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Exploitation & International Clinical Research: The Disconnect between Goals and Policy
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The last thirty years have seen a dramatic increase in the amount of biomedical research being conducted in low- and middle-income countries (LMICs). In the early 90s, only about 10% of clinical research was conducted in LMICs, but by the mid 2000's that number had ballooned to 40%.[1] Importantly, a significant amount of LMIC research is sponsored by pharmaceutical companies, NGOs, and public research institutions from high-income countries. Many of these institutions seek to develop interventions to address unmet health needs in LMICs, but many others utilize LMIC settings to reduce the costs of research while developing interventions intended for marketing in high-income settings.

Disparities in wealth and access to healthcare between those populations in which interventions are often tested (so-called "host communities") and those where many of them are ultimately marketed generate concerns about exploitation. While some exploitation involves interacting with vulnerable parties against their will or in ways that are ultimately harmful to them (slavery is a form of exploitation, for example), the concern in international research is more often a worry about some kind of unfairness in the distribution of the benefits and burdens generated in the process of the research interaction: research sponsors, researchers, and even healthcare consumers in high-income countries (HICs) benefit from such research whether via high profit margins or improvements to healthcare systems, while research subjects in LMICs take on the risks associated with research but continue to lack access to many of the health interventions considered standards of care in high-income settings.

Although there is ongoing theoretical disagreement about the precise shape of the moral wrong of exploitation, it is typically understood in these discussions as some kind of unfairness in the distribution of benefits and burdens between parties to an agreement or transaction. The claim is often that the exploited parties (research participants) receive a disproportionately small share of the benefits generated by the interaction as compared with the benefit to the exploiting party (the research sponsor and/or investigators), or that the exploited parties receive a share of the benefits generated that is disproportionately small considering the exploited party's needs.[2]

Such concerns have prompted many bioethicists and quasi-regulatory organizations to posit special ethical requirements for researchers and research sponsors conducting research in LMIC populations.[3] In this chapter, I will briefly canvas those ethical requirements that have been put forward as mechanisms for protecting LMIC research subjects from exploitation, as well as some of the debates around them, before going on to consider how effective these mechanisms are at combatting the transactional form of exploitation that is taken for granted in much of this literature. Finally, I'll indicate where our conceptual framework must be improved if we are to fully understand the nature of the moral claims and obligations that arise in LMIC research.

Guidelines for International Clinical Research

Standards of Care

One primary driving force behind the migration of clinical research away from high-income settings towards LMICs is the significant cost savings available to sponsors who conduct their

research in underprivileged settings. In many cases, disease is more prevalent in LMIC populations due to limited healthcare resources, making it easier to speed trial recruitment, which in turn makes research faster and less costly to conduct. Consent and oversight procedures are frequently less onerous, trial staff are less costly to employ, and background standards of care are less demanding than in high-income settings. Each of these factors contributes to incremental cost savings for trial sponsors which, when taken in aggregate, amount to a significant reduction in the costs of research and development.

Importantly, when existing standards of care are less demanding in low-income settings, it is usually not due to a lack of scientific consensus regarding the most effective interventions, but rather a reflection of background conditions of resource scarcity, lack of infrastructure, or other complex vulnerabilities. The ability to provide research participants with a standard of care that is less effective than standards that would be required in high-income settings in order to attract participants or withstand the scrutiny of ethical oversight is one way in which research sponsors can retain a greater share of the benefits that are generated by the research interaction between sponsors, investigators, and research participants. Additionally, this can lower the evidentiary burden sponsors are facing, since showing a new intervention is superior to placebo or a less effective intervention will generally be easier than showing it is superior to a more effective intervention.

The possibility of providing less-than-best standards of care, coupled with ongoing questions about the obligations of physician-researchers to patient participants in LMICs, has generated a robust debate regarding what standard of care should be offered to research participants in contexts where the background standard of care is lower than that found in

HICs.[4] Historically, some have argued that use of the local established standard of care as a control – in many cases no treatment at all – did not deprive trial participants of anything to which they would be entitled or have access outside of a trial, and therefore was not problematic.[5] However others have pointed out that the use of the de facto local standard of care in LMICs as the benchmark for standards within clinical trials introduces a troubling double standard in research ethics guidelines, and opens the door to further exploitation of LMIC populations in research.[6] The principle of defaulting to the global best standard of care is enshrined in international guidance documents such as the Declaration of Helsinki.[7]

