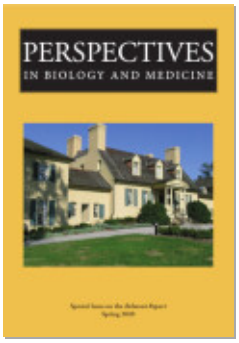
International Clinical Research and Justice in the *Belmont Report*



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International Clinical Research and Justice in the *Belmont Report*

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ABSTRACT The *Belmont Report* was written by a US Commission charged by the US Congress to advise on research supported by the US government. Its focus was understandably domestic. In the 40 years since its publication, clinical research has become increasingly international. Many clinical trials have sites in multiple countries, and many of the host countries are relatively impoverished. Such research raises some distinctive ethical issues. This paper outlines some of the key ethical challenges that have been raised by clinical research conducted in low- and middle-income countries (LMICs) and sponsored by high-income country (HIC) institutions. It then considers whether the *Belmont Report* has the resources to address these problems and argues that it does not. The article closes by noting some parallels between this international research and domestic US research, which suggest that the US might benefit from the discussions abroad.

There is a long history of Western scientists conducting medical research in other countries. Indeed, one of the first recorded cases of the use of a consent form for research volunteers comes from Walter Reed's studies of the transmis-

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sion of yellow fever in American-occupied Cuba at the turn of the 20th century (Lederer 2008). But in the 1960s and '70s, the volume of international clinical research was low relative to the present. The scandals that prompted the creation of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (the "Commission") were all domestic: the Tuskegee syphilis study, the Willowbrook State School hepatitis experiment, the Jewish Chronic Disease Hospital experiment, and others described in Henry Beecher's landmark "Ethics and Clinical Research" (1966). Information about the horrifying experiments sponsored by the US Public Health Service in Guatemala in the late 1940s would not be made public until 2010 (Reverby 2012).

The Commission's primary charge, as stated in Sec. 202(a)(1)(A) of the National Research Act of 1974, was to

> (i) conduct a comprehensive investigation and study to identify the basic ethical principles which should underlie the conduct of biomedical and behavioral research involving human subjects, (ii) develop guidelines which should be followed in such research to assure that it is conducted in accordance with such principles, and (iii) make recommendations to the Secretary [of Health, Education, and Welfare] (I) for such administrative action as may be appropriate to apply such guidelines to biomedical and behavioral research conducted or supported under programs administered by the Secretary, and (II) concerning any other matter pertaining to the protection of human subjects of biomedical and behavioral research.

This did not restrict the Commission to considering only domestic research. Nevertheless, the *Belmont Report* that described these "basic ethical principles" and their application to human subjects research makes no reference to international research or any associated ethical challenges (National Commission 1979). Nor is international research mentioned anywhere in the two volumes of background papers prepared for the Commission.

In the decades since the publication of the Report, medical research has become thoroughly international. Clinical trials with multiple sites in multiple countries are common and even typical for some areas of research, such as rare cancers. In particular, the amount of clinical research conducted in low- and middle-income countries (LMICs) has massively expanded. A 2003 paper notes that "Over the past decade, the drug industry has quietly exported its clinical testing overseas, where oversight is slim and patients plentiful. According to a largely unnoticed Health and Human Services (HHS) report, the number of foreign investigators seeking FDA approvals increased 16-fold between 1990 and 1999" (Shah 2003, 29). A 2007 analysis of clinical trials registered at ClinicalTrials.gov showed that "24 of the fastest growing 25 countries are from emerging regions" (Thiers, Sinskey, and Berndt 2008, 13). As of March 2019, about a fifth of the study locations currently registered on ClinicalTrials.gov are in LMICs. Most of these trials are

sponsored by high-income country (HIC) institutions—pharmaceutical companies, national research funding bodies, and philanthropic organizations.

