Embedding Ethical Considerations Relating to Global Representation

Introduction: The Ethical Imperative of an Inclusive Approach to Participation in Clinical Research

There is a strong ethical case for promoting diverse, equitable, and inclusive approaches to participation in clinical research.[1,2,3] Participants in clinical research should reflect those who have the disease, condition, or risk of the disease or condition. If research does not take into account the needs and experiences of diverse populations and subpopulations (whether defined by geography or by another characteristic), then the outcomes of research are less likely to be widely generalizable, relevant to people's needs, or feasible to deliver in different circumstances.

Different aspects of diversity are of greater or lesser relevance in different contexts and countries. In recent US and European considerations of diversity, equity, and inclusion (DEI), there has been a particular focus on questions of race/ethnicity because of the way these act as a proxy for disadvantage and discrimination. However, this is not necessarily similarly salient in many other parts of the world – for example, where populations may be more homogenous with respect to ancestry, or where other factors are more clearly associated with lack of representation in clinical research. Alternatively, cultural factors and ethnicity may be very important in terms of status and (dis)advantage, but the way in which differences are understood and categorized may vary significantly between countries and world regions: the categories of race and ethnicity put forth by the US Office of Management and Budget (OMB),[4] for example, will have little relevance in other countries.
In low-income settings, including those within wealthy countries, poverty and the associated lack of access to healthcare present particularly high barriers to participation in research. Access to cancer studies, for example, often remains the preserve of those able to access and afford specialist healthcare. In some countries, it remains difficult for women or those who live in rural areas to access research. In

[1] Wright K, DeCormier Plosky W, Ahmed H, White SA, Bierer BE. First Do No Harm: A Global Perspective on Diversity and Inclusion in Clinical Trials. Nature Reviews Drug Discovery. 2024 May 8; 23:481-482. https://www.nature.com/articles/d41573-024-00078-4

[2] Schwartz AL, Alsan M, Morris AA, Halpern SD. Why Diverse Clinical Trial Participation Matters. New England Journal of Medicine. 2023 Apr 1. DOI: 10.1056/NEJMp2215609

[3] The MRCT Center of Brigham and Women's Hospital, and Harvard. Achieving Diversity, Equity and Inclusion in Clinical Research: Guidance Document. 2021. https://mrctcenter.org/diversity-in-clinical-research/guidance/guidance-document/

[4] The Office of Management and Budget (OMB) standards define minimum standards for collecting and presenting data on race and ethnicity for all Federal reporting in the U.S. https://www.federalregister.gov/documents/2024/03/29/2024-06469/revisions-to-ombs-statistical-policy-directive-no-15-standards-for-maintaining-collecting-and

others, the prevalence of particular conditions may reinforce the importance of considering the impact of co-morbidities. Inclusion of sexual orientation or gender identity minority populations may be particularly challenging where national or local laws criminalize or actively discriminate against them.

Safeguards for research practices in low-resource settings

While exclusion from research may be discriminatory and decrease the generalizability of the research, greater inclusivity and diversity in clinical research may also be a source of ethical concern, particularly in low-resource settings. Recruitment of economically disadvantaged participants for reasons of convenience or cost may lead to exploitation, particularly in settings in which they and their communities may not be in a position to benefit from the findings. Here we propose a framework for the evaluation of low-resource settings and safeguards for consideration.

Research participation should be neither exploitative nor reserved for the privileged: the aim must be to offer a fair opportunity to participate in research, matched with a fair opportunity to benefit from the outcomes of the research.