While some argue that providing research participants with anything less than the global best standard of care would be exploitative, others insist that requiring such a high standard of care will disincentivize important research that can benefit host populations in other ways, such as the development of lower-cost effective interventions that are more relevant to low-income communities because more likely to be implemented locally.[8] In attempting to navigate these competing concerns, some propose more permissive approaches to standard of care, suggesting that the default use of the global best effective intervention is defeasible in certain instances. Wendler and colleagues argue that if a less than best comparator is scientifically necessary, if the research is relevant to the host community, if participants are not exposed to greater risks than they would be outside of the research context, and if the host community will benefit sufficiently in other ways then an exception to the global best standard can be made.[9] Others offer even more permissive standards, appealing to scientific need in a non-life-threatening condition with approval from a local ethical oversight board.[10]

Responsiveness

Another frequently repeated admonition is that research conducted in LMICs should be responsive to the health needs or deficits of host communities.[11] Although numerous interpretations of the responsiveness requirement are on offer,[12] the general idea is that for research in an LMIC to be ethical, it must be investigating interventions or procedures that could address existing health needs within that population. This might variously be interpreted to rule out clinical trials investigating conditions that are not very prolific in an area, to restrict research to only those conditions that are a local health priority, or to limit trials to those with the potential to influence local health policy or resource allocation. Insofar as the claim of exploitation points to a problematic distribution of the benefits and burdens of an interaction, responsiveness seeks to address it by ensuring that a greater proportion of research-generated benefits devolve to the population hosting the research rather than only to the populations from which sponsors and researchers hail.

The responsiveness requirement is included in several guidance documents, including CIOMS and the National Bioethics Advisory Commission's *Ethical and Policy Issues in International Research*.[13] Nevertheless, some theorists have raised concerns mirroring those canvassed above about standards of care. In particular, the conduct of clinical research in LMICs can often be seen to bring benefits other than research results to host communities. Participants often receive levels of care to which they would otherwise not have access, even if they wind up on the placebo arm of a placebo-controlled study, such that in some cases all participants benefit relative to a situation in which the trial was not conducted. Studies can

bring research and other healthcare infrastructure to otherwise underdeveloped healthcare settings. In some cases, participants may be compensated for their participation.

Importantly, if a trial sponsor cannot conduct a non-responsive study in a particular population, the alternatives are not limited to conducting a responsive study. The sponsor can instead choose not to conduct a study in that population at all. In light of the various benefits that can accrue to LMIC research participants and host communities from internationally-sponsored research, we might worry that requiring such research to be "responsive" in the relevant sense will only have the effect of preventing research that is beneficial to local communities in the above ways from being conducted in such settings. The upshot would be to deprive communities of benefits which are badly needed and not available via alternative means.[14] Such concerns have led some to argue that the benefits that externally-funded clinical research can bring to host communities to alleviate concerns of exploitation ought not to be limited to the value of research outputs. I say more about this in the next section.

Post-Trial Access, Fair Benefits, Socially Valuable Knowledge, and Human Development

A third mechanism that is frequently appealed to for preventing or ameliorating exploitation of host communities, often in conjunction with responsiveness, is some kind of assurance of post-trial access to study interventions. [15] There are a number of forms that this could take. One is to provide study participants with ongoing access to investigational therapies that are shown effective after a trial has ended. In this way, participants can continue to benefit from the knowledge gains that are made in biomedical research.[16] Others go farther, suggesting that host communities more broadly conceived might have a claim to post-trial access to study

interventions.[17] Shapiro and Meslin, for example, claim that "the ethical obligation to provide the intervention to others in the community who might benefit from it is considerably less strong, but a plan to do so would help reduce the risk of exploitation."[18] The admonition that research sponsors and investigators should work with local regulatory officials to ensure that study interventions are made reasonably available after the conclusion of a trial is included in guidance documents such as the Council for International Organizations of Medical Sciences *International Ethical Guidelines for Health-Related Research Involving Humans*[19] and the National Bioethics Advisory Commission's guidance for research conducted in LMICs.[20]

