The Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard Bioethics Collaborative

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Virtual Meeting

Reciprocity in Research: Does the Principle of Justice Support Community Investment

Introduction

It is generally agreed that sponsors and other entities undertaking medical research in limited-resource settings incur certain duties of reciprocity. This responsibility arises primarily because of the potential for exploitation of host communities due to the potential unfair distribution of benefits and burdens between communities and researchers. Host communities face the risks and burdens of research, including the possibility of strain on local infrastructure, and participants may or may not directly benefit from participation. By contrast, researchers and sponsors almost always benefit from the research, gaining valuable knowledge that can inform future therapeutic development. Therefore, the question at stake is how to avoid exploitation while ensuring that host communities are treated fairly and not exploited, given the burdens and risks of the research they undertake. The June 18 meeting of the MRCT Center Bioethics Collaborative was devoted to understanding and assessing different approaches to satisfying the ethical contours of reciprocity for research undertaken in resource-limited settings.

There is a consensus among the research community that we must design studies to meet familiar ethical norms no matter the location at which the research will be performed. Such ethical norms require that risks are minimized and reasonable in relation to the benefits the participants will endure, that participant selection is equitable, and that prospective informed consent be obtained. There is less agreement within the research community on how to meet these ethical norms or what ethical study design requires in resource-limited locales. Some examples of disagreements involve when it is ethical to use placebos, and whether comparator arms may use local standards of care or must contain the best available standard of care globally. Even when assuming that research studies are designed ethically, we can still ask whether there is anything else, over and above ethical study design, that is needed to avoid exploitation of host communities and, in particular, whether the principle of justice supports or even requires the provision of benefits to participants or the wider host community.

Bioethics literature has tended to assume that reciprocity is important and focuses on what exactly must be done to avoid exploitation. There are three prominent approaches in the bioethics literature: (i) the "reasonable availability" approach, (ii) the "fair benefits" framework, and (iii) the "human development" approach.

The reasonable availability approach, which is derived from the Council for International Organizations of Medical Sciences (CIOMS) guidelines 8 and 15, requires a commitment to making any intervention successfully developed in the research reasonably available to the host community. Such a commitment is taken by defenders of the view to be both necessary and sufficient to avoiding exploitation. Critics have focused on several questions, including whether such a commitment is enough, particularly when access remains challenging even after regulatory approval and registration, for example, due to the cost of the interventions.
The fair benefits framework holds that exploitation of host communities can be avoided by providing them a fair share of benefits.[i] What is important is not so much the specific benefits provided but rather that the host community receives a *fair share* relative to the risks and burdens they undertake and the benefits generated for the researchers. This view emphasizes the autonomy of host communities, stressing that it is up to host communities themselves, rather than researchers or sponsors, to decide what type of benefits are important and to work out in negotiations with researchers what counts as a fair share. The fair benefits framework thus acknowledges that benefits related to capacity building and infrastructure and other wider community benefits may be more important to host communities than the access to specific therapeutic products.

The fair benefits framework has been subject to significant interpretation and critique. One line of criticism charges that the fair benefits approach conceptualizes the interaction between researchers and host communities as a market transaction that may, in the actual world, end up resembling an auction, with different host communities in competition to attract research and being willing to accept less benefit than each other toward that end—which risks a "race to the bottom."[ii] Other questions involve whether the negotiation process should be constrained by independent principles of justice since giving host communities autonomy in deciding for themselves what is considered a fair share could actually result in communities accepting less than what is independently determined to be fair, given potential disparities in bargaining power between the community and researchers. Lastly, the fair benefits framework can be seen as treating partnerships between researchers and host communities as purely optional

and unconstrained by prior obligations, foreclosing the possibility that justice might obligate certain types of research and place limits on acceptable negotiations and outcomes.

By contrast, the human development approach affirms that justice demands the conduct of certain research and places constraints on what arrangements are fair.[iii] This approach starts from the idea that the state has an obligation to support robust social institutions that permit citizens to develop their capacities to pursue a life of their own choosing and, ultimately, to flourish. This includes an obligation to conduct health-related research, given that disease and death interfere with human flourishing. Governments of wealthy nations and private research sponsors should ask how current research proposals or past actions might play or have played a role in preventing lower-resourced nations from meeting these obligations to their citizens and communities and be attentive to the possibility that they might incur duties even apart from the details of explicit negotiations with host communities.

