POLICY FORUM

RESEARCH ETHICS

Streamlining ethics review for international health research

Single-site review means protection and efficiency

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International biomedical research, in which projects span borders and engage participants from multiple countries, has increased substantially during the last several decades. Despite the proven value of large, geographically, and ethnically diverse studies, further advancements are being impeded by the burden of submitting separate, and often numerous, applications for research ethics approval in compliance with country-specific laws or varied policy frameworks. To address this, we see promise in applying the international concept of "adequacy," contained in the European Union (EU) General Data Protection Regulation (GDPR) (*1*), to ethics review of international health research. We advocate for countries to publish their prior determinations about the adequacy of ethics review requirements in other countries to enable review by one institutional review board (IRB) or comparable body ("single-site" review) in the researcher's country, streamlining ethics review while safeguarding the welfare of local research participants.

Research ethics rules in nearly every country were developed when health research was small-scale, domestic, and clinical. Some of the most restrictive laws were enacted in response to a history of colonialism (or "ethics dumping") (*2*), economic imperialism, or ethically questionable research practices. Adding to these concerns were issues of national sovereignty and the entrenched system of single-country review.

There is general agreement about the criteria for research ethics review, but each country has its own procedures. Researchers planning international recruitment of participants must first overcome a dearth of information about ethics review in multiple countries. Although some compilations of international laws, regulations, and guidelines are published (*3*), obtaining accurate and current information about the ethics review requirements of numerous countries remains difficult (*4*). The lack of easily available resources means that researchers often must retain lawyers or research ethics consultants in their own country—and possibly in the prospective participants' countries—to discern the substantive and procedural elements of research ethics approvals. This often substantial and unexpected expense can create unnecessary delay. Thus, an essential starting point is ensuring access to continually updated and expertly translated online resources of research ethics materials.

Even then, researchers face the prospect of separate ethics reviews in each country. Multiple reviews are arduous, involving substantial and compounding costs and delays without necessarily improving protections for research participants. It is particularly impractical when recruiting small numbers of participants from multiple countries. Furthermore, multiple ethics reviews, even in the same country, are often inconsistent (*5*).

A recent study illustrates challenges that researchers face in such a balkanized system. The authors of this article were part of a team that surveyed laws in 31 diverse countries and detailed how common approaches to ethics review processes could facilitate international direct-to-participant (DTP) genomic research (*6*) in which researchers use the internet to recruit and enroll research participants, without using physicians, hospitals, or biobanks. As part of that study, we asked legal experts in these countries questions in the context of international DTP genomic research (*6*). Two conclusions from this survey are of particular interest (recognizing that the opinions of individual legal experts that we engaged might not be shared unanimously by others in the surveyed countries).

First, most of the experts reported that there was no official legal determination of how research ethics review requirements in their own country applied to foreign-based research. They could at best merely predict how existing laws would be interpreted. Second, experts from only five countries (Australia, Canada, Germany, Japan, and Spain) reported that approval by a review body in the researcher's country is sufficient, although exceptions may exist for clinical trials.

EQUIVALENCY, ADEQUACY, RECIPROCITY

Our proposal for single-site ethics review is based on international adoption of three fundamental concepts: equivalency, adequacy, and reciprocity. Equivalency means that the essential standards of ethical research with human participants are substantially equivalent from one country to another in theory and practice. Adequacy means that research ethics review in other countries is adequate to safeguard the interests of research participants and the national interests of their countries. Reciprocity means that one country recognizes the research ethics processes of another country, or two or more countries mutually agree to recognize each other's research ethics processes.

The possibility of eliminating multiple ethics reviews for international research is supported by the considerable equivalence in the national procedures and benchmarks for review of IRBs and similar bodies. Given this compatibility, it should be possible to identify a set of core criteria for appropriate ethics review that, if followed in one country, could be recognized as appropriate for review internationally. For example, the Global Alliance for Genomics and Health (GA4GH) compiled substantive elements and procedures for research ethics review around the globe (*7*) (see the table).

Moreover, there is consistency on the common values governing research ethics that need to be addressed by researchers in their protocols irrespective of jurisdiction (*8*). These "classical ethical" considerations are endorsed by respected international bodies, including the United Nations Educational, Scientific, and Cultural Organization (UNESCO) (*9*). The elements include informed consent, privacy/confidentiality, benefit/risk ratio, return of results, commercialization (if applicable), protection of the interests of vulnerable persons/communities, and research integrity and safety.

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Equivalence of international standards and processes makes single-site ethics review a promising alternative to multisite, multicountry review. Single-site ethics review has been shown to be more efficient and consistent on a national basis, including in the United Kingdom (*10*) and Canada (*11*). It is now required in the United States (*12*).

An international "adequacy" model, already used in the domain of data protection and international data transfer, could serve to frame, guide, and coordinate decisions as to whether biomedical research ethics review and oversight are essentially equivalent between two jurisdictions. For example, an adequacy decision by the European Commission recognizes that the data protection regime in a country offers an essentially equivalent level of data protection and can be considered as achieving a similar outcome as if Europe's GDPR (*1*) were followed.

Likewise, under a research ethics adequacy approach, researchers could "have their IRB approvals recognized in another country if the health research norms of both countries are demonstrated to be essentially equivalent, both in terms of their purpose and their effectiveness" (*13*). In this way the framework of single-site ethics review in the researcher's country is generalizable and serves to streamline ethics review while protecting the welfare of diverse participants in international health research.

