

2015

Setting a Minimum Standard of Care in Clinical Trials: Human Rights Law and Bioethics as Complementary Frameworks

Fatma E. Marouf

Texas A&M University School of Law, fatma.marouf@law.tamu.edu

Bryn S. Esplin

Follow this and additional works at: <http://scholarship.law.tamu.edu/facscholar>



Part of the [Law Commons](#)

Recommended Citation

Fatma E. Marouf & Bryn S. Esplin, *Setting a Minimum Standard of Care in Clinical Trials: Human Rights Law and Bioethics as Complementary Frameworks*, 17 Health & Hum. Rts. J. 31 (2015).

Available at: <http://scholarship.law.tamu.edu/facscholar/741>

This Article is brought to you for free and open access by Texas A&M Law Scholarship. It has been accepted for inclusion in Faculty Scholarship by an authorized administrator of Texas A&M Law Scholarship. For more information, please contact sphillips64@law.tamu.edu.

Setting a Minimum Standard of Care in Clinical Trials: Human Rights and Bioethics as Complementary Frameworks

FATMA E. MAROUF, BRYN S. ESPLIN

Abstract

For the past few decades, there has been intense debate in bioethics about the standard of care that should be provided in clinical trials conducted in developing countries. Some interpret the Declaration of Helsinki to mean that control groups should receive the best intervention available worldwide, while others interpret this and other international guidelines to mean the best local standard of care. Questions of justice are particularly relevant where limited resources mean that the local standard of care is no care at all. Introducing human rights law into this complex and longstanding debate adds a new and important perspective. Through non-derogable rights, including the core obligations of the right to health, human rights law can help set a minimum standard of care.

FATMA E. MAROUF, JD, is Associate Professor of Law at the University of Nevada, Las Vegas, USA.

BRYN S. ESPLIN, JD, is a Fellow in Advanced Bioethics at the Cleveland Clinic, Cleveland, Ohio, USA.

Competing interests: None declared.

Copyright © 2015 Marouf, Esplin. This is an open access article distributed under the terms of Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0/>), which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original author and source are credited.

Introduction

PROTECTING HUMAN DIGNITY and preventing exploitation are core concepts in both bioethics and human rights. In fact, the principles that guide biomedical research ethics were developed in response to specific incidents of exploitation, including the infamous Tuskegee Syphilis Study. Yet the rapid globalization of biomedical research in recent decades presents new challenges in preventing exploitation. Affluent countries and multinational corporations now commonly conduct clinical trials in developing countries, a practice known as “off-shoring.”¹ The advantages of this practice for the sponsors of the trials are clear: it significantly reduces the cost of trials, sometimes as much as 90%, helps avoid the increasingly bureaucratic regulatory environment in many wealthy countries, and renders legal accountability extremely unlikely.² However, these same factors increase the risk that research subjects will be exploited, especially since nearly half of the clinical trials in developing trials escape review by an ethics committee.³

One of the ongoing debates within bioethics related to the practice of “off-shoring” pertains to the standard of care owed to participants in clinical trials. Specifically, there is a dispute over when the use of placebo or no intervention for the control group is permissible. The Declaration of Helsinki, which provides ethical principles for medical research involving human subjects, generally requires researchers to test new interventions against the “best proven intervention.”⁴ The plain text of the Declaration does not clarify whether this means the best intervention available worldwide or the best intervention available locally. Some argue that providing the best worldwide standard of care is simply not feasible in developing countries and may obstruct important research that could improve health conditions in those countries. On the other hand, the unavailability of interventions in many developing countries often means the local standard of care is very limited or no care at all, creating a double standard in clinical trials involving the rich and the poor.⁵

In this article, we argue that international human rights principles are relevant to the standard of care debate and help define a middle ground that recognizes the practical challenges involved in providing the best worldwide intervention while also setting a minimum standard of care for control groups. Examining the standard of care issue through a human rights lens helps draw attention to the obligations of the States that both sponsor and host the trials, including their obligations to regulate corporations, rather than focusing on the subject-researcher relationship.⁶ Harnessing the language of human rights also helps build power among disadvantaged groups, which fuels advocacy and organizing efforts to challenge exploitation. Perhaps most importantly, applying complementary human rights principles can help provide guidance in situations where invoking bioethical principles alone leads to conflicting conclusions.⁷

Bioethics builds on the basic principles of autonomy, beneficence, and justice, which are non-hierarchical and require careful balancing of factors such as potential risks and benefits. Human rights law, on the other hand, identifies certain non-derogable rights from which no deviation is permitted, even in times of crisis. To the extent that hierarchy exists among human rights, these non-derogable rights represent the apex and cannot be balanced against other interests. We argue that these non-derogable rights, including the core obligations of the right to health, help establish a minimum standard of care for control groups in clinical trials.