Presentations and Discussion

After the introductory presentation, participants noted the historical injustices that have taken place in lower-resourced countries at the hands of wealthier nations in the context of medical research. For the human development approach in particular, participants wondered whether a new company or venture (or country), with no previous involvement in medical research injustices in LMICs, should be expected to take the same approach as a company (or country) that has historically participated in injustice and exploitation of host communities. It was noted that despite a company coming into the field with integrity, it would still be building on the foundations laid by those companies that engaged in previous unjust work. In addition, it was clarified that the human development approach takes into consideration the strain or burdens put on a community by the current research proposal, which can create duties even apart from historical considerations.

Building on this theme, attendees noted that research conducted in lower-resourced locales may involve consumption of the host community's resources and that researchers need to be conscious of what is consumed versus what comes back to the community. At the same time, sites partnered with or within host communities are typically, and should be, compensated for their role in a study, and care is needed to discern whether or to what extent research in fact places net burdens on a community. Historically, there is reason to believe that some research has imposed net burdens on host communities. One participant shared an example of a 2015

WHO study conducted in Latin America, which demonstrated that only 25% of drugs tested in the region reached the market in the host country and, of those drugs that reached the market, most were unaffordable for the average person living in Latin America. Another participant noted the need for an independent mechanism to measure and evaluate strains put on infrastructure.

The first speaker emphasized a need to look at two levels when evaluating the strains placed on a community as well as the adequacy of reciprocated benefits: the "grassroots" level and the "upper-middle" level. The grassroots level focuses on what lay community members perceive as the burdens and benefits of participating in research. The expectations and beliefs of community members may not always be easy to predict. As an example, the speaker adduced a vaccine study in Malawi, where the local population did not perceive immunization alone as a benefit and tried to negotiate additional benefits, such as subsidized fertilizer; when the request was denied, mothers refused to immunize their children. This example shows the crucial importance of understanding what host communities view as benefits. In this context, there is also a need to teach communities and help them better understand the potential health benefits of the research being conducted. Although there are community advisory boards throughout the African continent to help advise on these matters, some regional areas do not yet have them while others face regional challenges impeding their function. There may be challenges and conflicts of power at the community level, which are out of the hands of the researcher, as well as community practices that fuel disparities.

The middle- and upper-levels focus on actors more directly involved in decision-making about which studies to fund and run, and how to run them, in host communities. Decisions at this level have a profound effect on whether the benefits of research are realized and how they are distributed among a host community. For example, no matter how effective a therapy may be shown to be, if it is not accessible and affordable the host community will not realize its benefits. Wealthy nations and organizations conducting the research in lower-resourced locales need to work together with host communities to determine what type of capacity development and building needs to be put in place to fill the gaps in access and enable trust among host communities. Communities must be empowered to identify their needs and values and bring them to the negotiation table. However, it is also essential for researchers and other middle- and upper-level entities to convey that combating disease through intervention is a worthwhile investment, even if it does not immediately resonate with the community.

Attendees seemed to recognize some role for funders and researchers in discerning the needs of host communities, to build trust and rapport. For instance, research efforts may not be well-received within a community if the research staff present in low-resource villages wear expensive clothing and drive high-end vehicles, while the host community's basic needs, such as a footbridge to access the market, remain unmet. Other opportunities that were identified were a need for legal support and guidance for community negotiation. Establishing these resources will not only strengthen local research capacities but also empower communities to defend themselves against exploitation. Additionally, involving communities in the development of ethics and governance processes could fill research policy gaps across the different regions.

Discussion then turned, with the second speaker's remarks, to systematic reflections on the role of justice and equity in product development in resource-challenged locations. One key consideration for product development is the importance of addressing accessibility issues prospectively, given constraints that may not be present in resource-rich areas, such as transportation, storage, issues of communication, language barriers, and labeling. The speaker outlined a three-part pragmatic approach to support product development and accessibility. The first part is a regulatory component, where one considers what data is needed to establish safety and efficacy and to obtain regulatory authorization for the specific intervention. The second part is the target procurement profile, where the focus is on how the product will be procured and delivered to the intended population, should it gain regulatory approval. Consideration for price point, affordability for the intended community, and alternatives for sustainability are crucial for ensuring that the research is, and the sponsors are, serving the host community. The final step is establishing a target policy or target guideline profile regarding how to ensure access, since achieving regulatory approval is far from sufficient. The importance and emphasis of the three-part product profile is to think prospectively about the necessary ethical and reciprocity-based questions arising in the course of product development and to spur stakeholder reflection and action such that there is equitable market access and sustainability within the host community.

