

Justice, diversity, and research ethics review

It is time for institutional review boards and research ethics committees to address the ethics of inclusion

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The disproportionate impact of COVID-19 on certain populations, such as Black, Latinx, and Indigenous populations in the United States, has focused attention on inequalities in health and on the need to increase enrollment of racial and ethnic minorities and other underrepresented groups in biomedical research (1). Yet too often, in the United States and globally, participant enrollment in research has not reflected the demographic composition of the general population, those affected by the health conditions being studied, or those for whom the investigational product is intended (2), with racial and ethnic minorities and the young and the elderly, among others, being consistently underrepresented (3). Underlying causes for this underrepresentation have been described (4, 5), but change has been slow. Notwithstanding the roles of other stakeholders in addressing this issue, we maintain that the specific value of institutional review boards (IRBs) and research ethics committees (RECs) in promoting diversity has been underrecognized and their authority underutilized. Here, we substantiate the role of and outline practical steps for the IRB and REC (hereafter “IRB”) to help achieve greater diversity in clinical research.

The appropriate inclusion of diverse populations in clinical research is necessary if we are to understand how biological variability and social determinants of health contribute to disease prevalence, transmission, course, experience of illness, and treatment outcome. The inclusion of understudied and underserved groups informs clinical decision-making and health policy and can

serve efforts to address mistrust of research and health care (6, 7). Responsibility to the goals of diversity lies with all stakeholders in the clinical research enterprise (6), and a commitment to diversity, individually and collaboratively, by research sponsors, funders, academic institutions, contract research organizations, study sites, investigators, and IRBs is necessary.

RESPECT, BENEFICENCE, JUSTICE

Most regulated clinical research undergoes obligate review and approval by an IRB. IRBs are charged with safeguarding the rights and well-being of human participants in accordance with the foundational tenets of respect for persons, beneficence, and justice, as described in the Belmont Report (8). An IRB’s ethical responsibilities with regard to diversity derive from these and other principles, guidelines, and standards (9, 10).

The discussion of justice in Belmont cites “moral requirements that there be fair procedures and outcomes in the selection of research subjects.” As Belmont and other codes of ethics emerged from a historical backdrop of abuse and injustice in research, “fair procedures” have been applied by IRBs largely (and, we believe, too narrowly) to ensure that subjects are not exploited and enrolled as a matter of convenience. The idea of justice within the Belmont Report also includes the notion of access to the benefits of research (i.e., knowledge gained); this has direct implications for populations that have been understudied, whether incidentally or systematically. Subject selection cannot be equitable, and the requirements of justice cannot be met, when there is de facto exclusion of understudied populations.

This notion of justice is supported by the World Health Organization’s International Ethical Guidelines for Health-related Research Involving Humans, Guideline 3, which states, “In cases where the underrepresentation of particular groups results in or perpetuates health disparities, equity may

require special efforts to include members of those populations in research” (9), and by the World Medical Association Declaration of Helsinki, which states, “Groups that are underrepresented in medical research should be provided appropriate access to participation in research” (10). Therefore, consideration of diversity is essential to the question of fairness in subject selection and to IRB review.

Diversity in clinical research is responsive to the principle of beneficence, which places priority on the welfare of research participants and creates the obligation that research presents a favorable balance of benefit to risk, after risks and burdens have been minimized. In calling for “maximization of benefits” in the research, Belmont directs attention to both individual benefit and to the broader value of research to society. A clinical research enterprise that is not inclusive does not adequately address the health needs of a diverse society. Group differences in susceptibility to disease and in treatment outcome can only be identified when those groups are studied. It is the obligation of an IRB to maximize benefits through the inclusion of understudied groups in a manner that is consistent with the study aims and does not introduce unacceptable harm or burden.

Belmont describes two ethical convictions in relation to respect for persons, self-determination, and decision-making: the obligations to treat individuals as autonomous agents and to protect those with diminished autonomy. IRBs provide additional safeguards for research involving participants with compromised voluntariness (e.g., prisoners) or impaired comprehension. With regard to the inclusion of diverse populations, respect for persons demands efforts to foster informed and autonomous decision-making and, therefore, to address common barriers posed by age, language, culture, and educational disadvantage. Respect for persons requires the identification of opportunities and resources to engage understudied populations and to enhance awareness, access, and inclusion in research (4, 6). It also demands modification of those aspects of research and of consent that inadvertently limit the participation of understudied populations. For example, although inclusion of non-English speakers in a study may involve additional expenses of translation and/or interpreters, it strengthens the commitment to autonomy and justice.

