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Ethical considerations in international clinical trial site selection

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ABSTRACT

New medicines and vaccines are predominantly tested in high-income countries. However, as the COVID-19 pandemic highlighted, the populations who can benefit from these interventions are not limited to these wealthier regions. One-third of novel Food and Drug Administration approved drugs, sponsored by large companies, treat infectious diseases like tuberculosis and HIV, which disproportionately affect low-income and middle-income countries (LMICs). The medicines for non-communicable diseases (NCDs) are also relevant to LMIC health needs, as over three-quarters of deaths from NCDs occur in LMICs. There are concerns clinical trial data may not extrapolate across geographical regions, as product effectiveness can vary substantially by region. The pentavalent rotavirus vaccine, for example, had markedly lower efficacy in LMICs. Efficacy variations have also been found for other vaccines and drugs. We argue there are strong ethical arguments for remedying some of this uneven distribution of clinical trial sites by geography and income. Chief among them, is that these disparities can impede equitable access to the benefits of clinical research, such as representation in the evidence base generated to guide prescribing and use of medicines and vaccines. We suggest trial site locations should be made more transparent and for later stage trials their selection should be informed by the global distribution of disease burden targeted by an experimental product. Countries with high prevalence, incidence, severity or infection transmission rates for targeted diseases should have real opportunities to engage in and enrol their populations in trials for novel medicines and vaccines.

Summary box

- ⇒ There is an uneven global distribution of clinical trial sites by geography and income.
- ⇒ Clinical trial data may not extrapolate across geographical regions.
- ⇒ Product effectiveness can vary substantially by region.
- ⇒ We provide ethical arguments for remedying the uneven global distribution of clinical trial sites by geography and income.
- ⇒ We recommend more attention to the ethical question of who ought to benefit from research.
- ⇒ Site selection for later stage trials should be informed by the global distribution of disease burden targeted by an experimental medicine or vaccine.
- ⇒ Countries with high prevalence, incidence, severity or infection transmission rates for targeted diseases should have real opportunities to engage in and enrol their populations in trials for novel new medicines and vaccines and explanations.
- ⇒ Trial site locations and rationales should be made more transparent in trial registries and publications.

INTRODUCTION

New medicines and vaccines are predominantly tested in wealthier countries. A study of US Food and Drug Administration (FDA) approved novel therapeutics in 2012 and 2014 revealed they were tested in a median of 20 high-income and 6 upper-middle countries, but only 1 lower-middle and no low-income countries.[1] Similarly, the COVID-19 vaccines recommended by WHO for emergency use authorisation, and authorised for use in several low-income and middle-income countries (LMICs), were disproportionately tested in high-income and upper-middle-income countries.[2]

As the COVID-19 pandemic has illustrated well, the patients and populations who can benefit from new interventions are not necessarily limited to these wealthier regions. One in three new FDA approved novel drugs, sponsored by large companies, treat infectious diseases like tuberculosis and HIV, which disproportionately affect LMICs.[3] The other medicines, for non-communicable diseases (NCDs), are also often relevant to LMIC health needs, as over three-quarters of NCD deaths occur in LMICs.[4]

There are concerns clinical trial data may not extrapolate across geographical regions, as drug and vaccine effectiveness can vary substantially by region. The pentavalent rotavirus vaccine, for example, had markedly lower efficacy in LMICs, preventing severe rotavirus gastroenteritis over a season in 64% of vaccinated children in sub-Saharan Africa, and 51% in Asia, compared with 98% for children from high-income countries like the USA and Finland.[5] Sub-Saharan Africa was not included in the vaccines' pivotal trials,

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but Finland and the USA were.[6] Similar efficacy variations have been shown for other vaccines, including for polio,[7] cholera,[3] yellow fever[8] and BCG, as well as drugs, such as anthelmintics,[9] antimicrobials[10] and treatments for NCDs, such as cardiovascular disease.[11 12] Often, explanations for the variance are unknown—they might occur because of genetic differences, dietary and nutritional differences, differences in healthcare delivery, or different micro-organisms.[13]

Here, we argue there are strong ethical arguments for remedying some of this uneven distribution of clinical trial sites by geography and income. Chief among them is that these disparities can impede equitable access to clinical trials and their resulting benefits, such as representation in the evidence base generated to guide prescribing and use of medicines and vaccines. Patients have a justice-based claim in many instances that the evidence base for treating their disease is relevant to them.

To address these inequities on the global level, we suggest site selection for later stage trials should be informed by the global distribution of disease burden targeted by an experimental medicine or vaccine. Countries with high prevalence, incidence, severity or infection transmission rates for targeted diseases should have real opportunities for their populations to enrol in trials for novel new medicines and vaccines.[14] As a first step, we suggest trial locations should be more transparent, as studies have shown only about 37% of trials supporting FDA novel drug approvals have publicly available trial site locations in the medical literature or a registry like ClinicalTrials.gov.[1]

ETHICAL PRINCIPLES

Much of the ethical analysis related to international research has focused on the obligations of researchers and sponsors after sites have been selected. Recommendations often take the form, 'If you locate your study here,' wherever 'here' is, 'then these are the ethical obligations, challenges and considerations that apply.' Discussions have addressed, for instance, post-trial access to drugs for communities and individuals participating in research, barriers and facilitators for obtaining quality informed consent internationally,[15] acceptable standards of care for comparator agents in randomised control trials,[16 17] and research capacity and regulatory challenges,[18] among other issues.