As in the cases of standards of care and responsiveness, some worry that demands for post-trial access may ultimately harm low-income populations. In this case, there is a concern that requiring post-trial access might hamper biomedical progress in LMICs, effectively constraining them to take up interventions for which there exist prior agreements for dissemination. Moreover, demands for post-trial access or so-called "reasonable availability" of interventions after the conclusion of a trial can fail to have the exploitation-minimizing impact intended if, for example, a trial generates negative findings (and thus has no intervention to ensure access to) or access is insufficient to ensure a proper or fair distribution of the overall benefits of the research interaction. The primary critique of post-trial access is that it focuses on the *type* of benefit to be ensured to host communities, rather than on the *amount*, where it is the latter that is most relevant for addressing exploitation as a distributive concern.[21]

This seeming mismatch has motivated some to suggest that what is important is that the level of benefits that devolve to participants and host communities be fair, rather than what the content of those benefits are. Proponents of the so-called "fair benefits" approach

argue that benefits to research participants during a trial, benefits to host communities during a trial, and benefits to participants and host communities after the conclusion of a trial should be indexed to the benefits and burdens that the trial generates. As risks and burdens of research increase, so should benefits to participants and host communities, and as the benefits of the research to sponsors increase, so too should benefits to participants and host communities. And according to fair benefits proponents, the best way to ensure that the distribution of research benefits is fair in these ways is to allow the host community to determine for itself, in consultation with researchers and research sponsors and in the presence of transparency about the outcomes of other research agreements, what kinds of benefits it should receive in exchange for hosting research, and in what amount.[22]

Where the fair benefits approach does not specify what kinds of benefits to host communities are necessary to address exploitation worries, other approaches do. According to the "socially valuable knowledge" approach, a clinical trial must be expected to produce knowledge that itself can be construed as a benefit to the host community. This can be knowledge that a particular intervention is safe and effective, but it can also be knowledge that contributes to the development of new lines of research or feeds back into the scientific process in other ways. On this view, the expected knowledge gain from a trial plays an important justificatory role in the subjection of human subjects to research burdens, and that justification is context-dependent such that the expected epistemic gains should devolve to the same population that bears the relevant burdens.[23]

Similarly, the "human development" approach requires researchers and research sponsors to provide benefits that contribute to the capability of a host community to meet the

basic needs or distinctive health priorities of that community. Health needs are prioritized based on whether they can be addressed through the application of existing knowledge and resources, and as a community's existing capacity to meet citizens' basic needs decreases, the sponsor's obligation to provide access to proven therapies and additional infrastructure increases.[24] While the human development approach is not defended primarily as a means of preventing exploitation, it is offered as an alternative understanding of the obligations of researchers and research sponsors to bring benefits to those LMIC communities from which they recruit participants.

Exploitation and Research Ethics Standards: A Mismatch

The view of exploitation that is largely assumed in the research ethics literature is a transactional one.[25] Wrongful exploitation of the kind in question occurs when two or more parties interact for mutual benefit and one party receives less than its fair share of the social surplus created by the interaction. The adoption of this view of exploitation in research ethics is unsurprising, given the background understanding of clinical research as ultimately a transaction between researchers, sponsors, and research participants. On this view – one explicitly endorsed by prominent theorists such as Alan Wertheimer – protections such as prospective risk/benefit assessment and ethical oversight including the promulgation of standards such as those canvassed above are justified due only to the inability of otherwise competent adults to protect their own interests in clinical trials given asymmetries in biomedical knowledge.[26]

However, there is an important tension between this view of what constitutes exploitation and the solutions that are offered as means of ameliorating it between HIC

researchers and sponsors and LMIC communities and participants. While some of the standards ethicists promote as means of reducing exploitation, such as higher than local standards of care or post-trial access for study participants, focus on ensuring greater benefits for research subjects, many are focused instead on benefits to host communities. Ethical constraints such as responsiveness, the provision of fair benefits or socially valuable knowledge, and human development seek to ensure that local health systems, infrastructure, and research capabilities are improved, but don't clearly adjudicate the concern for exploitation when exploitation is construed as a worry about transactional fairness in a transaction comprised of research sponsor, investigators, and trial participants. We can see this if we consider that benefits to a community don't necessarily devolve to the participants in a clinical trial, who may be taking on significant burdens. Even if a trial is responsive to local health needs, generates locally valuable knowledge, and provides increased local healthcare and research capacity, individual research participants may have fairness-based claims to receive a non-exploitative share of the benefits produced via research.

