routine examinations.³⁰ Since daily life is not without risk, the minimal risk standard is distinct from a “near-zero” threshold. However, its application requires information about both the risks of daily life and the risks of research, which can sometimes be elusive and difficult to parse, as well as an understanding of whose daily life should serve as the relevant comparator.³¹

For example, one interpretation of the minimal risk standard might determine that the risks to NCBs of a Zika virus challenge study that could not perfectly protect against transmission to nonparticipants would qualify as minimal if the study was conducted at a site at which people generally face the possibility of Zika infection in their daily lives, but greater than minimal if conducted elsewhere. In the former scenario, the study would entail a risk similar to what might be present outside the research; in the latter, the study would entail a unique risk largely absent outside the research. Ultimately, a near-zero risk threshold for NCBs, as applied in the Zika consult, would bar this study from proceeding in any location, whereas a minimal risk threshold might allow it to proceed at some sites but bar it at others—or potentially bar it everywhere if the relevant daily life comparator is deemed to be universal rather than local.

The key point is that the minimal risk threshold could be used to constrain important research if applied to NCBs, with implications for scientific advancement. Of course, this is also true when the minimal risk threshold applies to nonconsenting participants—or when any risk threshold applies to research. Ultimately, research that would be socially valuable sometimes cannot be conducted ethically or in accordance with the regulations. So we must return to the question of consistency: is there good reason to treat NCBs differently from nonconsenting participants?

When researchers impose risks on participants to advance the ends of research, i.e., the creation of socially valuable knowledge, they incur special responsibilities based on the

principles of reciprocity and avoidance of exploitation.³² Thus, researchers must impose only those risks and burdens necessary to obtain that valuable knowledge, adequately care for participants in the event of harm, and potentially offer certain benefits. Consent offers some (imperfect) protection against the possibility that participants will be used as mere means to advance research ends, and in the absence of consent, researcher obligations are heightened.

Critically, the key source of these researcher obligations carries over to bystanders, on whom risks may necessarily be imposed to advance the ends of research. These risks may be substantial and foreseeable, just as they are to participants, and they represent a type of bystander contribution to the research enterprise that is susceptible to exploitation—namely, bystanders may be unfairly taken advantage of if the risks to which they are exposed are not given adequate consideration and balanced against appropriate protections. This is not to say that bystanders and participants are identical, but when the risks look similar, stem from the same source, are similarly foreseeable, and are of the same magnitude, it is unclear that we can justify differential treatment based simply on the fact that researchers directly intervene upon or interact with participants, or use their identifiable information, whereas they do not with bystanders. Why, for example, should researchers have an obligation to protect those they would directly infect with Zika virus but not those whom they can foresee will be infected with Zika virus as a result of their actions? Moreover, exposure to research risks can implicate public trust whenever it is unconsented—perhaps even more so for bystanders to whom risks are not required to be formally overseen by the IRB. This all seems to bear in favor of a presumption that the minimal risk threshold applicable to nonconsenting participants should also apply to NCBs. Indeed, a recent examination of the guidelines and literature addressing research risks to bystanders revealed that several commentators suggest granting bystanders protections similar to those granted to research participants, although there is substantial diversity in the positions taken.³³

Given that this remains an open question, it is important to consider alternative risk thresholds for NCBs should the minimal risk standard be deemed too restrictive or otherwise inappropriate. In addition, consideration of alternatives helps to highlight the potentially unique nature of the minimal risk standard in comparison to thresholds applicable outside the research context, raising important questions about whether that unique approach is justified for participants, let alone bystanders.

5 | AN ALTERNATIVE APPROACH TO NONCONSENSUAL RESEARCH RISK: THE REASONABLENESS STANDARD

If we look outside the context of research, the tort of negligence provides a useful lens by which to assess the appropriate threshold for nonconsensual research risk because it too involves the imposition of harm on others without their consent.³⁴ Importantly, however, not every nonconsensual harm leads to some party's liability for negligence; some harms are permissible, even if they are greater than minimal.