The prior ethical question of how we should think about locating trials in the first place is arguably underaddressed. When addressed, advice has historically been to avoid testing in poorer countries when there are concerns about exploitation, vulnerable participants or weaker regulatory governance systems.[19] This has held despite increasing awareness of disparities in research funding between research that studies products for wealthy patients and the health research needed by the majority of the world's population,[20–23] and known under-representation of LMICs authors in high-impact medical journal publications.[24]

We contend that two well-established ethical principles—social value and fair subject selection—provide relevant guidance in clinical trial site selection and support advancing more opportunities for the participation of countries with high disease burden from the condition targeted by a novel experimental medicine or vaccine.

SOCIAL VALUE

Biomedical research is valuable when it yields generalisable knowledge that can promote human health. As a result of this potential to help people, biomedical research is widely supported by many stakeholders, including patients and healthy volunteers who enrol in trials, hospitals and health systems that host study sites, and governments who fund studies, train researchers, and provide incentives like tax breaks and intellectual property rights over new medicines. The collective contribution made to research and the fundamental importance of health underlie the *social value* requirement: clinical research is ethical only if it generates generalisable knowledge that is expected to promote health.[25]

The social value requirement is quite permissive. Provided a research study is expected to generate information that has the potential to benefit someone or some population's health, it has social value. But recently, more attention has been focused on questions of who ought to benefit from research.

FAIR SUBJECT SELECTION

Governments, research sponsors and investigators have obligations to—collectively—promote the health of all. Yet, compared with the patients who actually have the conditions being studied, new medicines and vaccines are often disproportionately tested on populations who are healthier, younger, more likely to identify as white,[26 27] and live in urban areas[28] and high-income or upper-middle-income countries.[1] When the evidence base for new interventions is dominated by data from unrepresentative populations, it may not generalise to patient populations with different disease severities, comorbidities, dietary and nutritional profiles, access to supportive care, age groups and geographies. Research conducted in one country can have limited applicability to other countries when 'income levels, races, ethnicities… cultural practices' and other social determinants differ.[29] To give one example, patient age distributions and coexisting conditions can vary outside North America and Western Europe for diseases, such as heart failure, driven by social determinants, making it hard to extrapolate data across geographical areas.[22]

This is unfair. As bioethicists Doug Mackay and Kate Saylor argue, fair subject selection requires the social value requirement be extended so that, 'investigators and other relevant decision makers ensure that studies

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are sufficiently inclusive to produce knowledge that is generalisable to clinically distinct groups.'[30] They label this fair inclusion.

Of the many disparities in research evidence, the gap between enrolment of patients in more and less wealthy countries has arguably received the least attention, despite being a potentially severe problem. As mentioned, there is ample evidence that the effectiveness of vaccines and medicines can vary substantially across countries. This gap not only can impede good clinical decision-making, but also coverage decisions. Government-funded healthcare systems in most countries have to decide which interventions to pay for. Doing so in a way that promotes population health and health equity depends on data on the effects of an intervention in the population covered. If we continue to just test in rich countries, we may not realise that a new medicine or vaccine does not work as well or is even unsafe in poorer ones and thereby crowd out more beneficial interventions.

OBJECTIONS CONSIDERED

We have argued that the ethical requirements of social value and fair inclusion suggest there are ethical reasons to engage and select some trial sites over others when sponsors are planning later stage multinational clinical studies of novel drugs and vaccines. Specifically, they support gathering data from participants and engaging countries who represent—as far as possible—the global patient population with the condition being studied, especially for later stage premarket trials. This means sites, to a much greater degree than at present, should reflect the relative burden of disease across countries and sub-populations within countries and site locations should be made public. Our conclusions may prompt several objections.