International guidelines on biomedical research: Equivocal ethics?

The debate over the standard of care in clinical trials intensified in the 1990s, when placebo-controlled trials of AZT, a drug used to prevent the perinatal transmission of HIV, were conducted in numerous developing countries.⁸ Since effective

alternative treatments were available at the time in developed countries, Lurie and Wolf critiqued the use of placebos in these trials, arguing that allowing research methods that would have been unacceptable in the sponsoring country created a double standard and imposed unnecessary risks to participants.⁹ Critics responded that the use of placebos was necessary to obtain scientifically valid results that ultimately benefited the population as a whole.¹⁰ The issue of when placebos are permissible remains unresolved today, despite international guidance from multiple organizations.

One of the challenges is that different organizations have conflicting views. In 1949, WHO and UNESCO jointly established the Council for International Organizations of Medical Sciences (CIOMS), an international nongovernmental organization which in 1993 published “International Ethical Guidelines for Biomedical Research Involving Human Subjects.” These guidelines, most recently updated in 2002, generally require the control group to receive an “established effective intervention” but allow for exceptions where: (1) there is no established effective intervention; (2) withholding the established effective intervention would expose subjects, at most, to temporary discomfort or delay in relief of symptoms; or (3) use of an established effective intervention would not yield scientifically reliable results and use of placebo would not add any risk of serious or irreversible harm.¹¹

The commentary that explains these guidelines indicates certain additional conditions for invoking an exception.¹² First, the study should be designed to develop an intervention for use in a country where an established effective intervention is unlikely to become widely available (or available at all), usually due to cost or logistics. Furthermore, the purpose of the study should be to make an effective alternative available in that country. This means the investigational intervention should respond to the health needs of the population from which research subjects are recruited and be made reasonably available to that population if it proves safe and effective. Finally, scientific and ethical review committees must determine that using an

established effective intervention would not yield scientifically reliable results that would be relevant to the health needs of the study population. Thus, both benefit to the host community and scientific necessity are required.

In addition to the CIOMS guidelines, there is the Declaration of Helsinki, which was issued by the World Medical Association (WMA) in 1964 and likely represents the most influential statement of ethical principles for medical research involving human subjects. The Declaration also tends to be the focus of the standard of care debate because its language suggests a universal standard.¹³ Over the years, the Declaration has been revised nine times, including multiple revisions pertaining to the standard of care. Since 2008, the Declaration has required new interventions to be tested against the “best proven intervention” with two exceptions.¹⁴ The use of placebo or no intervention for the control group is permitted: (1) when “no proven intervention” exists; or (2) when there are sound methodological reasons to deviate from the “best proven intervention” and no additional risk of serious or irreversible harm.¹⁵ Prior versions of the Declaration, issued in 2002 and 2004, were more permissive with the use of placebos, allowing an exception solely for methodological reasons, but that triggered criticism that scientific grounds alone cannot determine whether the research design is ethical.

Comparing the Declaration to the CIOMS guidelines, it may initially appear that the Declaration imposes a higher standard of care because it requires the “best proven intervention,” rather than just an “established effective intervention.” Unfortunately, the Declaration fails to specify whether this “best proven intervention” is based on international or local availability. Some argue that using a worldwide standard would be at odds with the international consensus, while others dispute that any such consensus exists.¹⁶ Furthermore, some argue that it would be unreasonable to require all countries to provide the best worldwide standard of care, while others find it unreasonable to use a local standard that is determined largely by prices set by pharmaceutical

companies.¹⁷ In light of this ongoing debate, it remains unclear whether the Declaration's standard is actually higher than the CIOMS standard. The Declaration also does not include the restrictions mentioned in the commentary on the CIOMS guidelines, such as benefit to the host community.