In US law, a tort is a legal wrong, against either a person or property, leading to civil (rather than criminal) liability. Negligence is a type of tort claim involving an unintentional wrong

that occurs as a result of a party's failure to act with due care. For negligence liability to attach, there must be (1) a duty of one party to the other, and (2) breach of that duty must have (3) caused (4) damages. Thus, in negligence, the focus is first on the presence and scope of the duty and breach (i.e., rights violation), and only then on the harm. Moreover, there is no clear harm (or risk) threshold that if surpassed will automatically result in negligence liability, nor is there some level of harm below which liability necessarily will be avoided.

The key point is that negligence law permits one party to impose risk and burden on another without consent for doing so (or without consent to the level of risk and burden imposed) and without any compensation so long as no duty has been breached. The duty imposed by negligence is not to limit one's behavior to minimal risk (or minimal harm), as required for research consent waiver, but rather a duty to behave *reasonably*. Importantly, what is reasonable is heavily context-dependent. In contrast, while the minimal risk standard contextualizes research risk against the risks of daily life, it does not consider additional context such as potential benefits and available safeguards.

Others have contemplated the possibility of tort liability in the context of research risks to bystanders, asking whether bystanders might have a legally cognizable cause of action for negligence if harmed by research.³⁵ The first question in such an analysis is whether anyone owes a duty to bystanders. Although this is a contested question,³⁶ for purposes of this article, I have assumed the answer to be yes—otherwise risk thresholds for NCBs would be irrelevant because no one would be responsible for abiding by them. If there is such a duty, then, what would it entail?

In general, the duty of care in negligence is defined by asking “what would a reasonably prudent person have done in this situation?”³⁷ Answering that question involves balancing a variety of factors.³⁸ On one side is the social value of the interest sought to be advanced by the conduct that is causing (or at risk of causing) harm and the possibility of advancing that interest through an alternative, less damaging course of conduct.³⁹ On the other side is the social value of the interest imperiled by the conduct,⁴⁰ as well as the ability to self-protect in light of the obviousness of a potential danger.⁴¹ Thus, the reasonableness standard in negligence takes into account the magnitude and likelihood of the harm that may be caused, just like the minimal risk standard. However, it also considers the feasibility and burden of preventing or reducing the harm through various precautions (and who can reasonably be expected to bear those burdens), as well as the utility of the conduct in question.⁴²

Ultimately, the reasonableness standard can be used to justify high risk to others if there is also high value in the conduct at hand and appropriate precautions have been taken to avoid unnecessary risks in light of the nature of those risks and burden of avoiding them. It is important to note that this combination of factors is often elusive. Many reported negligence cases ultimately result in liability either because the conduct that caused harm is deemed to have insufficient social value or inadequate precautions were taken. Where the behavior that causes harm is clearly reasonable given the circumstances, there is a lower likelihood of a negligence action being brought in the first instance, let alone proceeding to the point of a judicial decision. Nevertheless, the fact that negligence cases often lean toward findings of

unreasonable risk does not mean that high risks are unreasonable, nor does it change the well accepted legal standard for evaluating the breach component of negligence liability based on a balancing of risk, utility, and precautions in order to assess reasonableness.⁴³

While this balancing is utilitarian at heart, it is also capable of incorporating deontological principles, giving substantial attention to the interests of the party that may be exposed to harm. To take an extreme case, a reasonableness analysis would not conclude that it is acceptable to kill a person in order to harvest their organs to save several others, given the inherent value of the interest imperiled by the conduct, namely the inalienable right to life. In this regard, a reasonableness analysis can account for the importance of advancing foundational principles, such as autonomy, beneficence, and justice.

To understand how the reasonableness standard might apply in the context of a negligence action, consider the behavior of running on a crowded subway platform. In the first case, a man runs in order to prevent a toddler from falling onto the tracks and being struck by an oncoming train, while yelling for others to “Get out of the way!” If the runner collides with a bystander, breaking her arm, his conduct is nonetheless likely to be deemed reasonable by a court considering a negligence claim brought by the bystander, given the relative interests at stake and the efforts taken to avoid the collision. The bystander has suffered substantial harm, but only to prevent more serious harm. In the second case, the man runs not to save a child in danger, but rather to avoid missing his train and arriving late to work. If he breaks the bystander’s arm, his conduct will almost certainly be deemed unreasonable. The harm is the same in both cases, but reasonableness is dictated by the context. And this is the key point: although different decision-makers may reach different conclusions depending on their balancing of the relevant facts, the reasonableness standard allows consideration of the potential benefits of the activity in question when determining whether the associated risk of harm is acceptable and what precautions are appropriate.⁴⁴ In contrast, the minimal risk standard considers the level of risk in isolation without regard to the benefits that may accrue as a result of its imposition.