We outline four recommendations for an international adequacy model of single-site research ethics review: (i) International research approved by an ethics review body in the researcher's country should be deemed approved in the participant's country if the overall ethics review regime in the researcher's country has been determined to be adequate by the local participant's country; (ii) a list of countries for which an ethics review undertaken by a competent foreign ethics review body is deemed adequate should be posted on the website of the regulatory authority responsible for the ethical conduct of research with human participants in each country; (iii) regulatory authorities responsible for the ethical conduct of research with human participants should inform ethics review bodies under their jurisdiction of the approval criteria for international health research; and (iv) in applying this framework, special attention should be given to the specific ethical provisions required by the participants' country as well as the sociocultural traditions or vulnerabilities of various population subgroups in the participants' country, including minority and Indigenous populations.

In assessing these recommendations, a key element is that the approval process begins in the participant's country. Only if research regulatory officials in the participant's country have made a prior determination that ethics review in the researcher's country is adequate does the researcher-country–based ethics review body have authorization to consider the research protocol.

Furthermore, any country may add limitations or conditions to an adequacy decision and require approval of certain types of research in their country. Requirements may include local approval for clinical research, collaboration with a local researcher, community engagement with certain participants, specific consent procedures in accordance with cultural expectations, additional privacy and confidentiality protections, special provisions on data access, a requirement of insurance or other compensation in the event of injury, or more general benefit sharing (*14*). Thus, within this broad framework of equivalent research ethics criteria, countries can require additional features deemed essential to protecting the well-being and interests of participants in their countries.

Procedural elements of effective ethics review

Drawn from (*7*).

- Established norms of conduct, including authority and independence
- Resources to carry out the work
- Competence of members
- Understandable procedures and forms
- Equitable treatment of the protocols of all researchers
- Attention to vulnerable populations and cultural differences
- Record of due diligence
- Transparency of decisions
- Continuing oversight of approved protocols
- Accountability of all reviewers and public authorities

IMPLEMENTATION CHALLENGES

Implementation of this proposal will be challenging. Each country would need to formalize legislation, regulations, or professional guidance recognizing the ethics review processes of other countries. Endorsement of the recommendations in the ethical guidelines and best practices of international organizations could generate momentum for global adoption. Some key organizations include the Council of Europe, the Council for International Organizations of Medical Services, the World Health Organization, the Africa Union Development Agency–New Partnership for Africa's Development, UNESCO, and the World Medical Association. Funders of international research, such as the Bill & Melinda Gates Foundation and the Wellcome Trust, also could play an important role in harmonizing international standards for the ethical conduct of health research.

It is important to recognize that, at least initially, the countries mainly benefiting from single-site ethics review in the researcher's country are likely to be high-income countries that perform most international health research. Low- and middle-income countries might stand to lose the most if single-site ethics review means a loss of research partnerships and ethics review capacity building (*15*).

Successful implementation strategies could include initial implementation between high-income, major research countries; limiting international ethics review to IRBs and similar bodies that have special training and receive certification to evaluate international research protocols; or phasing in single-site review after a period of systematically comparing the results of ethics review of the same protocol by ethics review bodies in different countries. Ultimately, adoption of a new way of conducting international ethics review will depend on equal measures of altruism, trust, and hope in realizing the possibilities of biomedical research. ■

REFERENCES AND NOTES

1. Regulation (EU) 2016/679 of the European Parliament.
2. D. Schroeder, J. Cook, F. Hirsch, S. Fenet, "Ethics Dumping: Introduction," in *Ethics Dumping Case Studies from North-South Research Collaborations*, D. Schroeder, J. Cook, S. Fenet, V. Mythuswamy, Eds. (Springer, 2018), pp. 99–106.
3. Office of Human Research Protections, International Compilation of Human Research Standards, www.hhs.gov/ohrp/international/compilation-human-research-standards/index.html.
4. P. Andanda, J. Wathuta, K. Leising, D. Schroeder, National and International Compliance Tools, A Report for TRUST, http://trust-project.eu/wp-content/uploads/2017/02/TRUST-664771-National-and-International-Compliance-Tools-Final.pdf.
5. D. Resnik, *J. Clin. Res. Best Pract.* **10**, 1 (2014).
6. M. A. Rothstein *et al.*, *J. Law Med. Ethics* **47**, 705 (2019).
7. Global Alliance for Genomics and Health, "Enabling responsible genomic data sharing for the benefit of human health," www.ga4gh.org.
8. M. H. Zawati *et al.*, *J. Law Med. Ethics* **47**, 582 (2019).
9. UNESCO, https://unesdoc.unesco.org/ark:/48223/pf0000146180.
10. Royal College of Physicians, *Guidelines on the Practice of Ethics Committees in Medical Research with Human Participants* (Royal College of Physicians, 2007).
11. J. V. Lavery, M. McDonald, E. M. Meslin, *Health Law Rev.* **13**, 86 (2005).
12. Code of Federal Regulations, Title 45, sec. 46.114.
13. A. Thorogood, M. J. S. Beauvais, *Philosophies* **6**, 93 (2021).
14. E. S. Dove *et al.*, *Science* **351**, 1399 (2016).
15. COVID-19 Clinical Research Coalition, Ethics Review Mutual Recognition and Multinational Research Collaboration in Pandemic Response Settings, (2021); https://covid19crc.org/wp-content/uploads/2021/03/Covid19-Ethics-Working-Group-Report_FINAL_.pdf.

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