Justice in Translation: From Bench to Bedside in the Developing World

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Abstract

Discussions about the ethics of conducting clinical research in the developing world have revolved around large-scale, late phase clinical research. However, we have uncovered various instances where researchers in the developed world have recruited developing world subjects into small scale, early phase translational trials of highly innovative treatment strategies. Among the criteria for ethically acceptable international research that are enunciated in ethical guidelines, two are of particular relevance to research of this kind: post-trial access to study interventions and responsiveness to host community health needs. After acknowledging the difficulty of applying the former to early phase translational studies, we argue that the question of access to benefits cannot replace the more fundamental question of whether or not a research initiative is responsive to the health needs of host community members. We advance ethical criteria for fulfilling the condition of responsiveness, and apply them to four types translational trials that might seek subjects from the developing world.
Much of the debate surrounding the conduct of clinical trials involving subjects from the developing world has centered on ethical issues that apply most directly to large scale, late phase research. As clinical research takes on an increasingly global character, however, individuals from low and middle-income countries (LMICs) have been recruited into small scale, translational trials of novel technologies such as gene transfer. The distinctive ethical concerns raised by such practices have received almost no attention.

In the analysis that follows, we consider four rationales for recruiting LMIC subjects into translational trials. The first is fortuity. LMICs occasionally present investigators with a research opportunity that would otherwise be unavailable if they used volunteers from high-income countries (HICs). Thus, an Italian gene transfer study of ADA-SCID would not have been ethically possible in HICs, because it required that subjects discontinue enzyme replacement therapy. Investigators imported subjects from Palestine and Colombia who were unable to afford the HIC standard of care. The second rationale is expedience: investigators sometimes recruit from LMICs to ease recruitment bottlenecks. An example would be a recent hemophilia gene transfer trial that sought subjects in Brazil. A third rationale is ultra-rarity. Some orphan diseases are of such low incidence that trials necessitate worldwide recruitment. Genzyme’s trial of alpha-glucosidase replacement, for instance, imported subjects from Palestine and elsewhere to clinical research centers. The last is prevalence: some trials involve diseases that primarily afflict populations residing in LMICs. For instance, Gates Foundation-supported initiatives are presently planning adenovirus-based malarial vaccine trials.
Research, LMICs, and Responsiveness

By what standard should the fairness of trials that propose to enroll LMIC subjects be judged? Various policy statements approach the question through an assessment of study objectives and the prospect that host communities will benefit from the research. For example, the Belmont Report states that justice requires that research participants not be selected because of their “easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied.” It goes on to require that research “should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research.”

CIOMS enunciates similar requirements under the headings of *responsiveness* and *reasonable availability*. According to guideline 10, research conducted in populations or communities with limited resources should be “responsive to the health needs and the priorities of the population or community in which it is to be carried out,” and “any intervention or product developed, or knowledge generated, will be made reasonably available for the benefit of that population or community.”

Although language within ethics codes varies in terms of its stringency, and some commentators reject all but the most permissive interpretations, there is a general international consensus that research in resource poor settings should be responsive to the needs of host communities (table 1). Nevertheless, serious consideration of what it takes
to fulfill the responsiveness requirement has been overshadowed by debates about reasonable availability. Of particular relevance to the present discussion, the latter has been attacked for being inapplicable to early phase trials, since they are not designed to vindicate interventions.

An operational definition of responsiveness is therefore badly needed. The last decade has witnessed a substantial increase in research that is sponsored by entities from HICs and carried out in LMIC populations. However, the Nuffield Council recently noted “in countries where nearly all research related to healthcare is externally funded, the priorities for research have been largely set by the external sponsors.”

We propose that protocols be defined as responsive to the health needs of the host community only if (a) they are part of a program of inquiry that will expand the capacity of health-related social structures in the host community to (b) meet urgent health needs.

We recognize that there are myriad ways in which host communities can benefit from research. Fundamentally, however, we think that the question of responsiveness should focus on the most distinctive and profound social value of clinical research: its capacity to generate information that communities can use to better meet the urgent health needs of their members. Whether a research initiative is responsive to the health needs of participating communities should be determined by examining the relevance of the research as a form of scientific inquiry, rather than as a conduit for supplementary
benefits. As such, satisfying the first condition requires that a protocol generate information that can enable hospitals, clinics, or public health entities to better address the health needs of community members, or be part of a process of developing interventions that can reasonably be projected to be effectively deployed in the host population.

We also recognize that host communities can have a wide range of health needs, not all of which might be urgent. Nevertheless, when host communities face difficult choices about how best to allocate scarce resources, both justice and beneficence require that those resources be used in ways that have significant social value. Whether a health need is regarded as “urgent” should be determined in light of a variety of factors. These include the severity of the condition, its prevalence in the host community or among special subpopulations, and the value of ensuring that the health infrastructure of a community is capable of addressing a wide range of health needs. However, evaluations of the responsiveness of protocols to the health needs of host communities should give special attention to the extent to which new knowledge, as opposed to better access to existing interventions, will enable a community to more effectively address that health need.