The ethical positions presented above compel attention to inclusion of diverse populations in clinical research and define a specific duty for the IRB. In a 2019 survey (11), a majority of IRB chairs, IRB ad-

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ministrators, and investigators agreed that “IRBs should play a key role in ensuring diversity among participants in terms of gender, ethnicity, and language.” Despite this, there has been scant regulatory consideration, and little formal discussion within the field, as to whether diversity falls within the IRB’s remit. There are also little data as to whether and when IRBs exercise this authority, but the observed underrepresentation in completed studies suggests that IRBs do not consistently attend to this responsibility. Further questions relate to recent U.S. regulation and policy requiring a single, designated IRB to serve as the IRB of record for multicenter research and whether this will offer benefit in consistency and reach with regard to diversity and inclusion.

INCLUSION AND PROTECTION

In the face of the persistent problem of underrepresentation in clinical research, institutions should establish policies and provide necessary resources at all institutional levels to ensure that reviewing IRBs fulfill this obligation. The specific approaches we outline here will serve to help incorporate the ethical oversight of diversity in IRB procedures, deliberations, and expectations (see the box).

An IRB has authority to require that a research protocol details study elements relevant to considerations of diversity. A description and justification by the investigator of the demographics of the intended study sample (e.g., by age, sex, race, ethnicity, social determinants of health) and a description of either the demographics of the condition or those using or intended to use the product in the general population permit the IRB to make an assessment of the appropriateness of the recruitment plan. When the makeup of the proposed sample deviates substantially from that of the demographics of the condition being studied in the general population or for whom the intervention is intended, and no valid scientific justification is offered, the IRB can require modification of the study to recruit a more representative sample. Such requirements are tailored to the nature

Institutional review board oversight: Points to consider by reviewers

INITIAL REVIEW

Study aims and subject selection

- Do the demographics of the proposed sample reflect those of the population affected by the condition or for whom the intervention is intended?
 - When they do not, is the deviation adequately justified?
- Is planned under- or overrepresentation by age, race, ethnicity, sex, gender, or social determinants of health in the sample scientifically justified?
- Is there a statistical plan for examining heterogeneity in outcome or across subgroups?

Criteria for inclusion and exclusion

- Will inclusion and exclusion criteria inadvertently or unnecessarily result in under- or overrepresentation of understudied subgroups?
- Have alternative approaches to minimizing risk that do not rely on exclusion been considered?

Recruitment

- Have recruitment procedures considered specific approaches to engage underserved populations?

Study conduct

- Are study procedures flexibly organized to accommodate the needs of underrepresented groups?
- Do all participant-facing materials conform to health literacy principles?
- Are participant materials translated? Is back translation necessary? If not, why not?

Payment

- Is payment sufficient to cover costs of participation?

Return of results

- Are study results intended to be returned in a manner that meets the needs of populations studied?

CONTINUING REVIEW

- Has the study fulfilled its recruitment and accrual goals?
- Is demographic distribution on track to approximate the study goals?
- If not, are adequate corrective actions described, sufficient, and likely to be successful?

and phase of the study, the study’s specific aims, and the study location, as discussed further below.

Note that inclusion of a demographically diverse study population does not imply that statistical conclusions regarding heterogeneity of treatment outcome will be possible, but it may allow directional assessments of efficacy and safety that can then be further investigated. Inclusion will, at a minimum, address the equitable selection of participants and the principle of justice in research.

During review, an IRB should consider the feasibility of study methods that seek to identify, recruit, and retain underrepresented populations. Research team partnerships with patients and their families, advocacy groups, and community representatives have been shown to be effective in informing recruitment and retention strategies (12) as well as in providing input on study questions and participant-relevant endpoints, study conduct, and culturally and linguistically appropriate communications. The IRB should require a statement in the study proposal summarizing the nature, process, input, and impact of such patient and community engagement and how this information has shaped the study itself and the recruitment plan; simply asking the question will prompt consideration by investigators.

The IRB can review and provide specific feedback to facilitate successful recruitment of specific populations, including language use, translation, placement of advertisements, and workforce characteristics. The IRB should also ensure that all study materials adhere to health literacy principles and that user-testing is utilized where indicated. The IRB should identify factors, such as excessive time commitment, restricted clinic hours, the costs of travel, and inadequate compensation, that have a foreseeable and negative impact on the enrollment of an appropriately representative sample (13).