Clinical research studies like these, which I'll henceforth label as just "international research," have provoked a set of interesting and difficult ethical problems. In this article, I outline some of the key ethical challenges that have been raised by clinical research conducted in LMICs and sponsored by HIC institutions, and I consider whether the *Belmont Report* has the resources to address these problems. I close by noting that the US might benefit from applying some of the lessons learned in LMICs to domestic research.

Four Ethical Issues in International Research

In what follows, I describe four ethical issues that have been extensively discussed in the context of international research. For each, I illustrate it with a case, explain the nature of the issue, and sketch a range of views on how to address it. My goal is to explain why these ethical problems have arisen for international research, not to render a verdict nor to be comprehensive regarding the solutions that have been proposed.

Ancillary Care

US-funded researchers are conducting a study in Bamako, Mali, to assess whether children with severe malaria develop pulmonary hypertension.[1] The study enrolls children aged one to five years with severe malaria and healthy controls. Participants have blood drawn and an echocardiogram to estimate pulmonary arterial pressure. The study procedures reveal various infectious diseases in addition to malaria. In one case the echocardiogram finds that a three-year-old girl has a ventricular septal defect—a hole in the heart—which would require surgery that is unavailable in Mali.

This case illustrates a common occurrence for researchers working in LMICs. Whether through their study procedures or otherwise, they identify participants with unmet health needs. In countries where participants have access to good quality medical care outside of the research, this typically presents minimal ethical challenge: participants identified as in need of care can be referred to their own physician or appropriate specialists.[2] In LMICs, many participants may not have access to such care or obtaining it would require substantial out-of-pocket expenditure. What obligations do researchers have to provide or arrange for this so-called "ancillary care," care that Henry Richardson and Leah Belsky (2004)

[1]Case drawn from Dickert and Wendler 2009.

[2]One exception to this concerns the return of incidental findings, where the issue concerns the obligations of researchers to look for or to return information that may be relevant to a participant's health, but that the participant would likely not obtain through their normal interaction with their health care provider. This has been the subject of extensive debate within HIC health-care settings, as well as LMICs.

define as "care not required by sound science, safe trial conduct, morally optional promises, or redressing subject injury" (26)?

One answer to this question is to say that researchers have no ancillary care obligations. The job of medical researchers is to generate socially valuable knowledge that can help improve health, not to provide clinical care to their research participants. Providing care is the job of clinicians, such as physicians and nurses. Confusion arises because the people who are conducting the research are often also people who are trained to provide medical care, and because some medical care is often a necessary part of scientific protocols. Nevertheless, the two roles—and their accompanying role moralities—are distinct.

Most commentators, and most researchers, find this line of reasoning unpalatable. Given that anti-malarial drugs are cheap, that the researchers in the case described will be diagnosing malaria, and that children with severe malaria face a substantial chance of dying, it seems obviously unethical for them not to treat malaria. Likewise, if a child presented with high fever that resulted from a bacterial infection, not malaria, most people would regard it as unethical not to treat the child with antibiotics, even though the condition was not related to the scientific goals of the study. On the other hand, surely there are limits to the care that researchers are obligated to provide. In environments where the burden of disease is high, they could exhaust their funds before meeting the health needs of everyone they screen in a clinic, and research would never get done. The challenge, then, is where to draw the line between ancillary care that is ethically required and ancillary care that is ethically optional.

Post-Trial Care

A pharmaceutical company is testing a new medication to control blood glucose levels in type 2 diabetes. Its proposed multi-site phase 3 placebo-controlled trial will compare the experimental medication plus metformin to metformin alone. Half of the trial sites are in India, where prevalence of type 2 diabetes is growing. Though metformin is available as a generic drug in India, the new medication is not expected to be licensed there for several years after a successful clinical trial. Even when it is licensed, it is likely to be priced substantially out of reach of many of the lower-middle-class Indian patients who are expected to enroll in the trial.