A third organization that is more permissive with the use of placebos than either CIOMS or the WMA is the International Conference of Harmonization (ICH), comprised of the US, European Union, Japan, and experts from the pharmaceutical industry. In 2001, the ICH adopted guidelines entitled Choice of Control Group and Related Issues in Clinical Trials (CCG).¹⁸ While the US abandoned the Declaration of Helsinki in 2008, it continues to endorse the CCG guidance, which provides only one rule restricting the use of placebos. The CCG states that “[i]n cases where an available treatment is known to prevent *serious harm, such as death or irreversible morbidity* in the study population, it is *generally inappropriate* to use a placebo control” (emphasis added).¹⁹ In other situations, “it is generally considered ethical to ask patients to participate in a placebo-controlled trial, even if they may experience discomfort as a result, provided the setting is noncoercive and patients are fully informed about available therapies and the consequences of delaying treatment.”²⁰ Thus, in trials where there is no risk of serious harm, placebos may be used as long as there is informed consent.

As further guidance, the CCG notes, “Whether a particular placebo-controlled trial is ethical may in some cases depend on what is believed to have been clinically demonstrated under the particular circumstances of the trial,” which suggests that a trial may be deemed ethical in hindsight and justified if the overall benefit outweighs the harm involved in using placebos.²¹ The CCG also recommends considering modifications to the research design, such as “early escape” from ineffective therapy, a limited placebo period, or an “add-on” study, where the new intervention is added to standard treatment, as ways to reduce ethical concerns.²² These statements reflect some recognition that the restriction on use of placebos only in cases of serious harm does not eliminate ethical concerns.

We believe these various approaches to the

use of placebos leave participants in developing countries vulnerable to exploitation for several reasons. First, the guidelines discussed above do not set any hard rules prohibiting the use of placebos in certain situations. Avoiding clear rules and relying on determinations of scientific necessity or benefit to the host community might be feasible if trial protocols received careful review, but many protocols in developing countries never come before ethics committees, as mentioned above. Furthermore, insofar as the guidelines permit a local standard of care, they fail to take into account the serious public health consequences of not providing treatment, especially for infectious and epidemic diseases. In addition, liberally permitting placebos based on the local standard of care due to lack of resources in the host country ignores the international obligations of high-income countries to provide assistance in improving access to health care in developing countries. Lastly, the international guidelines examined here do not mention special protections for particularly vulnerable populations as a condition of involving them in placebo-controlled trials.

In light of these concerns and the persistent controversy surrounding the appropriate standard of care, we propose using human rights law as a complementary framework to help move the discussion forward. While human rights law does not settle the debate, it can be interpreted and applied in ways that help establish a minimum standard of care. If no such baseline of care is established, then when a country cracks down on ethical violations, clinical trials will simply move to another poor country with a weak regulatory regime. This is exactly what has happened in India, where clinical trials have dropped by 93% in response to the government's recent efforts to stop unnecessary deaths.²³

A human rights approach to the standard of care in clinical trials

To date, international human rights bodies have issued only very limited guidance on the applicability of human rights norms to clinical research trials.

The only major report on this topic, issued by the Special Rapporteur on the right to health in 2009, pertains to informed consent.²⁴ This report includes a single sentence flagging the standard of care as an area of concern: “It continues to be questioned whether conducting clinical trials in developing countries can ever be considered ethical, especially when using placebos despite the existence of appropriate non-placebo interventions.”²⁵ Recognizing the need for ethics review boards to “eliminate double standards applied to developing countries,” the Special Rapporteur called for “the most protective standards” if conducting research abroad changes the requirements for informed consent.²⁶

Similarly, we utilize the human rights framework to call for protective standards when conducting research in a developing country changes requirements regarding the standard of care. The International Covenant on Civil and Political Rights (ICCPR) and the International Covenant on Economic, Social, and Cultural Rights (ICESCR) both have provisions relevant to the standard of care in clinical trials. The ICCPR includes at least three relevant non-derogable rights: the rights to life, freedom from nonconsensual medical experimentation, and nondiscrimination.

In addition, the ICESCR provides a right to the “highest attainable standard of health,” which is generally subject to progressive realization but has certain “core obligations” that must be implemented immediately. In General Comment 14, an authoritative interpretation of the right to health, the Committee on Economic, Social, and Cultural Rights (CESCR) enumerates these “core obligations” and explains that “a State party cannot, under any circumstances whatsoever, justify its noncompliance with the core obligations . . . which are non-derogable.”²⁷ Since the core obligations of the right to health are non-derogable, they reflect the minimum core content of the right to health, the non-negotiable foundation of the right to which all individuals are entitled, regardless of the economic situation in a country. Such clear prioritization of certain aspects of the right to health is striking,

since CESCR does not always describe the core obligations of a right as non-derogable.²⁸

We argue that these non-derogable rights, including the core obligations of the right to health, provide guidance in setting a minimum standard of care for clinical trials. Although the concept of minimum core obligations has been subject to various criticisms, it remains one of the two main ways that tribunals approach economic and social rights and is therefore highly relevant.²⁹ Furthermore, by emphasizing the responsibilities of developed countries to provide assistance and regulate corporations, this proposal counters the criticism that focusing on minimum core obligations ignores the violations of affluent countries.