When planning and designing a study, and when making choices about study sites, close attention must be paid to how risks of exploitation may be minimized. Before any research begins, one or more ethics committees must review and approve the study protocol. Optimally, the ethics committee(s) should be familiar with the local setting(s), customs, culture, and potential vulnerabilities. Sponsors, investigators, and the responsible ethics committees should attend to certain concerns, including:

- questions of social justice, for example, asking why a particular study is taking place in this country and this location, who is likely to benefit from study findings and the likelihood that study participants themselves and their wider communities will be able to access effective interventions in the future. While these questions are of central importance in any study being conducted in low-resource settings, they become particularly acute when explicitly seeking to include individuals who are currently underrepresented in clinical research and/or who have inadequate access to healthcare.
- concerns about potential vulnerabilities, particularly in connection with groups traditionally underrepresented in research such as older adults, children, LGBTQIA+ people, economically and/or educationally disadvantaged people, people with disabilities, and those unable to consent to participation for themselves.
- safety concerns, such as the inclusion of people with multiple health conditions or on multiple medications, and carceral populations.
- risks to privacy and security, including undocumented immigrants, migrant populations, and people with diseases or conditions that are stigmatizing.

Research ethics committees should also seek information about the research team's **engagement with local communities** across all aspects of the study aims, design, and conduct. The development of respectful relationships between the research team and local populations that help shape the study, ensure its relevance to local health needs, and provide transparency with respect to safety measures, will provide research ethics committees with important assurances that potentially vulnerable

participants will not be exploited. The MRCT Center has developed a suite of resources to support effective and respectful engagement with participants and communities.[5]

Reducing barriers to participation

In addition to providing assurances that plans to recruit diverse participants are ethically justifiable, research teams will also need to **identify and reduce barriers to participation**. These may be practical barriers: for example, the costs involved in taking time away from work, the distance to be traveled, or the physical accessibility of the site. There may also be psychological barriers: for example, a lack of knowledge as to what research is, an inaccurate assumption by a person that they would not be a suitable participant or a belief that participation in research will be beneficial.

Ethical concerns about risks of 'undue inducement' to participate can sometimes lead to inadequate reimbursement of the actual costs of participation, creating unnecessary and unjustified barriers to enrollment of underserved and underrepresented populations. If a clinical study is approved by an appropriately constituted ethics committee that considers the risks and benefits of the study in the absence of remuneration, then reimbursement of the costs of participation cannot be characterized as 'undue inducement.'[6] Guidance issued by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO) makes clear that, "Research participants should be reasonably reimbursed for costs directly incurred during the research, such as travel costs, and compensated reasonably for their inconvenience and time spent. Compensation can be monetary or non-monetary. The latter might include free health services unrelated to the research, medical insurance, educational materials, or other benefits."[7] Fair payment for research participation may permit the participation of economically-vulnerable populations who would otherwise be unable to join.[8] [9] [10]

[5] Note that the term 'community engagement' is widely used in research to refer to engagement with all affected groups within a relevant population.

[6] Gelinas L, Largent EA, Cohen IG, Kornetsky S, Bierer BE, Fernandez Lynch H. A framework for ethical payment to research participants. New England Journal of Medicine. 2018 Feb 22;378(8):766-71.

[7] Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO). International Ethical Guidelines for Health-related Research Involving Humans. 2016. Guideline 13. Pp 53-54. https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf

[8] Gelinas L, White SA, Bierer BE. Economic vulnerability and payment for research participation. Clinical Trials. 2020 Jun;17(3):264-72.

[9] Bierer BE, White SA, Gelinas L, Strauss DH. Fair payment and just benefits to enhance diversity in clinical research. Journal of Clinical and Translational Science. 2021 Jan;5(1):e159.

[10] May 2021, the MRCT Center hosted a webinar on "Inducement or Fair Compensation" to highlight the importance of ensuring that concerns about undue inducement do not, in practice, create injustice to participants and barriers to more diverse participation. See: https://mrctcenter.org/diversity-in-clinical-research/news-and-events/mrct-center-leaning-in-webinar-series/#1619798235339-35c0f103-0023.

Global Representation Considerations Prompt List

While ethical considerations tend to be most explicitly discussed at the point when a proposed study is scrutinized by an ethics review committee, ethical considerations should be taken into account throughout the research process, from the very beginning, when research aims are identified and operational strategies developed. In 2013, the MRCT Center launched a 'Protocol Ethics' toolkit to support the explicit documentation of ethical issues in protocol development, with the twin aims of promoting ethical reflection and of improving communication and understanding between study sponsors and ethics review committees.[11]

Building on that work and linking to other tools in the MRCT Center's Diversity Inclusion and Equity in Clinical Research Toolkit, the prompt list below identifies key ethical considerations relating to diverse, equitable, and inclusive trial participation in global clinical trials. Sponsors are invited to document their processes and actions with respect to each of the issues identified, and to share these with ethics review committees.