Research participants frequently leave studies still needing care for their condition. If an experimental therapy is effective but non-curative, as with antiretroviral treatment for HIV/AIDS and many treatments for chronic noncommunicable diseases, then the participants would likely benefit from continuing to receive the treatment (or getting it for the first time, in the case of control groups). An experimental treatment may not be available outside of clinical trials because it is not yet licensed. In many LMICs, it may be a long time before such new treatments are approved, and even longer before the majority of residents can access

them—LMIC populations are rarely the primary market for new medications. Further, even if no new treatment results from the study, patient-participants may have received standard care as part of the study design that they are no longer eligible to receive. If they do not have access to care outside of the trial, then they will yet again suffer the ill effects of their disease. Is there an ethical obligation to provide this sort of care?

Discussion of this issue has focused on the question of post-trial access to experimental interventions shown to be effective; relatively little attention has been given to the related matter of post-trial care that is not simply continuing to receive an experimental intervention (see Cho, Danis, and Grady 2018b). Some guidance firmly endorses an obligation. For example, the 2013 version of the World Medical Association's Declaration of Helsinki says: "In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial" (MWA 2013, Guideline 34). In some countries, such as Brazil, there is even a legal requirement to provide post-trial access (Wang and Ferraz 2012).

Everyone agrees that it would be a good thing for research participants to have access to beneficial treatments after research is completed. But to what extent there is an obligation to provide it to research participants—rather than to other needy patients—and on whom such an obligation would fall remains contentious (Millum 2011). Researchers and sponsors are the most proximate actors and the most likely to be accused of ethical shortcomings if their former participants do not receive care. However, they may lack the resources to provide care and may reasonably question why they have an obligation to provide care rather than just transition participants to whatever local sources of care are available. After all, if the treatment was beneficial relative to what participants would otherwise have received, it seems as though the research has already benefited them. On the other hand, governments plausibly have the duty to ensure that residents of their country can access affordable health care, which makes them much more plausible bearers of a duty to provide new treatments. But governments owe this duty to all their residents, not just to research participants, and they may legitimately prioritize access to different interventions—perhaps cheaper, established treatments for different conditions.

In the face of uncertainty about who is obliged to provide what to former participants, one possibility is to place the obligation on all parties, as Helsinki appears to do. An alternative is for researchers and sponsors only to carry out research in populations who are likely to be able to access care after a trial is complete. For example, the US National Institutes of Health (NIH) interprets its mandate to exclude the provision of post-trial treatment to participants. Therefore, its guidance on the provision of antiretrovirals to participants in LMICs following treatment trials states:

> NIH expects investigators/contractors to address the provision of antiretroviral treatment to trial participants after their completion of the trial. The NIH recommends investigators/contractors work with host countries' authorities and other stakeholders to identify available sources of antiretroviral treatment. . . . Priority may be given to sites where sources are identified for the provision of antiretroviral treatment following the completion of the trial. (NIH 2005)

Carrying out research only where participants will be able to access care through other sources afterwards relieves the researchers and their sponsors of the duty to provide care themselves. On the other hand, it sweeps the problem under the carpet. Refusing to conduct research in populations who already lack access to care seems to doubly disadvantage poorer prospective participants, who then do not receive treatment in or outside of research.

Notwithstanding the contentious and ongoing debates about the ethical obligations of researchers and their sponsors, various groups have worked on developing solutions to post-trial access that are consistent with (limited) obligations to participants and practically feasible. For example, the HIV Netherlands Australia Thailand Research Collaboration (HIV-NAT) established a drug fund mostly funded through research revenue to support Thai participants who could not afford their own treatment (Ananworanich et al. 2004). Alternatively, research sites may work with sponsors to find additional trials for participants to enroll in, or may be able to negotiate limited periods of post-trial access from the sponsors (MRCT 2019).