Applying these principles to a research setting, consider again the example of a Zika virus challenge study. It may be that the importance of the research—in particular, the potential to develop ways to prevent severe damage to affected children in the future—renders proceeding with it reasonable even if the study poses substantial risks to bystanders. The nature of the risks in this case suggests that substantial care must be taken to avoid them, including by favoring less risky alternative designs whenever possible; reasonableness demands that greater risk be met with greater care. But the risks need not be eliminated completely or even rendered minimal for reasonableness to be achieved if there is a sufficient possibility of countervailing social value. Instead, the duty is to balance potential benefits and risks, and to *minimize* risk through feasible and appropriate precautions, a familiar concept in research ethics that demands risks be limited only to those necessary to achieve a study’s valuable aims, without restricting the risk level itself. For this reason, the reasonable risk standard should not be conflated with a *high* risk threshold; it does not always permit high risk, although it sometimes may. When the benefits of an activity are unlikely or trivial, however, the reasonableness standard will allow little to no risk.

Thus, whereas a minimal risk standard would flatly preclude greater than minimal risks to NCBs, a reasonableness standard drawn from tort law analogies might permit them. More starkly, the same Zika virus challenge study that might be barred under a minimal risk standard (on at least some interpretations, at least at some sites) could potentially be allowed under a reasonable risk standard, assuming a finding of adequate social value and precautions. When there is insufficient social value to justify heightened risk, however, both standards may reach the same result.

It is important to acknowledge that both the minimal risk standard and the reasonable risk standard are incapable of producing formulaic results with perfect consistency from decision-maker to decision-maker, or IRB to IRB. Evidence demonstrates that IRBs struggle to apply the minimal risk standard as the risks of daily living are not always clear or statistically accessible.⁴⁵ Similarly, because the reasonable risk standard entails weighing competing considerations, different people may weigh them differently.⁴⁶ The potential for inconsistency and/or disagreement in interpretation is a weakness of both standards, but the reasonable risk standard offers greater flexibility to consider context. Whether this is desirable depends largely on one's views as to whether the research regulations (potentially more conservative) or tort law (potentially less conservative) offer the right level of protection to those exposed to risk without consent.

6 | IS REASONABLENESS THE RIGHT STANDARD FOR NONCONSENSUAL RESEARCH RISKS?

Given that we accept the imposition of nonconsensual but reasonable risks outside the research setting, as a matter of consistency we must ask whether this is also the right approach to NCBs exposed to research risks—and indeed, the right approach for anyone exposed to research risks. The discussion above in section 4 suggested that nonconsenting participants and NCBs may be entitled to the same level of protection, but the more specific question that now arises is whether the *source* of those risks matters: should research risks be regulated differently than other types of risk?

This question strikes at the heart of the exceptional regulatory system applicable to research. The history of scandal and importance of public trust to the research enterprise have been held up to support the application of more stringent standards,⁴⁷ but it is possible that a reasonableness standard for nonconsensual research risk would have sufficient flexibility to avoid scandal and protect public trust. The most concerning examples of nonconsensual research—take the Tuskegee syphilis study or Guatemala STD inoculation studies, for example—are often concerning precisely because of their unreasonableness.

There seems to be little to differentiate nonconsensual research risks from the sorts of nonconsensual harms addressed by tort law. The risks of harm may be of similar likelihood and magnitude, and perhaps uncertainty, for research and other types of activities. And although research involves the risk of harm for the benefit of others, the same can be true in the context of alleged torts, as when one party imposes harms on others in the course of conducting some otherwise beneficial activity. The question in tort as in research is how much harm is too much?