Attendees stressed that, when looking at lower-resourced communities, for instance across Africa, communities are far from monolithic, with different communities having different systemic infrastructures and different histories and experiences with clinical trials. This complicates efforts to address questions of equity and justice, given the variability in local infrastructures and clinical trial sites and among local authorities and community

representation mechanisms. One participant noted the baleful effects of substandard and falsified therapeutic products in lower-resourced locales, which undermines the whole clinical trials process and the community's confidence in dependable products. Other participants noted the systemic issues of justice and equity that arise when trials are not done, even when it is apparent that there is a need for them in lower-resourced settings. With COVID-19 vaccine trials, for example, trials were performed across the globe except in Africa. Once the vaccines were authorized, it raised questions about whether and how these vaccines might work in populations that could have different functioning immune systems and different social and economic determinants of health, which may mediate or contribute to differential biological responses. This example amplifies how the confidence and trust of community members can be undermined when decisions about therapy development are not made thoughtfully and transparently, taking into account the realities of specific communities and their perceptions and expectations.

One participant raised a question regarding the appropriateness of conducting a clinical trial in a lower-resourced community when it is known beforehand that access, due to price or sustainability, could not be guaranteed, but when there is nonetheless a commitment to building capacity and developing infrastructure in the process. The speaker argued that infrastructure building is not enough when the community takes part in the research. A price guarantee was suggested for a two-year period until a generic could be brought into the community at a more affordable price. It was emphasized that factors contributing to sustainability should not be considered only at the end of trials but need to be addressed from the onset.

The final speaker noted the longstanding nature of the questions being discussed and emphasized the complexity of these situations and accompanying debates. In addition, these discussions sometimes require acknowledging positions of power, a relinquishment of power that has been unjustly concentrated through the effects of colonialism, increased acknowledgement of marginalized communities, and serious reflection on what needs to be done to improve their well-being. This demands a reprioritization and reinvestment in fair modes of collaboration to push research forward in an equitable way, with institutions recently emphasizing the need for inclusive, sustainable, and transparent partnerships with stakeholders, governments, and communities. Without this structure it becomes extremely hard to advance equitable research. Even when the normative dimensions are relatively clear, translating guidelines into practice and determining the appropriate incentives to promote

ethical action has proven to be challenging. While better relationships are likely part of the answer, there are unanswered questions regarding how funders and sponsors can best build those relationships and advance sustainable partnerships. In addition, it is not always clear who should be responsible for ensuring that partnerships between researchers and communities are operating in a fair and just manner and whether (for example) independent third-party entities might have some role to play.

The speaker also reflected on recent changes in the global clinical trials ecosystem, with COVID-19 spurring urgency in research and the rise of decentralized technologies, which can present challenges in simultaneously realizing the goals of advancing science quickly and advancing equity in research. Decentralized models using central nodes of trial governance and more remote forms of trial conduct can serve as a potential threat to equitable partnerships, insofar as they remove researchers from trial sites and local leadership that could and should be involved in governance decisions. In addition, the integration of pragmatic trials into health systems and hospitals with the intention of capturing real-world data poses a risk that trials will emulate and reproduce inequities and injustices that are embedded in health systems. Attendees briefly considered ancillary care and the tensions between distinguishing research care versus clinical care. One member posed the question of whether positing strong ancillary care obligations would unduly burden research or perpetuate therapeutic misconception, with others suggesting that ancillary care could itself be viewed as a form of community investment or benefit.

The Bioethics Collaborative ended with a discussion concerning the importance of industry sponsors setting clear expectations and being transparent about decisions to market investigational products in the locations in which they perform research. Many African nation's regulators have reported that companies often do not apply for marketing authorization upon completion of trials due to difficulties and expense. Industry representatives confirmed that the majority of companies have every intention of pursuing approval and marketing in the research location at the beginning of the study but that matters may change due to economic realities, such as a decision from the country's health authorities not to reimburse the costs of the therapy. Other industry representatives noted the importance of this question and agreed on the need for further empirical work to understand how often the intention to pursue regulatory approval and registration is abandoned based on different factors as the therapeutic development process unfolds.

NOTES / REFERENCES

[i] Participants in the 2001 Conference on Ethical Aspects of Research in Developing Countries. Ethics. Fair benefits for research in developing countries. Science. 2002 Dec 13;298(5601):2133-4. doi: 10.1126/science.1076899. PMID: 12481120.
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[iii] London AJ. Justice and the human development approach to international research. Hastings Cent Rep. 2005 Jan-Feb;35(1):24-37. PMID: 15799498.