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DOI
10.1080/15265161.2025.2488270

Publication date
2025

Document Version
Final published version

Published in
The American journal of bioethics : AJOB

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THE AMERICAN JOURNAL OF BIOETHICS
2025, VOL. 25, NO. 5, 86–88
https://doi.org/10.1080/15265161.2025.2488270

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OPEN PEER COMMENTARIES

Which Risks Can Undermine Benefits in Research?

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As van Rijssel and colleagues (2025) reason, determining the ethical permissibility of a research intervention requires a careful evaluation of its risks and benefits. We agree with the authors' argument that distinguishing between direct and collateral benefits facilitates a more fulsome account of participants' incentives to enroll in clinical trials and that collateral benefits may differ materially across different types of studies. However, we propose that if risk-benefit assessments should consider collateral benefits, then to mitigate an unbalanced analysis, they should also consider collateral risks. Our commentary will provide a brief exegesis of the authors' argument, followed by our contention that the broadening of scope to consider collateral effects must extend equally to both benefits and risks to inform research ethics procedures in an unbiased manner. We will then propose a brief account of "collateral risks" aligning with the framework put forward by van Rijssel and colleagues. Finally, we briefly consider objections to our claim that collateral risks should be included in risk-benefit assessments.

In their article, "Which benefits can justify risks in research?", van Rijssel and colleagues argue that indirect or "collateral" benefits borne by trial participants ought to be considered by research ethics committees (RECs) evaluating the design of these trials (van Rijssel et al. 2025). The authors describe collateral benefits as "all individual benefits that research participants potentially receive, that do not result from the intervention itself" (van Rijssel et al. 2025). Using decentralized clinical trials (DCTs) as a principal example in which the setting of a trial may confer collateral benefits, van Rijssel and colleagues distinguish these types of benefits from direct benefits (e.g., receiving a study drug which improves their health) and broader forms of social value (e.g., the

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advancement of scientific knowledge) (van Rijssel et al. 2025). A core function of RECs is identifying potential risks and benefits in research, weighing them, and judging whether they are appropriately balanced to consider the study ethical (Coleman 2021). Within this context, van Rijssel and colleagues argue that collateral benefits are essentially similar to other benefits considered by RECs and ought to be included in risk-benefit assessments for DCTs in particular (van Rijssel et al. 2025).

We are persuaded by the authors' suggestion that a framework able to differentiate between different classes of participant benefit may offer useful granularity to RECs and their decisions. However, this framework appears to disaggregate only participant benefits without similar attention to participant risks or burdens. As van Rijssel and colleagues note, RECs are charged with ensuring that "risks to participants are minimized and appropriately balanced" relative to benefits and social or scientific value (Council for International Organizations of Medical Sciences (CIOMS) 2016). Just as a REC could not evaluate the ethical permissibility of a trial by considering only direct benefits while ignoring direct risks, this balance cannot be judged by an assessment of collateral benefits alone. Hence, if we advocate that RECs should consider participant benefits with greater granularity, a commitment to balance demands an equally granular examination of risks. In plain, if collateral benefits are included in risk-benefit assessments, collateral risks should be included too.

We propose the following description of collateral risks to complement the authors' account of collateral benefits. If direct risks arise from the intervention that is studied, such as an adverse reaction to a study drug, collateral risks arise from participation in research studies but not directly from the study intervention. For example, these collateral risks could include contracting a transmittable illness from other patients or participants when in a hospital setting. Another collateral risk might be the revelation of information that the participant was—and may prefer to be—ignorant of, precipitating emotional distress or stigma. For example, participating in a trial involving genetic tests that reveal that a patient harbors a risk allele for early-onset neurodegenerative illness. van Rijssel and colleagues note that DCTs bear some collateral benefits by virtue of being conducted within the participant's home. However, these trials also present a unique profile of collateral risks such as a lack of access to medical care in the event of misadventure (e.g., if an intervention being researched has an unexpected adverse effect for a patient at home), compromises to consent processes and patient education if participants are enrolled by phone or video call rather than in-person, and data privacy and security concerns whilst participant data is transmitted to researchers.

So far, we have argued that if we consider collateral benefits in risk-benefit assessments, we should also consider collateral risks. Here, we briefly consider a counterargument: that including collateral benefits in risk-benefit assessments can be justified while intentionally excluding collateral risks. In other words, it could be argued that collateral benefits ought to be considered, but collateral risks have not been accidentally unaccounted for; instead, it is both true that there are good reasons to include collateral benefits and there are good reasons to exclude collateral risks on purpose. This objection may posit that collateral risks are less useful in risk-benefit assessments than collateral benefits since, in theory, the list of potential collateral risks might be many times longer than potential collateral benefits. For example, on their way to participate in research, a person may encounter unforeseen events such as a traffic accident, robbery, or inclement weather—these events constitute a collateral risk of participation (Appel and Wilets 2023). However, these also seem excessive to include in risk-benefit assessments, as indeed they are risks borne when traveling anywhere, raising the question of whether considering collateral risks would unnecessarily overburden RECs. Here, we might also appeal to the literature on risk aversion and framing effects, which demonstrates that people are more sensitive to risks than to benefits (Redelmeier, Rozin, and Kahneman 1993). Discussions of risk are more charged than discussions of benefits, as individuals tend to weigh potential losses more heavily than equivalent gains. Given this, one might worry that consideration of collateral risks may skew risk-benefit assessments by focusing on unlikely collateral risks that could be unfairly perceived as significant.

To respond to this potential objection, we suggest that failing to consider collateral risks in order to avoid overcomplication could also mean dismissing valid and important risks. For example, while the possibility of catching a viral illness such as COVID-19 during participation in a trial could be written off as a collateral risk, it is "arguably precisely the sort of indirect yet consequential risk that the consent process should overtly address" (Appel and Wilets 2023). Hence, if we consider only collateral benefits in our risk-benefit assessments and exclude collateral risks, such relevant cases might be overlooked by RECs and patients choosing whether to participate in research.

Ultimately, it is ethically complicated to intentionally exclude collateral risks intentionally. If risk-benefit assessments ought to be "balanced" and in a "favourable ratio" (Weijer 2000), then preventing skewed analyses requires consideration of these collateral concerns in parallel.

In summary, we find van Rijssel and colleagues' argument in favor of including potential collateral benefits in calculations of net benefits—and therefore in risk-benefit assessments—astute. Our observation is that the collateral benefits described in the authors' framework are significant yet inseparable from an accompanying set of collateral risks. We propose that if collateral benefits are to be considered in risk-benefit assessments, collateral risks should be considered as well. Recognizing that attempts to consider both collateral risks and benefits might be unwieldy, it remains an issue of if and how RECs should attempt to incorporate both (or neither) in their decision-making frameworks.

DISCLOSURE STATEMENT

SC, CB, and JM have no conflicts to disclose. SD discloses the following: I receive research funding from Synaptive, VPIX Medical and Cure51. I am the Provincial Lead for CNS Oncology at Cancer Care Ontario. I receive royalties from Oxford University Press. I am on the Speaker's Bureau for the American Association of Neurological Surgeons and Congress of Neurological Surgeons.

FUNDING

CB receives salary support from the Vanier Canada Graduate Scholarship, as well as operating support from the Canadian Anesthesia Research Foundation. SC is supported in part by funding from the Social Sciences and Humanities Research Council.

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