1. **Are there good reasons for this study to take place in this country/setting/site?**

    a. Why has this country/setting/site for this study been selected?

        Consider: the *epidemiology of target condition in country/region, unmet patient need, priority for local healthcare system, relevant relationships such as long-term research partnership between sponsor and stakeholders in-country, capacity of both research and healthcare system to conduct trial safely, relevance to national research priorities, local demographics.*

    b. What value will the findings of the study, and the process of conducting it, bring to local communities?

        Consider: the *possible improvement of local health; commitments for future access for study interventions shown to be effective, including through dialogue with the Ministry of Health and other authorities; support for locally relevant and sustainable research or health infrastructure.*

    c. Will the study participants be able to access the study intervention prior to marketing authorization if they have benefited from the intervention and it is safe?.

[11] Li RH, Wacholtz MC, Barnes M, Boggs L, Callery-D'Amico S, Davis A, Digilova A, Forster D, Heffernan K, Luthin M, Lynch HF, McNair L, Miller JE, Murphy J, Van Campen L, Wilenzick M, Wolf D, Woolston C, Aldinger C, Bierer BE. Incorporating ethical principles into clinical research protocols: a tool for protocol writers and ethics committees. J Med Ethics. 2016 Apr;42(4):229-34. doi: 10.1136/medethics-2014-102540. Epub 2016 Jan 25. Erratum in: J Med Ethics. 2016 Jul;42(7):449. PMID: 26811365; PMCID: PMC4819642.

d. What is the likely and/or planned timeframe within which study participants and the populations and communities that they represent will be able to access and afford interventions that are shown to be safe and effective?

2. Who should be offered the opportunity to take part in this study?

a. What are the inclusion/exclusion criteria for participation in this study, and how do they support diverse participation?

b. Explain the justification for your inclusion criteria

Consider: *reference to the national and/or global epidemiology of the disease or condition, including any known or suspected heterogeneity of effect; include plans to mitigate possible safety concerns in order to facilitate the opportunity to include as many diverse participants as possible (e.g. older participants and those with other health conditions); identify at the local level those groups who are most likely to be under-represented in research or less able to access healthcare, and hence where proactive approaches to support recruitment may be required.*

c. Explain the justification for any exclusion criteria

Consider: *the relevance to specific population groups; safety concerns with respect to specific groups of patients where such concerns cannot be mitigated; any considerations as to why the opportunity to participate in research might be harmful to particular groups, in ways that cannot prevented or mitigated*.

3. How are local populations and community stakeholders engaged with this study and its DEI strategy?
[see MRCT resources on diverse community engagement for tools and strategies]

a. Explain how the engagement with local community stakeholders and wider community members will contribute to confidence in the study and DEI strategy.

Consider: *what steps have been taken to engage with diverse parts of the local population, including barriers and enablers to research participation; what is or has been the response to community input and concerns; what systems are in place to ensure effective multi-directional communication throughout the research endeavor, including informing participants and local populations of the outcomes of the research*

4. How have barriers to diverse participation been reduced?

a. What are the barriers (and enablers) to participation, particularly for those who are underrepresented in research and/or have poor access to healthcare?

   Consider: *financial and other costs involved in participating, including travel, subsistence, and lost earnings capacity; physical accessibility of the study site; language; stigma; knowledge of research and what participation means.*

b. What action have been taken to address these barriers?

   Consider: *reimbursement arrangements; steps to minimize time commitment, for example by minimizing the need for site visits; translation and interpretation arrangements; information-sharing sessions; working with local champions.*

c. Is there a policy for reimbursement and compensation of the costs of participation that ensures that participants will not suffer financially or materially because of participation in this study?

   Consider: *the basis reimbursement of incurred expenses and the compensation of participants for their time and inconvenience, including who was consulted in the development of this policy.*