Since governments are the primary duty-bearers in the international human rights system, one question that arises is what if the sponsor of the clinical trial is a non-state actor, such as a pharmaceutical company? General Comment 14 helps answer these questions by emphasizing that “States parties have to respect the enjoyment of the right to health in other countries, and to prevent third parties from violating the right [to health] in other countries, if they are able to influence these third parties by way of legal or political means.”³⁰ Even more specifically, General Comment 14 describes “the failure to regulate the activities of . . . corporations so as to prevent them from violating the right to health of others” as a violation of the obligation to protect.³¹ Thus, “Violations of the right to health can occur through the direct action of States or other entities insufficiently regulated by States.”³² These provisions impose a responsibility on States to regulate domestic and foreign clinical trials in ways that protect human rights. The standards that developed countries adopt for approving investigations of new drugs and marketing of drugs based on foreign clinical trials should be consistent with the core obligations of the right to health. Similarly, developing countries need to ensure that proposals to conduct clinical trials undergo close scrutiny by independent ethics committees that apply standards designed to uphold these rights.

Deprivation of essential drugs, as defined by WHO

One of the core obligations of the right to health is “[t]o provide essential drugs, as defined under WHO Action Programme on Essential Drugs.”³³ This is the most well-defined core obligation, since it references a specific list of medications. In 1975, WHO defined essential drugs as “those considered to be of the utmost importance and hence basic, indispensable and necessary for the health needs of the population.”³⁴ Two years later, despite major opposition from the pharmaceutical industry, WHO published its first Model List of Essential Drugs, which included the generic names of more than 200 drugs and vaccines, most of which were no longer protected by patents.³⁵ The Model List has since been updated every two years and serves as a guide for countries in creating their own national lists. By relying on WHO’s expertise in defining this core obligation, CESCR stresses “the key function assigned to WHO is realizing the right to health.”³⁶

Some commentators have critiqued the core obligation to provide essential drugs as impracticable, arguing that few states can comply due to resource limitations.³⁷ One response is that developing countries can take certain measures that are inexpensive, such as removing legal barriers to accessing essential drugs. For example, certain analgesics on the list of essential drugs remain very difficult to access in developing countries. The Special Rapporteur on the right to health has noted, “Although the developing world has nearly half of the world’s cancer patients and nearly all new HIV infections, it consumes only 6 percent of the licit morphine supply.”³⁸ In fact, “About 89 percent of all legally controlled medicines, including morphine, is consumed by North America and Europe.”³⁹

Another response to the criticism based on resource limitations is that CESCR imposes a duty on “States parties and other actors in a position to assist, to provide ‘international assistance and cooperation, especially economic and technical’ which enable developing countries to fulfill their core . . . obligations.”⁴⁰ CESCR specifically provides that, “Depending on the availability of resources, States should facilitate access to essential health

facilities, goods and services in other countries, wherever possible and provide the necessary aid when required.”⁴¹ Taking these obligations into consideration, we propose that the minimum standard of care in clinical trials should include providing essential drugs, as defined by WHO, to the control group; if the trial takes place in a country where the essential drug is not readily available, then the sponsor of the trial, which stands to reap the profits, should cover the cost of providing the essential drug. This proposal is not unprecedented. The European Group on Ethics in Science and New Technologies similarly advises that the sponsor should pay if an intervention is not available due to cost, and South Africa requires all participants in HIV vaccine research to have access to high quality treatment financed by the sponsors of the trials.⁴²

Shifting the financial burden to the sponsor of the trial not only challenges how core obligations are typically construed, but also creates an incentive for developed countries to support donor programs designed to promote access to essential drugs, for example through their membership in international financial organizations. Such action would reinforce CESCR’s position that “international financial institutions, notably the World Bank and the International Monetary Fund, should pay greater attention to the protection of the right to health in their lending policies, credit agreements and structural adjustment programmes.”⁴³

One limitation in using the WHO list of essential drugs to establish a minimum standard of care is that new drugs are not added to this list until clinical trials establishing their efficacy are completed. For example, while antiretroviral drugs for HIV are now included, there were no medications for HIV on the list in the 1990s when ethical controversies arose about the failure to provide HIV-positive control groups with any treatment.⁴⁴ The principles proposed below help address this limitation.