One way we might resolve this tension is to appeal to indirect benefits. We might think, for example, that research participants benefit from improvements to local health systems or improved local access to effective interventions because they are likely to draw on those health systems in the future, and that these indirect benefits make research transactions with LMIC citizens less exploitative.[27] But note that if this is the way that ethical requirements such as responsiveness and fair benefits address exploitation, it seems better suited to addressing the exploitation of host communities than that of research participants. If participants were provided a greater share of benefits, via direct payments or post-trial access, sufficient to make

the research transaction "fair" in the relevant sense, ethical requirements demanding indirect benefits of this kind would appear to be ungrounded. At the very least, they would no longer be justifiable by appeal to the exploitation of research subjects.

An alternative justification for standards requiring benefits to host communities might appeal to the drain that trials place on local healthcare systems and the opportunity costs to communities inherent in the diversion of local resources and infrastructure towards research support.[28] While these observations have merit, such standards would nevertheless only be a response to concerns about exploitation if our concern was for the exploitation of the host community, rather than the exploitation of trial participants. But just as sufficient payment to research subjects could make exploitation claims fall away even in the absence of community benefits, individual exploitation claims can persist even when a host community benefits greatly, since benefits to a community may be distributed very unequally among community members.

These considerations suggest that perhaps what is actually intended by many of these standards is an amelioration of community, rather than individual, exploitation. If the concern is that LMIC communities fail to receive enough benefits from research interactions, then calls for fair benefits or development or community-wide post-trial access seem to make more sense. The trouble is, the conceptual apparatus that is currently relied upon to discuss and assess claims of exploitation doesn't lend itself easily to discussions of exploitation of a community. It is difficult to explain who the relevant parties are in an exploitative "transaction" with a host community. Which members of the community are being exploited, if not the participants in a trial?

We might suggest that each individual community member is potentially exploited and so owed benefits, but if this is our answer it runs into the same problems as above: it is not clear that benefits such as improvements to local research infrastructure or access to particular interventions benefit all community members, and it is difficult to ensure that the distribution of such benefits is equal. Alternatively, in the case in which healthcare resources are diverted from other important uses, it is plausible to claim that those who are impacted by that diversion are owed something in return. But then of course it is difficult to identify who those parties are, and equally difficult to establish that policies such as responsiveness or capacity building are ultimately benefiting those same parties, and consequently reducing exploitation.

It's important to note that the tension here is the same tension that is found in balancing risks to subjects with benefits to society in any clinical research. Generally speaking, clinical research is not conducted with the intention of providing benefits to the participants in that research, but rather to future patients. The upshot is that all research interactions have the potential to be exploitative. The primary difference between research conducted in high-income settings and that conducted in low- and middle-income settings is that research participants in HICs already disproportionately benefit from the advances in medicine that have been driven by the last several decades' worth of biomedical research, whereas many of those benefits have failed to devolve to LMIC communities. It is this difference in who is ultimately benefiting from the research being conducted – in LMICs and elsewhere – that seems to primarily motivate so many exploitation concerns, and ultimately leads to the question: under what conditions is it reasonable to ask someone to participate in research?

Much of the research ethics focus on exploitation seems driven by this question, but it's not clear that the answers provided are satisfactory if worries about exploitation are the motivating consideration. On the one hand, we might think that the mismatch between the standards proposed for addressing worries about exploitation highlights a deficit in the conceptual apparatus we have for discussing exploitation. Where the dominant account of exploitation is transactional, it is focused on the exploitation of individual research participants, when what is needed is an account of exploitation that can address the exploitation of communities as distinct from the exploitation of individual members of those communities, or which is better able to account for structural rather than transaction-specific exploitation.

On the other hand, we might think that the kinds of interactions being assessed – research interactions involving LMIC communities, participants drawn from those communities, and researchers and research sponsors disproportionately from HICs – are not transactional in the limited sense that is often assumed in discussions about research or exploitation. Perhaps, in other words, there are more parties to clinical research interactions than merely participants, sponsors, and investigators. And in particular, we might think that the members of LMIC host communities are parties with legitimate moral standing with respect to research conducted in their communities above and beyond their identification as parties to transactions.