Responsiveness and Reasonable Availability

A joint venture between the US Navy and GlaxoSmithKline sought to test an antimalarial drug combination—atovaquone/proguanil (Malarone)—for prevention of *P. vivax* malaria in a population of recent immigrants to a malaria-endemic region of Indonesia. The randomized, placebo-controlled trial enrolled approximately 300 participants aged 12 to 65 who were malaria naïve. The study team tested for malaria parasitemia every week or upon participants complaining of symptoms and treated infected participants (Ling et al. 2002). In addition, they funded clinics that provided other health services to participants and others in the community. Local community leaders were supportive of the trial because of the ancillary benefits to the community. The research ethics committee in Jakarta argued that the trial was unethical because its results would be irrelevant to the community: there were no plans for Malarone to be made available to community members after the trial. Rather, the results of the study would be relevant for travelers from nonmalarial regions who needed chemoprophylaxis for limited periods of time.

A common criticism of many trials conducted in LMICs and supported by HIC entities is that the results of the trials are irrelevant to the countries that host

them. A 2009 paper that looked at changes in clinical trials between 1995 and 2005 reported: "among the ongoing phase 3 clinical trials that we examined that were sponsored by U.S.-based companies in developing countries, none were trials of diseases such as tuberculosis that disproportionately affect the populations of these countries. In contrast, we found a variety of trials in developing countries for conditions such as allergic rhinitis and overactive bladder" (Glickman et al. 2009, 819). Many people respond to such trials with instinctive concern. Given the extensive health-care needs of LMICs, it seems prima facie unethical to use their populations for the benefit of patients in wealthy countries, rather than to help their compatriots.

One possible explanation of why such research could be unethical is that it is harmful to the populations that host research. This might be because research sites draw away clinicians from the public sector, or it might be that the research prioritized by pharmaceutical companies and the like displaces other, more important research that would otherwise be carried out at those sites. However, even if this is true sometimes, it is clearly not true as a rule. The Malarone trial is one example of how research that fails to respond to local health needs can nevertheless be good on balance for the host population. These poor immigrant communities got clinics and health care that they would otherwise have not received, and the participating communities were not being considered as possible sites for other trials.

An alternative explanation for the underlying ethical concern is that such research is exploitative—that is, it takes unfair advantage of the LMIC hosts. Even if it is (sometimes) beneficial, on balance, for a community to host the research, nevertheless the primary beneficiaries are companies and patients in HICs whose relative power allows them to dictate the terms on which the research is carried out. Plausibly it is views like this that underlie prohibitions on research that is not "responsive." For example, the 2002 version of the Council for International Organizations of Medical Sciences' *International Ethical Guidelines for Biomedical Research Involving Human Subjects* stated:

> 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; and
> - any intervention or product developed, or knowledge generated, will be made reasonably available for the benefit of that population or community. (CIOMS 2002, Guideline 10).

These two requirements—*responsiveness* and *reasonable availability*—have engendered substantial debate. Critics of the reasonable availability requirement argue that exploitation is a matter of how much benefit different parties to a transaction receive, not what type of benefits they receive (El Setouhy et al.

2004). In order to avoid exploitation, it is therefore neither necessary nor sufficient to provide host communities with the interventions being tested in research. Providing that intervention might be insufficient—for example, if the trial results are negative. Providing other benefits, such as unrelated clinical care, might be enough, if those benefits are sufficiently high to be fair. In response, it has been argued that opening up the benefits that are provided to host communities to negotiation risks engendering a "race to the bottom" among potential hosts of research (London and Zollman 2010). Without some substantive standard for what counts as a fair level of benefits, sponsors will shop around for the sites that require the least from them.

The responsiveness requirement is more widely accepted. Nevertheless, even it has been criticized by ethicists who regard it as an inappropriate response to potentially legitimate concerns about the research that is conducted globally (Shah, Wolitz, and Emanuel 2013). Key questions are whether a responsiveness requirement leads communities to miss out on beneficial research and whether it generally leads to a sufficiently high level of benefits (Millum 2012). In any case, the responsiveness debate has shone welcome attention on the need to justify non-responsive research and on the so-called "parachute" researcher "who drops into a country, makes use of the local infrastructure, personnel, and patients, and then goes home and writes an academic paper for a prestigious journal" (*Lancet Global Health* 2018).