It is plausible to hypothesize that nonconsensual risk of harm stemming from research need not be capped at a lower threshold than nonconsensual risk of harm stemming from other types of activities. Indeed, it seems a problematic conclusion to suggest that we must forfeit potential scientific advances even though similar risks might be tolerated in non-research settings (unless we have reason to think that similar risks should *not* in fact be tolerated outside of research). If that is correct, it suggests that the reasonableness threshold from tort law could be justifiably applied to NCBs, and perhaps also to nonconsenting participants, rather than the minimal risk threshold. This could entail heightened protection for NCBs compared to a regulatory system that largely ignores the risks they may face, although it would reflect a less stringent approach to nonconsenting participants than currently required by regulation. If, however, research risk is indeed exceptional in relevant ways, heightened protection beyond tort law standards would be appropriate.

7 | OPEN QUESTIONS

As noted at the outset, the analysis presented here is intended to be preliminary and hypothesis-generating, drawing attention to the lack of a clear standard for research risks to NCBs and the different approach taken to the imposition of risks outside the research setting. In addition to the questions left open above about whether research participation is special (as compared to bystander status) and whether research risks are special (as compared to non-research risks), as well as the scoping caveats mentioned previously, there are several other components of the analysis that require further consideration.

Perhaps most important is that the entirety of the argument so far has rested on use of analogical reasoning, taking for granted that the analogies used for comparison rest on solid normative ground and focusing instead on whether deviation from those analogous circumstances can be justified as a matter of consistency. But perhaps the minimal risk standard is not really appropriate for nonconsenting participants or the reasonable risk standard is not appropriate for assessing negligence. The next step is to move beyond reliance on analogies to focus on the normative force of the argument that nonconsensual risks should be held to a threshold of reasonableness in and out of research. There are likely also other analogies worth considering beyond those introduced here.⁴⁸

It also remains to be seen whether the outcomes of applying the minimal risk standard and the reasonable risk standard would be meaningfully different in practice. Outcomes could converge for at least two reasons. First, given the difficulty of understanding and applying the minimal risk standard, review boards may already be applying something like the reasonableness standard as a heuristic for whether research without consent is acceptable. Second, perhaps the risks of daily living are synonymous with those that are reasonable. On the other hand, perhaps the risks of daily living are necessarily reasonable, but greater risks may be reasonable too.

Overall, it could be helpful to examine the minimal and reasonable risk standards empirically, for example, asking various review boards to apply them to the facts of several research protocols to assess whether and to what extent they come out differently and why. Community consultation could also be a helpful way to determine what should be viewed as

reasonable and whether trust in research might be negatively affected by application of the reasonable versus minimal risk threshold.

8 | CONCLUSION

Instead of the current regulatory vacuum, this article has sought to introduce two potential options for how review boards could analyze research risks to NCBs: either a minimal risk threshold adopted from the approach taken to waiver of participant consent, or a reasonable risk threshold adopted from nonconsensual harm regulated by tort law. The right approach to NCBs depends on whether one believes that bystanders are meaningfully different from participants when neither is consenting, and on whether one believes that research risks are somehow special. Although arguments have been advanced to challenge both premises, further analysis of these issues of research exceptionalism is needed in this specific context of bystanders. Nonetheless, the realm of possibilities has helpfully been narrowed: research risks to NCBs should not be ignored completely and probably do not need to be limited to “near-zero” given relevant comparators.

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Biography

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2. See Kimmelman J. (2007). Missing the forest: Further thoughts on the ethics of bystander risk in medical research. *Cambridge Quarterly of Healthcare Ethics*, 16, 483–490. [PubMed: 18018930]
3. Shah SK, Kimmelman J, Lyerly AD, Fernandez Lynch H, McCutchan F, Miller FG, ... Zorrilla C. (2017). Ethical considerations for Zika virus human challenge trials: Report and recommendations (p. 16). (emphasis added). Retrieved from <https://www.niaid.nih.gov/sites/default/files/EthicsZikaHumanChallengeStudiesReport2017.pdf>.