IRBs should require investigators to detail study inclusion and exclusion criteria and, when not self-evident, to

provide a rationale for exclusion. Review of eligibility criteria should ensure that understudied populations are not inadvertently or unnecessarily excluded and that criteria are only as restrictive as necessary for safety and to minimize harm. For example, the exclusion of older populations with a specific age criterion might be revised to exclude individuals with specific health concerns who would be at increased risk, regardless of age. When laboratory measures serve as the basis for eligibility criteria, they should be adapted to reflect known sex-, age-, race-,

or ancestry-specific normal values, when failure to do so would unnecessarily decrease eligibility of some individuals (14). IRBs should identify common practices that limit enrollment of immigrant or minority language speakers in multilingual communities, restrict the participation of women of child-bearing potential (when requiring appropriate contraception would suffice), and introduce bias in participant selection by using overly subjective criteria (such as “investigator discretion”).

In exercising the regulatory requirement for continuing oversight of ongoing research, the IRB should periodically review the demographic breakdown of the accrued sample by age, race, ethnicity, sex, and social determinants of health where applicable to the research. Along with these data, IRBs should require an explanation of any meaningful departures from the recruitment plan and request, review, and approve proposed corrective action when indicated. Ongoing tracking

“Equitable subject selection requires the balancing of inclusion and protection...”

of accrual by the IRB, as well as dialogue between the IRB and investigator, communicates the importance of diversity, promotes transparency with regard to progress or lack of progress, provides a measure of accountability, and, ultimately, will change behavior.

IRB requirements with regard to study demographics should be flexibly tailored to individual study purpose, phase, setting, and size. For example, for some research (e.g., phase 3 studies, comparative effectiveness research), an IRB may adopt the principle, as a rebuttable presumption, that a study sample should reflect the demographic makeup of the condition being studied or for whom the intervention is intended. Other studies, such as small exploratory, proof-of-concept, early phase studies, or research that seeks to learn about specific communities, would not be expected to be representative of those affected by the condition. Similarly, a local site in a multi-site study may be selected because it proposes to recruit a specific racial or ethnic group to diversify a larger study population.

Equitable subject selection requires the balancing of inclusion and protection and, like all aspects of research with human participants, grounding in good science. When a study proposes to recruit a sample that is composed predominantly or solely of a racial, ethnic, or other minority, the IRB might reasonably ask why the selection of this sample is scientifically necessary, how

the findings are generalizable, and whether an alternative recruitment strategy might yield a more diverse or less burdened, stigmatized, or disadvantaged population.

Flexibly adapting requirements to specific study types will encourage dialogue between investigators and the IRB. When an investigator faces particular challenges in the recruitment and retention of specific populations, the IRB could offer guidance or consultation on protocol revision.

The IRB itself should be diverse in composition, with membership and input reflecting the demographic compositions of the communities and populations studied in the research it reviews through the use of ad hoc consultants and by appointing members with experience working with diverse communities. However, a recent study showed that 87% of IRB members and 91% of IRB chairs were white (11). A diverse IRB will be better attuned to the experience and needs of participants and better able to offer input from the perspective of varied populations. At a minimum, training in cultural competence and implicit bias should become part of required ethics education for all IRB members and staff. Finally, IRBs should develop expertise in providing concrete recommendations for investigators in methods and tools to achieve greater diversity (6).

Impediments to inclusion of underrepresented and underserved populations in research are numerous and complex. There are no specific regulatory mandates of the kind that typically drive accountability in clinical research. Institutional commitment to diversity is uneven, the research workforce itself is inadequately diverse, and resistance from the research community to any additional oversight is likely. Further, expertise in the engagement and study of hard-to-reach populations is variable and related infrastructure is limited. Finally, in the United States, some question whether Belmont or the Common Rule are appropriately applied to matters of social justice.

Institutions should support, educate, and resource IRBs, investigators and their study teams, and others in research so that they can give necessary attention to diversity as a fundamental value in the ethical conduct of research. The application of diversity to research review is neither simple nor without risk, but we do not believe the requirement fundamentally differs from other components of IRB review. Overly prescriptive approaches by the IRB and REC, specific mandates, or the application of quotas to study samples will not serve the interests of science and would not be justifiable or palatable to the research community. Drawing attention to diversity and inclusion as a goal and setting reasonable expectations as

a condition of study approval, however, will give rise to necessary discussion and collaboration between IRBs and among investigators and the evolution of best practices in the field. Of course, the obligation to promote diversity in clinical research does not rest solely on the IRB or REC or the investigators. Sponsors, regulators, research and academic institutions, funders, patients and patient advocates, and others must build capacity and infrastructure in what, in the end, must be a collaborative enterprise.

As entities that hold investigators accountable, IRBs are themselves accountable to their ethical and regulatory mandates and ultimately to those who serve as participants in research. The duty of IRBs to view subject enrollment and retention beyond the lens of “protection,” to deliberate on the benefits and risks of greater inclusion, and to exercise their authority to promote diversity should be recognized and actively implemented as a matter of justice. ■

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