Standards of Care

In the early 2000s, multiple candidate HIV vaccines were under development. In order to show the efficacy of an experimental vaccine, a trial would have to show a statistically significant difference in the number of people infected in one arm compared to another. The ideal populations for testing such vaccines are therefore populations at high risk for HIV infection, such as are found in many countries in sub-Saharan Africa. The design of such trials poses the following challenge. There already exist multiple preventive interventions that are known to reduce the probability of contracting HIV, including counseling about safer sex practices, provision of barrier methods of contraception, pre- and post-exposure prophylaxis with antiretroviral drugs, and male circumcision. If researchers seek to minimize the risks to trial participants, then they should provide such interventions as part of the standard of care to both arms of the study. However, as the preventive standard of care increases, the rate of infection decreases, which means that greater numbers of participants are needed for adequate statistical power. Not only does this make the study cost more and take longer, it reduces the number of studies that can be conducted and makes them less likely to give a clear verdict on the experimental vaccine (Essack et al. 2010).

The "standard of care" debate concerns what care should be provided to participants in clinical research as a matter of trial design. As the HIV vaccine ex-

ample shows, varying the standard of care has scientific, practical, and ethical implications. Changing the standard of care changes the questions that the trial is designed to answer, the likelihood of it answering those questions, its length and cost, and the risks and benefits of trial participation.

The most controversial cases are those in which there are strong scientific reasons to provide participants with less than the best proven standard of care. For example, major depression has a waxing and waning course, patients are often very responsive to placebos, and the effectiveness of antidepressants varies widely across populations. As a result, it can be hard to interpret studies of new antidepressants without a placebo arm (Temple and Ellenberg 2000). An active-controlled trial that seems to show that an experimental antidepressant is no worse than an existing antidepressant may just be a case in which neither intervention had more than a placebo effect. In populations in LMICs who lack access to quality medical care, the relevant scientific question may be whether a new intervention is better than what they have, not whether it is better than the best that is globally available. If the global best is unattainable, using it as a standard of care risks generating information that is irrelevant to local needs. In addition, if the standard of care provided to trial participants is too high, it may be impossible to adequately power the study, even though the data would be vitally important for the local population. This was one concern about raising standards of prevention in HIV vaccine trials.

How considerations of the social value of alternative study designs and the risks to participants should be balanced is a highly complex matter. Judgments about them are inevitably highly sensitive to context. Nevertheless, the literature distinguishes different situations in which it might be ethical to offer participants less than the best proven care. First, not offering the best proven care would be acceptable if the effects of not being treated are relatively trivial. For example, not being treated for transient pain would not be ethically problematic. Second, not offering the best proven care may be acceptable if it is scientifically necessary to withhold it in order to answer a socially valuable question *and* if those who receive less than the best standard of care are not exposed to serious harm (Miller and Brody 2002).[3] This might apply to trials of antidepressants, for example, where the risks of nontreatment are not trivial, but, if managed carefully, are not in excess of what it is permissible to ask competent adults to take on in research.

Third, and most relevant to LMICs, it has been argued that not offering the best proven care may be acceptable if (1) the lower standard of care is scientifically necessary to answer a socially valuable question; (2) participants are not thereby

[3]As the Declaration of Helsinki puts it: "Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention" (Guideline 33).

deprived of treatment that they would otherwise have received; *and* (3) the research is responsive to the needs of the communities hosting the research (Wendler, Emanuel, and Lie 2004). The second condition implies that the research is not harming participants, while the third condition implies—if we agree with this view of the function of the responsiveness requirement—that the research does not exploit them.

ETHICAL ISSUES IN INTERNATIONAL RESEARCH: A DIAGNOSIS

The four issues I have described are not exhaustive of the ethical issues that arise for clinical researchers working in LMICs. For example, I have not explored some of the fascinating questions that arise with regard to consent as a result of differences in cultures, nor the important work that has been done on community engagement. I have described these four issues because they have engendered the most heated debate and because they arise in virtue of similar features of the relationship between rich countries (and their inhabitants) and poor countries (and their inhabitants).