4. Ibid.
5. Ibid: 8.
6. See, e.g., Resnik & Sharp, op. cit. note 1, pp. 6–7; Battin MP, Francis LP, Jacobson JA, & Smith CB (2009). The patient as victim and vector: Ethics and infectious disease. Oxford University Press (Ch. 10); Kimmelman, op. cit. note 2, 488.
7. See 45 C.F.R. 46.111(a)(2) (2019)
8. For an overview of approaches to bystander research offered by different international guidelines, articles, and trials, see Eyal N, Kimmelman J, Holtzman LG, & Lipsitch M. (2019). Regulating impact on bystanders in clinical trials: An unsettled frontier. *Clinical Trials*, 16(5), 450–454. [PubMed: 31368813]
9. For discussion of the challenges around third party consent, see Resnik & Sharp, op. cit. note 1, p. 5.
10. Miller FG, and Joffe S. (2009). Limits to research risks. *BMJ*, 35, 445–449.
11. See, e.g., Council of International Organizations of Medical Sciences (CIOMS) (2016). International ethical guidelines for health-related research involving humans: Guideline 10. Retrieved from <https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf>. In contrast to US regulations, CIOMS guidelines indicate that while the minimal risk standard is generally applicable when it is not possible to obtain consent from participants for research offering no potential individual benefits, research ethics committees may permit “a minor increase above minimal risk when it is not possible to gather the necessary data in another population or in a less risky or burdensome manner, and the social and scientific value of the research is compelling.” Guideline 4. Although this approach permits some balancing, the risk standard is still quite low.
12. 45 CFR 46.116(f)(3)(i)(2019). For FDA’s approach to consent waiver, see Guidance: IRB waiver or alteration of informed consent for clinical investigations involving no more than minimal risk to human subjects. July 2017. Retrieved from <https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM566948.pdf>. In November 2018, FDA issued a proposed rule to allow consent waiver by regulation rather than enforcement discretion; the proposed rule remains pending as of February 8, 2020.
13. 45 CFR 46.102(j)(2019).
14. See, e.g., Resnik DB (2005). Eliminating the daily life risks standard from the definition of minimal risk. *Journal of Medical Ethics*, 31(1), 35–38; [PubMed: 15634751] Wendler D. (2005). Protecting subjects who cannot give consent: toward a better standard for “minimal” risks. *Hastings Center Report*, 35(5), 37–43.
15. Gelinas L, Wertheimer A, & Miller FG (2016). When and why is research without consent permissible? *Hastings Center Report*. 46, 1–9.
16. 45 CFR 46.116(f)(3)(2019).
17. The regulations also carve out certain activities from the definition of “research” with “human subjects,” which thereby avoid any requirement to obtain consent. 45 CFR 46.102(e) and (l) (2019). Because these are deemed non-research, they seem to fit best in the context of nonconsensual risks outside the research setting, explored in section 5 below.
18. 45 CFR 46.104 (2019).
19. 21 CFR 50.24 (2016).
20. Ibid.
21. 45 CFR 46.102(i), 46.111(a)(4), and 46.116(a)(1)(2019).
22. 45 CFR 46.404–407 (2019).
23. 45 CFR 46.408 (2019).
24. 45 CFR 46.204(b) and (d)(2019).
25. 46 CFR 46.204(b)(2019).
26. 45 CFR 46.204(d) and (b)(2019).
27. But see Goodwin M. (2014). Fetal protection laws: Moral panic and the new constitutional battlefield. *California Law Review*, 102(4), 781–875.
28. 46 CFR 46.101(i)(2019).