A seminal paper by Glickman *et al* on the ethical implications of the globalisation of clinical research suggested that clinical research should be 'conducted in populations in proportion to the potential uses of the products after approval.'[31] Implicit in this formulation could be an objection that trials should be conducted in populations who will actually use, rather than just need, a product. Since testing a product in poorer countries does not guarantee they will have market access, it will be affordable, there will be reasonable supply, or payers and formularies will cover it, it may be argued that these populations should not be included in research. To be sure, studies have found substantial gaps between where FDA approved medicines are tested and where they become commercially available to patients, showing approvals are more likely and faster in high-income countries.[1] The COVID-19 pandemic has highlighted this problem; high-income countries that helped test the COVID-19 vaccines recommended for emergency authorisation by the WHO have received proportionately more doses than LMICs, allowing them to vaccinate more of their populations.[2] In response, we agree testing medicines and vaccines in countries who need them without providing suitable access to effective products is unethical. We note that both goals need to be worked on, ensuring products are both tested in and reasonably available for patient groups who need them. At a minimum, products should ordinarily be submitted for regulatory approval in the countries where they are tested, which does not routinely happen. Ideally they should also be made affordable and available in sufficient quantities.[1]

Second, it might be objected that our proposal could encourage research that violates the 'responsiveness principle,' defined as a requirement that research should be responsive to the health needs or priorities of the communities or populations where the research will be conducted.[32] While novel products often target unmet needs, a local population may not value prioritising that unmet need over another, even if the disease burden is high, because, for example, it has limited resources and judges it could make more of an impact with those resources on a different area. We agree countries should be able to make these decisions for themselves, however this is only possible if research sponsors and other actors advance real opportunities for their participation. Ultimately, to achieve fair participant selection and broad social value in clinical research, both burden-specific site selection and local control of trials among LMICs are important. This paper focuses on the first issue, without diminishing the importance of the second.

Third, someone might agree in principle on the importance of enrolling more representative patient groups in research, yet note serious practical challenges, suggesting inequities may be currently unavoidable. After all, many LMICs have limited research capacity, which can be difficult, expensive and time-consuming to improve. Further, there can be regulatory system obstacles to conducting efficient multisite trials.[33 34] Notwithstanding, multiple examples suggest that research and regulatory capacity can be incrementally strengthened over time and geographical gaps in research access closed. For example, Canada and the US—who have recognised the problem of unrepresentative study populations at the national level[35]—are bridging their rural-urban and academic-community hospital gaps in trial access through new academic–community hospital partnerships.[36] Internationally, organisations such as the Wellcome Trust and the Fogarty International Center (FIC) have long track records of training and funding researchers in LMICs. FIC has used innovative funding models to support LMIC institutional research capacity advancement, including by supporting research ethics committee (REC) offices, grant management, and manuscript writing.[2] Contrary to sceptical views about LMICs, some studies suggest substantial research capacity now exists in many countries.[37]

Fourth, it might be argued that enrolling study populations proportional to disease burden may not be the best way to ensure that the data collected on new interventions is relevant to all patient groups. For many diseases or treatment modalities, geographic variation

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might not be a significant issue and researchers should focus on other potential confounding factors. In response, we agree that our proposed standard is crude. Further work needs to be done to ascertain when geographic variation matters. However, in the meantime, best ways to ensure that evidence reflects patient needs is to enhance transparency around who is included, and to ensure patients everywhere are represented in that evidence base. As we have argued, this is a matter of justice.

A final objection could be cost related, as pivotal trials may need to be larger, or more inclusive postmarketing studies completed, to allow for subgroup analyses across specific geographies and demographics. This could theoretically raise costs for sponsors. However, there is some evidence showing larger trials neither take significantly longer nor eat into patent time.[38] Even if costs are higher, this should be accepted by research sponsors. At present, physician prescribing is done without adequate supportive data for some populations. The patient populations who are under-represented are also more likely to be disadvantaged. They are not the people who should be bearing additional burdens.

PROCEDURAL RECOMMENDATIONS

While this article is focused on advancing consensus on the ethical importance of equitable global access to clinical research, rather than on providing practical strategies for implementation, we nonetheless offer two preliminary procedural recommendations. In addition to research sponsors, other actors can also help advance more equitable clinical trial access. RECs, contract research organisations (CROs), and medical journals should consider the ethical principles of social value and fair inclusion when reviewing and accepting study protocols. Specifically, they should require transparent reporting of trial site locations, on the country level, descriptions of the representativeness of country site selections to the global burden of the condition being studied, and explanations when high-burden countries are excluded from a study, consistent with recent efforts by major journals.[29] While enhanced transparency is not a panacea, as Justice Louis Brandeis famously argued in 1913, sunlight can be a good disinfectant, and understanding the root causes of why countries with high disease burdens are left out of studies can help us better address this problem and measure progress towards solving it.[39] To further aid with adoption of these procedures by researchers, organisations like the World Medical Association and the Council for International Organization of Medical Science should update their ethical guidelines for clinical research to specify the fair inclusion principle's application for international site selection and, at a minimum, recommend increased transparency around site locations, selection, and exclusion rationales.[23]

CONCLUSION

It is unjust when people suffer worse health simply because of where they were born. And, it seems hard to disagree with the need to optimise clinical outcomes for everyone infected or suffering from a condition or disease, not just higher-income patients and countries. We have argued that researchers and research sponsors, as well as CROs, RECs, journal editors and government agencies, have ethical obligations to help improve transparency around country trial site locations and help locate certain trial sites in countries and populations that reflect the burden of disease caused by the condition being studied. Further research will be needed to identify best ways to operationalise these ethical requirements.

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