https://doi.org/10.1038/s41591-023-02442-0

Conflicts of interest in institutional review boards are a threat to ethical research

Jonathan M. Green & Stephen Rosenfeld

The introduction of publicly funded not-for-profit institutional review boards would realign incentives to promote research participants' interests and improve accountability.

Prospective review by an independent body is recognized as an ethical requirement of research with human participants[1]. It assures that research is designed so that participants are not exposed to unnecessary risk of harm, risks are justified by the importance of the question and appropriate steps are taken to protect participants' rights and welfare. In the USA, this requirement is codified in Federal Regulation (45 CFR 46 and 21 CFR 56) and implemented through institutional review boards (IRBs).

Owing to concerns over the growth of investor-owned IRBs, the US Congress requested that the General Accounting Office (GAO) analyze the IRB marketplace and the effectiveness of federal oversight[2]. The report highlights the growth and consolidation in the for-profit IRB industry and the resultant market distortion. It notes declining federal oversight of all IRBs, asserting that the federal agencies charged with overseeing IRBs fail to conduct sufficient inspections to assure that the IRBs are operating in compliance with regulation. Finally, the report notes that there is no consensus on how to measure IRB quality or effectiveness and that without such measures the utility of inspections is questionable[3]. Although it raises important issues, the report is limited in its considerations and does not explore the implications of its findings. It ignores the inherent conflicts of interest that impact all IRBs, whether independent for-profit or embedded in academic medical centers. Furthermore, it fails to recognize that the role of federal oversight is not simply to ensure compliance, but to represent the interests of research participants, who otherwise remain voiceless.

Stakeholder incentives and accountability

The relationships of IRBs to their major stakeholders are not aligned to support IRB independence or participant protections, and do not further the IRB's primary obligation to act in the interest of research participants. IRBs have six major stakeholder groups, four of which are direct recipients of the IRB's service and five to which the IRB can be held accountable (Table 1). Of note, research participants are the only stakeholder to which the IRB has no direct accountability. Of the five stakeholders to which the IRB is accountable, four stand to gain financially or otherwise from rapid and minimally burdensome approval of research.

The interests of the research participant should be the main concern of the IRB. Regulations promote this by requiring that IRBs assure that the risks are commensurate with potential benefits of the research, risks are as low as possible and, except in limited circumstances, individuals are given the opportunity to make a free and informed decision to participate.

Research participants may be motivated by a variety of factors and are also the stakeholders most likely to experience direct harm. However, despite being the intended beneficiaries of IRB oversight, participants have no mechanism to hold the IRB accountable for its determinations and no mechanism through which to advocate on their own behalf.

Investigators and research institutions are recipients of IRB services, and the IRBs can be held accountable to the interests of investigators and institutions in several ways, including through control of the IRB office, which provides administrative support and influences what the IRB reviews and how it functions.

Review for profit

Existing independent IRBs are privately held for-profit entities, and the two largest US-based commercial IRBs are owned by private equity investors. Management has a fiduciary responsibility to investors, who can take their investment dollars elsewhere. Although these IRBs tout the separation of the business function from the review function, this supposed separation can be one way only. The review committee may not be privy to business functions such as fees, but the business is aware of committee decisions and their impact on clients. Management would be expected to allocate and control resources in ways to

Table 1 | Accountability of the IRB to its stakeholders, along with their incentives

Stakeholder	Interests	IRB accountability
Research participant	Altruism Hope for personal benefit	None
Investigators	Trial completion Answering the research question Publication, peer recognition, promotion and future funding opportunities Direct payments for enrollment Salary support	Complaints to institutional leadership that control IRB office resources Threats to leave and take their research portfolios and funding elsewhere Institutional IRB members are often colleagues of the investigators whose research they review and may protect the interests of their peers to serve their own future interests
Research institutions	Trial completion Answer to the research question Direct payment to support research faculty salaries Indirect cost payments to support research infrastructure Reputational enhancement Attract faculty and patients	Exert direct pressure on IRB leadership to change processes or staff Management of physical and financial resources of IRB office
Industry sponsors	Rapid and least burdensome review Minimize delay of getting product to market	Take future business elsewhere (to another IRB or institution)
For-profit IRB equity holders	Maximize return on investment Increase future revenue by increasing number of approved protocols that require ongoing review Increase future revenue by meeting customer need for fast and minimally burdensome review Decrease costs of review	Control of corporate leadership through the boards of directors Withdraw investments from the company
Regulatory agencies	Regulatory mandate Serve public interest	Issuing findings of non-compliance through audits and monitoring of IRBs

promote the speedy and least burdensome review process in order to satisfy paying clients.