Note, first, that each of the four issues arises because of an *absolute* lack of resources among LMIC participants and the populations from which they are drawn. Participants are in need of ancillary care because they lack access to good-quality health care outside of clinical research. Similarly, participants need post-trial care because they lack access to such care once the research is over. The concern about research that is not likely to lead to benefit to the host populations would be much less pressing if their health-care needs were not so great. And there would be far fewer opportunities to offer lower standards of care to participants if people living in LMICs already had access to the globally best treatments.

Second, these issues are also a function of *relative* disparities. For example, ancillary care arises as an ethical problem only because researchers and sponsors from HICs do sometimes have the resources to provide additional clinical care to participants. In general, these ethical problems are a function of the wealth and power differences between HIC entities and LMIC populations. The opportunity for exploitation exists only because the institutions and individuals that support and carry out research have the power to take advantage of the desperate need of poor populations in LMICs. Consider the controversial Surfaxin trial, which was proposed to study a new surfactant for the treatment of respiratory distress syndrome in premature babies in Bolivia and three other South American countries (Lurie and Wolfe 2011). Respiratory distress syndrome is a very serious condition caused by insufficient surfactant in the lungs, and it is fatal in about 30% of cases. This study would have randomized half the premature babies to receive just air rather than one of the existing artificial surfactants. However, since premature babies in these countries generally did not have access to any therapy and would

get various forms of supportive care just by virtue of trial participation, parents would be highly motivated to enroll their children.

These ethical issues for international research arise, then, in virtue of what many regard as structural injustice. Many LMIC populations are badly off because they live in countries that are unjust. But injustice is also global. There are massive and unnecessary differences between countries in terms of wealth and opportunities for well-being. Global injustice is also maintained through institutions that are largely shaped by and for the benefit of HICs and corporations. For example, the WTO agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) has expanded intellectual property protections, such as patents on medicines, around the world. This has had the effect of restricting access to generic medicines, which are generally cheaper and so more accessible for poorer patient groups, but it is highly profitable for large pharmaceutical companies who can use their monopoly power to set prices to maximize profits rather than patient access (Pogge 2008).

Individual researchers and the funders of research carry out their work against a backdrop of global injustice. Many are beneficiaries of that injustice. They then face the question of how to respond ethically to the needs that injustice has engendered.

APPLYING THE *BELMONT* FRAMEWORK

I return now to the *Belmont Report*. The objective of the report was "to provide an analytical framework that will guide the resolution of ethical problems arising from research involving human subjects" (National Commission 1979). That is, it was intended to be general in its scope. Does the *Belmont* framework provide resources that can help with the problems in international clinical research I have described?

The basic ethical principles enunciated in the Report do apply to research carried out in LMICs. Differences between countries do not affect whether there are requirements for informed consent, risk/benefit assessment, and fair subject selection. The authors of the Report also signaled their awareness of some of the questions of justice that underlie the ethical issues in international research. For example, they wrote that: "whenever research supported by public funds leads to the development of therapeutic devices and procedures, justice demands both that these not provide advantages only to those who can afford them and that such research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research." Nonetheless, I now argue, the *Belmont Report* lacks the conceptual resources needed to provide guidance for international research.

Consider what would be needed to answer questions regarding the obligations of researchers and sponsors to provide ancillary care during a trial and continue

to provide care after the trial. In its discussion of beneficence, the *Belmont Report* talks about maximizing the benefits and minimizing the harms *from research*. But the benefits involved in ancillary and post-trial care are distinct from research benefits. We need a framework for thinking about duties of beneficence that extends beyond research design but still takes into account the special obligations that individuals have in virtue of being clinical researchers (Rulli and Millum 2016).