These conditions are supported by two additional considerations. First, we believe that there is a moral imperative to assist LMICs in the process of developing the capabilities necessary to more effectively address their most pressing, unmet health needs. When research satisfies the above conditions it can make a profound contribution to this goal.
Second, research that violates these conditions creates a division of labor that is at least *prima facie* unfair, to the extent that it enlists those who suffer the heaviest health burdens to advance science that will create the greatest social value for residents of HICs.

**LMICs and Translational Trials**

Whether a trial can strengthen health-related social structures will depend on the relevance of the information generated to the health institutions in that community. However, infrastructure requirements, intellectual property complexity, high development and manufacturing costs, and the mixed record of distributing HIC health interventions to LMICs provide grounds for examining carefully claims of relevance. Additionally, many such studies are viewed by sponsors or others as having objectives that extend beyond the disease being targeted. ADA-SCID\textsuperscript{13} and hemophilia,\textsuperscript{14} for example, are widely regarded as systems for validating general principles of human gene transfer. Whether such studies are also directed at the health needs of LMICs may be ambiguous.

With these observations in mind, consider how our responsiveness criteria might be applied to the four rationales for translational researchers that recruit in LMICs. Fortuitous studies may target important medical questions—ADA-SCID, despite its low prevalence, is a severe affliction. However, many such translational protocols do not seem to enhance the ability of host communities to meet the needs of individuals afflicted with such disorders. Individuals with fortuitous research characteristics, such as treatment naïveté or lack of access to standard treatments, are generally sought for their
membership in groups whose deprivation stems from their marginal social or economic circumstances. But these are also groups whose access to the fruits of scientific advances is often severely limited. Whether protocols are exported to LMICs or subjects imported to research sites in HICs, such recruiting practices transfer to disadvantaged populations risks that are justified by the prospect that the research will enhance the functioning of health systems from which these populations are excluded.

Similar concerns apply to the types of trials that enroll LMIC subjects for expedience. Since trials recruiting because of expedience often also recruit from HICs, this rationale may seem ethically distinct from fortuity. However in some instances, expedience may be fortuity in disguise. A trial’s balance of risks and benefits is often dramatically different for LMIC and HIC subjects; because of their medical deprivation, the former may be more willing to endure invasive procedures and indeterminate trial risks than persons who can access an adequate standard of care. Deprivation thus creates fortuitous recruitment opportunities for researchers.

Ultra-orphan trials present a more complicated problem. Because they are so widely dispersed, it may not be possible to recruit subjects from any single jurisdiction. When studies cannot be conducted without international collaboration, including the participation of LMICs, it may not make sense to require that such studies produce knowledge that will specifically enrich a local health infrastructure. Whether the requirement of responsiveness has been met will thus depend more directly on whether reasonable provisions are in place that ensure that the results of such initiatives will be
used to address the ultra-orphan condition as it arises within the larger international community. These might involve pretrial agreements between a sponsor and international bodies like the WHO to distribute eventual products to persons in LMICs at vastly diminished cost.

Of the four justifications, prevalence can make the strongest claim to satisfying the requirement of responsiveness. Nevertheless, diseases like Hepatitis C or HIV/AIDS also afflict persons in HICs. For example, the U.S. Department of Defense presently sponsors research on adenoviral vectors for malarial vaccines. Such research is undertaken primarily because malaria adversely affects military deployments. Our view would not prohibit the U.S. military from testing malarial vaccines in LMIC volunteers, provided that such trials are designed to produce information that will advance the development of interventions that are also compatible with the economic, cultural, and infrastructural conditions of host communities.

We would therefore underscore the importance of the responsiveness requirement, not simply as a litmus for evaluating research proposals within IRBs, but as an ethical objective that should shape the direction of clinical research long before it reaches IRB review. In particular, consciously fostering research that satisfies this requirement is key to unlocking the power of research to advance health and development in LMICs.

We anticipate three major objections to our analysis. First, our scheme might be accused of denying LMIC countries, and individuals residing in them, the opportunity to
participate in trials that they regard as offering tangible, immediate benefits. Such a potential outcome is not the product of our ethical analysis per se, but of a willingness to carry out research in LMICs only if it advances the priorities of HIC sponsors. Given the substantial bargaining advantage of sponsoring countries, the willingness to accept such transactions may represent the desperation of host communities more than their zeal for advancing the HIC research agenda. Rather than changing the ethical analysis to permit the provision of \textit{ad hoc} ancillary benefits to outweigh the fact that the knowledge generated by a research initiative is of limited relevance to the urgent health needs of LMIC communities, we believe that more resources should be committed to increasing the amount and quality of research that responds to the urgent health needs of LMICs.