Industry sponsors are dependent upon the IRB to review and approve their research. There is a substantial advantage in being first to market, and sponsors will seek to minimize delay. Given that the cost of IRB review is a very small fraction of the costs involved in drug development and the potential for lost revenue from delayed startup, speed — not price — is of the utmost importance.

When market structures create incentives that are not in the public interest, those interests can be represented by government oversight through regulations and disincentives for noncompliance. The ability of regulatory agencies to monitor research and make those disincentives real is constrained by their resources, which are subject to political and economic pressures. As discussed extensively in the GAO report, regulatory agencies do not have adequate processes for selecting IRBs to monitor, nor do they monitor a sufficient number of IRBs[2]. As these agencies are essentially the proxy for the research participant, these shortcomings leave the participant with no effective voice.

Furthermore, regulatory change is difficult and slow, and is not sufficient on its own to ensure that participant interests are fully respected in a dynamic research environment. Agency authority can be extended by guidance, but it is typically members of the research community, including sponsors and investigators but not research participants, who are involved in discussions that would inform such guidance.

Misalignment with mission

The stakeholder relationships demonstrate that neither incentives nor accountability promote the IRB's primary mission to protect human participants. Those who should be the most important beneficiary of IRB services — research participants themselves — are the only parties to which the IRB has no direct accountability.

The current IRB system has not failed completely, in part because research and its oversight are human activities, and most stakeholders are motivated by the desire to conduct sound and ethical research and look to the IRB for both guidance and approval. Researchers, institutions and sponsors fear the consequences of public disclosure of research gone bad, whether that means direct physical harm to research participants or an ethical transgression that would be publicly embarrassing. Concerns about liability and reputational harm are strong motivators, but can be balanced by ambition, profit-seeking and complacency. Hypothetical risks can be underestimated in the face of tangible personal gain and can be perceived as a cost of doing business. Accepting this cost is defensible when the entities that stand to gain assume the risk, but this is problematic when the risk falls on research participants who have little or no voice.

Incentives and accountability should be aligned with the IRB mission, and IRBs should be directly accountable to research participants and incentivized to better serve them. Ideally, incentives (financial or otherwise) should reinforce the desired outcome (better protections for human participants), with explicit accountability to the most important stakeholder (the research participant). However, as noted in the GAO report, there are no accepted measures of "better protections"[3,4].

Independent, publicly funded IRBs

Concerns about the IRB system are not new, and suggestions for improving accountability to participants have included increasing the number of unaffiliated members on the IRB[5–7], involving participants in the design and implementation of research, community engagement, and requiring compensation of research participants who experience research-related harms[8]. Although these proposals have merit and would increase the participants' voice in research, none create IRB accountability.

Financial realities influence organizational decision making. To properly align incentives, IRBs should be not for profit, independent of institutions and funded by the government, as they have a duty to act in the public interest. In such a system, the primary incentive would not be to generate revenue, but to serve the public interest. Although this would still not provide direct accountability of the IRB to individual participants, public funding would provide accountability to an entity that has a duty to act in the public interest. Accountability could be further enhanced by the creation of a process for adjudicating participant claims of possible harms attributable to the IRB. IRB membership could be drawn from the local community that the IRB serves. Funding could come from taxes on the entities that ultimately profit from the research the IRB oversees, but IRBs would no longer be directly accountable to these entities for the outcomes of their reviews.