This might be due to research burdens that devolve to host communities, as suggested by some theorists.[29] But it leaves open the possibility that community members have standing for other, non-transactional, reasons as well. For example, the community itself might have moral claims against researchers and sponsors not due to any burdens taken on by the community in particular research interactions, but instead due to researchers' and sponsors'

contributions to the maintenance of a particular global structure that is both imposed non-voluntarily on LMICs and maintains a large disparity in access to health between LMICs and HICs.[30] Such considerations ground obligations to host communities not in claims about exploitation, but rather rectification for harms done, whether directly or indirectly.

But we might also think the community has moral standing with respect to clinical research by virtue of the role that clinical research plays as part of the social institutional structure that determines what health systems look like. The basic motivation behind clinical research is to impact medical practice. Non-profit research entities target high-impact diseases or specific health burdens to try to ameliorate, while for-profit research sponsors seek to develop marketable interventions that can be disseminated as widely as possible into profitable healthcare markets. All researchers seek to circulate their research results among professional spheres consisting of practicing physicians, public health officials, policy-makers, and regulatory bodies. Without these complimentary efforts, clinical research would be a wasted investment. But importantly, it is generally not up to individual patients how the results of clinical research will impact the health care that is available to them or the health systems to which they have access. Those decisions are often dispersed across a range of actors, and often are not the result of discrete decisions at all, but rather of long, complex processes involving stakeholders at many levels of medicine, industry, and bureaucracy.

Despite their lack of input into the way the research enterprise impacts local health systems and the healthcare that is available to them, these impacts nevertheless have a deep and lasting effect on the life prospects of all members of a community. Importantly, individual members of a community have no opportunity to opt into or out of a health system in most

instances. Rather, what is available to them is determined by the dispersed decision-making processes described above. But given the deep and lasting impacts that access to health and healthcare have on a human life, citizens arguably have moral standing to claim consideration in the determination of which questions are studied and how those studies are used to benefit themselves, their communities, and the health systems within which they participate. And importantly, those claims can be grounded not only in transactional fairness, but also in the basic moral claim to live within a just institutional structure.

But perhaps this proves too much: if members of host communities have claims to be considered during research negotiations, and if those claims are grounded not in worries about transactional exploitation, but in the impacts that clinical research has on local health systems, on what basis can that moral standing be limited to members of host communities? Given the way that medical knowledge is disseminated into practice, research conducted in one community will also impact the health systems that members of other communities, far removed, participate in.

One potential response to this is to differentiate between those aspects of the research agreement that are most relevant to considerations about the basic structure, and those which are more appropriately construed as grounded in some form of community or structural exploitation. Considerations of the former kind may, indeed, ground justice-based claims to consideration for those outside of a host community. But this doesn't seem too demanding: if the health research enterprise is in fact a part of the basic structure, then it is a natural upshot that all participants in health systems that could be impacted by health research would have a justice-based claim to potentially benefit from that research, for example. Meanwhile,

considerations about the appropriate benefits to local communities from hosting research seem best answered by appeal to a conceptual framework that is capable of adjudicating claims of structural or community exploitation – a conceptual framework that is sorely lacking within contemporary bioethics. If research ethicists want to be able to assess such claims, the necessary next step is the development of such a conceptual framework.

Conclusion

Much of the current discussion about research conducted in LMICs is predicated on a transactional view of research that pairs naturally with accounts of exploitation that are similarly transaction-specific. In this paper, I've spelled out a number of considerations that speak against relying exclusively on the framework of transaction-specific fairness to adjudicate the obligations of researchers and sponsors conducting research in low-income populations.

First, research stakeholders conduct biomedical research with the intention of altering health systems. Second, the impacts that such research has on health systems are not dictated by, nor able to be avoided or opted out of, by those who are impacted by them. Third, the shape and content of local health systems is an important piece of the basic institutional structure that governs the life chances of all community members within the scope of a health system. Given these considerations, the conception of clinical research as a transaction between sponsors, investigators, and trial participants is inadequate for understanding both the ethical obligations of research stakeholders, as well as the moral claims of those within host communities to benefit, perhaps in particular ways, from health research. To understand the competing claims and obligations in these settings, we must recognize the role of the research

enterprise as part of the basic institutional structure and therefore subject to claims of structural justice. Moreover, a framework of structural exploitation may be helpful in such discussions, but the current framework of transaction-specific fairness is limited in the insights it can offer. To make headway in these debates, the development of a more appropriate conceptual framework of exploitation is necessary.

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