29. Office for Human Research Protections (2016). Federal Notices for Secretarial Waiver. <https://www.hhs.gov/ohrp/regulations-and-policy/guidance/secretarial-waivers/index.html>.
30. 45 CFR 46.102(j)(2019).
31. See, e.g., Rid A. (2014). Setting risk thresholds in biomedical research: Lessons from the debate about minimal risk. *Monash Bioethics Review*, 32, 63–85. [PubMed: 25434065]
32. Litton P, & Miller FG (2005). A normative justification for distinguishing the ethics of clinical research from the ethics of medical care. *Journal of Law, Medicine, and Ethics*, 33(3), 566–574.
33. Eyal, Kimmelman, Holtzman, & Lipsitch, op. cit. note 8. For an argument against according bystanders the same rights and protections as participants, see Eyal N, & Wikler D. (2019). Ethical complexities of responding to bystander risk in HIV prevention trials. *Clinical Trials*, 16(5), 458–460. [PubMed: 31368789]
34. There might have been consent to the activity, but not for the harm or the particular risk.
35. Resnik and Sharp, op. cit. note 1, p. 6.
36. See Eyal & Wikler, op. cit. note 33 (arguing against a duty to research bystanders); *Kennedy Krieger Inst., Inc. v. Partlow*, 460 Md. 607 (Ct. App. Md. 2018)(finding a duty to a research bystander).
37. 57A Am. Jur. 2d Negligence § 7 (2017); 57A Am. Jur. 2d Negligence § 155 (2017).
38. This balancing test for negligence was famously described in *United States v. Carroll Towing Co.*, 159 F.2d 169 (2d Cir. 1947).
39. 57A Am. Jur. 2d Negligence § 158 (2017).
40. 57A Am. Jur. 2d Negligence § 159 (2017).
41. 57A Am. Jur. 2d Negligence § 155 (2017).
42. 57A Am. Jur. 2d Negligence § 8 (2017).
43. Restatement (2d) of Torts (1965). § 291 Unreasonableness; How Determined; Magnitude of Risk and Utility of Conduct; § 292 Factors Considered in Determining Utility of Actor's Conduct.
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46. For example, in November 2019, a jury awarded damages to a sibling bystander living in the same home as a participant in the Kennedy Krieger Institute's lead paint abatement study. Although juries do not issue opinions with their decisions, this jury must have determined that the risks to which the sibling was exposed were unreasonable under the circumstances. This is a contested conclusion, however, given arguments that the study's risks were minimal in light of the non-research alternative of living in homes that had not undergone lead abatement. Ross LF (2002). In defense of the Hopkins lead abatement studies. *Journal of Law, Medicine, and Ethics*, 30(1), 50–57. It is also possible to contest whether adequate precautions were taken. The case is currently under appeal. Cohn, M. (Nov 14, 2019). Court orders Kennedy Krieger to pay woman harmed in 1990s-era lead paint study \$1.84 million. *Baltimore Sun*. <https://www.baltimoresun.com/health/bs-hs-kennedy-krieger-lead-paint-judgment-20191114-fxlxcyzg5hvnojmyy5onpwriystory.html>.
47. See, e.g., Resnik DB. (2010). Public trust as a policy goal for research with human subjects. *American Journal of Bioethics*, 10(6), 15–17.
48. See Eyal, Kimmelman, Holtzman & Lipsitch, op. cit. note 8.

TABLE 1

Potential sources of a risk threshold for nonconsenting bystanders

Examples	Risk threshold	Analogous to NCBs?
Research risk without consent		
Consent waiver	Minimal risk	Yes
Not "research"	No threshold	No
Exempt research	Minimal risk	No
Emergency research	Greater than minimal risk	No
Research with incompetent adults	No threshold	No
Pediatric research	Variable depending on benefit	No
Fetal research	Variable depending on benefit	No
Departmental waiver	No threshold	Potentially
Negligence	Reasonable risk	Yes
Other risk without consent		

TABLE 2

Assessing potential risk thresholds for nonconsenting bystanders

Research Participation	If research participation is special...	Participants may be more stringently protected than bystanders from research risks.
		The minimal risk threshold for nonconsenting participants may not necessarily apply to NCBs (and an alternative threshold is needed).
	If research participation is <i>not</i> special...	Participants and bystanders should be similarly protected from research risks.
		The minimal risk threshold should apply to both nonconsenting participants and NCBs—or a different risk threshold should apply to both.
Research Risk	If research risk is special...	Research risks (to any party) may be more stringently regulated than non-research risks.
		The minimal risk threshold may be appropriate for research risks.
	If research risk is not special...	Research risks should be treated similarly to non-research risks.
		The reasonableness threshold should apply to research risks (to any party).