This idea is not new. A similar suggestion was published by Wood and colleagues as a solution to the "diversity of structural, procedural and performance assessment problems undermining human participants' protections" and to eliminate the many inherent conflicts of interest afflicting both institutional and independent IRBs[9,10].

A public system is not without its own risks, nor is public funding immune to the concerns that affect the current system. Changing the priorities of the system that oversees the ethics of research will require public understanding, advocacy and engagement to avoid creating another bureaucracy. On the other hand, a public IRB system could greatly improve the efficiency of ethical review, realizing one of the goals of the NIH single IRB policy[11] and the revised Common Rule, by adopting a single set of policies, a single set of submission forms and a single set of procedures, transforming the experience of sponsors, investigators and institutions. Further, a transparent public IRB system might substantially increase public understanding of, and trust in, the scientific research enterprise.

The need for change

Many claim that the system is working and there is no need to change, a presumption we challenge. Even though the system functions, it can and should be optimized. Operating with an incentive structure that is counter to mission is inherently inefficient and counterproductive[12,13].

Implementation of the measures outlined in the GAO report will not be sufficient to address these concerns. Although more agency inspections will identify more instances of IRB non-compliance, the probable long-term impact would be a greater consolidation of the IRB marketplace. In response to a finding of IRB non-compliance, many institutional or smaller independent IRBs may choose to close, sending their protocols to independent IRBs. In addition, compliance with the letter of the regulations is not a reliable measure of ethics or participant protections; an increase in sanctions may only result in a greater market share for the large commercial IRBs.

In addition to compliance, existing metrics for speed and efficiency have no relationship to whether the IRB fulfills its objective of protecting participants and promoting ethical research. Relevant measures of IRB effectiveness must be developed, an effort already initiated by the academic consortium to Advance Effective Research Ethics Oversight (AEREO)[14]. Researchers working with AEREO are actively studying what makes for an effective IRB, but as with all research, it will take time to find the answers. We believe that these problems are sufficiently urgent that action must be taken now.

Jonathan M. Green [1] ✉ **& Stephen Rosenfeld**[2]

[1]Office of Intramural Research, National Institutes of Health, Bethesda, MD, USA. [2]North Star Review Board, Freeport, ME, USA.

✉e-mail: jmgreen31@sbcglobal.net

Published online: 24 July 2023

References

1. Emanuel, E. J. *JAMA* **283**, 2701 (2000).
2. US Government Accounting Office. GAO-23-104721 (2023).
3. Lynch, H. F. et al. *Soc. Sci. Med.* **292**, 114614 (2021).
4. Emanuel, E. J. et al. *Ann. Intern. Med.* **141**, 282–291 (2004).
5. Allison, R. D. et al. *IRB* **30**, 8–13 (2008).
6. Hogg, C. & Williamson, C. *Health Expect.* **4**, 2–9 (2001).
7. Sengupta, S. & Lo, B. *Acad. Med.* **78**, 212–218 (2003).
8. Resnik, D. B. et al. *IRB* **36**, 12–19 (2014).
9. Emanuel, E. J. et al. *PLoS Med.* **3**, e309 (2006).
10. Wood, A. et al. *Nat. Med.* **10**, 1283–1288 (2004).
11. US NIH. NOT-OD-16-094 (2016).
12. Gibbons, R. *J. Econ. Perspect.* **12**, 115–132 (1998).
13. Roberts, J. *J. Inst. Econ.* **6**, 125–132 (2010).
14. Lynch, H. F. et al. *J. Empir. Res. Hum. Res. Ethics* **14**, 190–196 (2019).

Acknowledgements

The authors thank C. Grady, H. Fernandez-Lynch, E. Hurley, C. Auston and R. Dresser for their thoughtful critique of this manuscript.

Competing interests

S.R. is co-founder of North Star Review Board, a nonprofit IRB.

Disclaimer J.M.G. is employed by the US National Institutes of Health (NIH), but this paper is being submitted in his personal capacity and not in his official capacity. The views expressed herein are those of the authors and not necessarily the views of the National Institutes of Health, the Department of Health and Human Services, and/or the USA.