Second, critics might argue that some trials aim to develop interventions that offer persons in LMICs with particular afflictions the best chance of a sustainable cure,\textsuperscript{16} and that such innovations will eventually “trickle down” to LMICs. Such critics might further argue that it’s nearly impossible to project from early trials how an intervention might ultimately be applied. While we acknowledge this difficulty, we believe that it is important for early phase trials to anticipate and address foreseeable constraints and realities of applying interventions in LMICs. Although there may be some sense in which scientific research eventually benefits all of humanity, the fact that as much as 90\% of the avoidable mortality in LMICs stems from a handful of causes for which effective interventions already exist illustrates the glacial pace at which such a “trickle down” approach proceeds.\textsuperscript{17}
It is also important to avoid a simplistic dichotomy between “access” and “innovation.” Even an unprecedented effort to increase LMIC access to existing interventions would not eliminate the need to invest in new knowledge that is directly relevant to the health needs of those communities. In some cases, this is because the most far-reaching health gains would come from interventions that require an investment in clinical research, such as vaccines for diseases such as HIV, TB and malaria. In other cases, this is because research is necessary to help LMICs address unique health threats (e.g. drug resistant variants of tuberculosis), or more widespread health problems that LMICs must address under severe resource constraints (e.g. heart disease).

Third, critics might point out that some affluent persons in LMICs may enjoy a standard of care that compares favorably with persons in HICs. We agree that recruiting such persons into HIC-sponsored trials that are driven primarily by HIC priorities may not raise the same ethical problems as recruiting their less affluent compatriots. In part, this is because such persons do not face the same social and economic deprivations as their compatriots. As a result, such research may meet the condition of responsiveness for the inhabitants of such “islands of affluence,” to the extent that they participate in a global market for medical care. However, for some of the recruitment rationales we are concerned with here, it is precisely this feature that makes such persons unattractive candidates for research.

In conclusion, we have attempted to clarify two questions relating to international research that have received limited attention: by what criteria might small-scale, early-
phase research be judged to fulfill the requirement of responsiveness, and when can HIC sponsors ethically recruit subjects from LMICs into such trials? Our criteria make it difficult to justify recruiting persons from the developing world for reasons of fortuity, raise questions about expedience, and provide conditions for the ethical conduct of trials involving ultra-orphan and highly prevalent diseases.
Table 1: Language on Responsiveness in Selected Research Ethics Reports or Policies*

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<tr>
<th>Organization</th>
<th>Report / Policy</th>
<th>Statement</th>
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<tr>
<td>CIOMS / WHO, 2002</td>
<td>International Ethical Guidelines for Biomedical Research Involving Human Subjects</td>
<td>Before undertaking research in a population or community with limited resources, the sponsor and the investigator must make every effort to ensure that: the research is responsive to the health needs and the priorities of the population or community in which it is to be carried out</td>
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<tr>
<td>European Group on Ethics in Science and New Technologies to the European Commission, 2003</td>
<td>Ethical Aspects of Clinical Research in Developing Countries. No 17</td>
<td>In the evaluation of a research protocol, special attention should be paid to the following issues: the relevance of the research to be carried out in a developing country. Specific attention should be paid when the objective of the clinical trial does not comply with health priorities of the host country</td>
</tr>
<tr>
<td>Islamic Organization for Medical Sciences (in cooperation with CIOMS and WHO), 2004</td>
<td>International Ethical Guidelines for Biomedical Research Involving Human Subjects -- An Islamic Perspective</td>
<td>That the sponsor and the investigator should make every effort to guarantee the responsiveness of the research to the health needs and priorities of the population or community of limited resources in which it is carried out is a requirement recognized in Islamic Law</td>
</tr>
<tr>
<td>UNAIDS, 2000</td>
<td>Ethical Considerations in HIV Preventive Vaccine Research</td>
<td>The conduct of clinical trial components in a country or community that is relatively vulnerable to harm or exploitation is ethically justified if... the vaccine development programme is necessary for and responsive to the health needs and priorities in their country</td>
</tr>
<tr>
<td>World Medical Association, 2004</td>
<td>Declaration of Helsinki</td>
<td>Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research</td>
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**National Reports / Policies**

| National Bioethics Advisory Committee (U.S., 2001) | Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries | Clinical trials conducted in developing countries should be limited to those studies that are responsive to the health needs of the host country |
| National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (U.S., 1979) | Belmont Report | ... research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research |
| Nuffield Council on Bioethics (U.K., 2002) | The Ethics of Research Related to Healthcare in Developing Countries | ... all externally-sponsored research should be required to fall within the ambit of the national priorities for research related to healthcare within developing countries, unless the reason for not doing so can be justified to the appropriate research ethics committee within that country |
| South Africa, Department of Health 2000 | Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa. | Whilst maintaining the highest standards of clinical research it is important that clinical trials are based on priority, country specific research questions. Relevant and important questions should also be problems that significantly affect local and regional population |
| Tanzania National Health Research Forum, 2001 | Tanzania Guidelines on Ethics for Health Research in Tanzania | The outcomes of the research should benefit the population from which the research participants are drawn |

* reports / policies listed in alphabetical order by organization
References