Other questions require analysis of the nature of exploitation and how to avoid it. This is essential, for example, in order to understand the nuances of debates about whether and how research should be responsive to local health needs. The *Belmont Report*'s discussion of justice provides no tools for analyzing exploitation, despite its acknowledgment of the problems with using disadvantaged groups as research subjects for the benefit of more privileged individuals.

Finally, I suggested that the four issues in the ethics of international research described above arise as a result of structural injustice. No researcher or research funder is (fully) responsible for or in a position to rectify such injustices themselves. The question then is what each individually should do. Does a US researcher working in Uganda have different obligations to a researcher who stays in the US? Does she have obligations to change the type of research she conducts to maximize local benefits? Does she acquire special duties to participants or other members of communities in which she works? To what extent is she accountable for rectifying injustice, and to what extent can she legitimately say that it is not her fault and so not her business? These are challenging questions that responsible researchers in LMICs grapple with. There is little in the *Belmont Report* to assist them.

IMPLICATIONS

Do these gaps in the *Belmont Report* matter? In one respect, no. The Report could not be expected to cover all ethical issues and all the ethical principles needed to address them. Further, *Belmont*'s gaps are unsurprising. As I noted in the opening section of this article, outside of tropical medicine there was little clinical research being conducted in developing countries at the time of *Belmont*'s writing, and the focus of ethical concern in the US was inward-looking. Later work by the US National Bioethics Advisory Commission (2001) would, eventually, acknowledge a number of the important ethical issues raised by international research.

In another respect, though, the fact that the *Belmont Report* did not address these issues represents a shortcoming, even granted its limited focus. The causes of the ethical challenges for international research that I have described are problems that could be identified—then and now—*within the US*. Within the US, there are millions of people living in absolute poverty (Alston 2018). In 2017, approximately 27 million people did not have health insurance (Kaiser Foundation

2018). Tens of millions more were underinsured, meaning out-of-pocket costs or deductibles were high relative to income (Collins, Bhupal, and Doty 2019). This is not a new problem. In 1978, the year the *Belmont Report* was published, some 23 million Americans were uninsured (Cohen et al. 2009).

Thus, within the US, there are people who lack access to good quality health care outside of enrolling in clinical trials. Consequently, clinical researchers within the US face the question of what ancillary care they should provide to research participants who need treatment unrelated to the research and how to ensure access to treatment for participants after clinical trials. Sometimes they may have institutional resources at their disposal, such as social workers who can help identify sources of care or other trials they can recommend. Sometimes they may ignore the problem, as not their business. But the question of what care is owed to participants and former participants is pressing and should be acknowledged (Cho, Danis, and Grady 2018a).

Patient groups within the US who lack access to good-quality medical care are also less likely to benefit from the results of research. They might benefit from new preventive interventions by virtue of herd immunity, and we might optimistically look forward to a future time when everyone in the US has adequate health insurance coverage. But as matters stand, a great deal of clinical research is aimed at developing and marketing patented pharmaceuticals. A disproportionate amount of the benefit from these new medicines will go to wealthier Americans. Thus, the questions of responsiveness and reasonable availability apply within the US, too (Pace, Miller, and Danis 2003). To what extent should public funds go towards the development of medicines to which many patients will have limited access? To what extent should we allow or encourage such patients to enroll in clinical trials testing these medicines? These are questions that merit careful consideration, but which the *Belmont Report* did not supply tools to answer.

Conclusion

For understandable reasons, the *Belmont Report* did not discuss international clinical research. However, in the decades since, the amount of research sponsored by HIC institutions but carried out in LMICs has dramatically increased. Such research has prompted discussion of a number of important ethical issues, none of which can be analyzed using the framework of the *Belmont Report*. The novel ethical challenges of international research derive in large part from the challenges of conducting research against a background of massive inequality. These challenges also arise within the US domestic context, where they have received much less sustained attention. Perhaps it is now time for American researchers to apply some of the lessons learned in LMICs back at home.

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