Use of placebos in trials involving life-threatening illnesses

The right to life, set forth in Article 6 of the ICCPR, is “the supreme right from which no derogation

is permitted even in time of public emergency.”⁴⁵ According to the Human Rights Committee (HRC), which interprets the ICCPR, the right to life should not be interpreted narrowly. We contend that respect for the right to life prohibits the use of placebos in trials involving treatable illnesses that may result in serious harm or death. This interpretation provides a bright-line rule, unlike the CCG guidelines, which, as discussed above, simply state that it is “generally inappropriate” to use placebos for treatable illnesses that may result in serious harm.

A more difficult question arises when there is a life-threatening illness with high mortality rates and only experimental treatments are available, as in the case of Ebola. All of the international bioethics guidelines discussed in the previous section allow the use of placebos where no proven treatment exists. Yet there is currently a heated debate over whether clinical trials involving Ebola interventions should use placebos (plus basic supportive care) for the control group. The US government plans to conduct Ebola trials with placebos, but Médecins Sans Frontiers, WHO, and a coalition of European countries have all rejected this approach, opting instead for trials involving multiple experimental interventions.⁴⁶ While this specific debate is beyond the scope of this article, we note that even scientists who support the use of placebo trials for Ebola agree that as soon as an experimental drug shows some benefit, it should become the new standard of care for all treatment groups.⁴⁷ One approach short of providing experimental treatments to all groups in such situations may be requiring the use of adaptive experimental designs to minimize the loss of life.⁴⁸ The CCG mentions that such “modifications” may help avoid ethical concerns but does not require them.

Use of placebos in trials involving major infectious, epidemic, or endemic diseases

Of “comparable priority” to the non-derogable core obligations are the obligations to “provide immunizations against major infectious diseases” and “take measures to prevent, treat, and control epidemic and endemic diseases.”⁴⁹ These obligations

reflect a public health approach, emphasizing the collective aspects of the right to health.⁵⁰ While the former obligation is absolute, like the obligation to provide essential drugs, the latter uses the limiting language of “taking measures.” We therefore approach these two obligations differently. Regarding trials involving immunizations for major infectious diseases, we take the same hard line that we took for essential drugs, which is that the sponsor should pay for the control groups to receive an immunization known to be safe and effective, rather than a placebo, if such an intervention is not available in the host country. With respect to clinical trials involving the treatment of epidemic and endemic disease, we adopt a more nuanced analysis.

As a precursor to this analysis, we define the terms “epidemic” and “endemic.” According to the *Dictionary of Epidemiology*, a disease is an “epidemic” when its occurrence in a given community or region clearly exceeds the normal expectancy, while it is “endemic” if constantly present within a geographic area or population group.⁵¹ The *Encyclopedia Britannica* further explains:

When a disease is prevalent in an area over long periods of time, it is considered to be endemic in that area. When the prevalence of disease is subject to wide fluctuations in time, it is considered to be epidemic during periods of high prevalence. Epidemics prevailing over wide geographic areas are called pandemics.⁵²

Endemic and epidemic diseases claim countless lives, stifle human development, and drain health care systems, especially in developing countries with weak infrastructures. They therefore tend to be top priorities in setting health policies, and combating them is foundational to the right to health.

If an epidemic or endemic disease can be treated by an essential drug or is life threatening, then, under the principles discussed above, the use of placebo would be prohibited. In other situations, we contend that the obligation to “take measures” should include, at a minimum, having certain protections in place if placebos are used.

This approach is consistent with the one taken by the Special Rapporteur on the right to health in the report on informed consent, which stressed that “A rights-based approach to medical research means that special protections must be in place to ensure that the autonomy of potential participants, particularly those from vulnerable groups, is not compromised as a result of power imbalances inherent in the research-subject relationships.”⁵³

In suggesting these particular protective measures, we are mindful of the dearth of guidance from human rights bodies or courts. We therefore take into consideration the protections mentioned in the Special Rapporteur’s report on informed consent, as well as a 2004 article by David Wendler and his colleagues arguing that the default position of ethics review boards should be to require the best worldwide standard of care unless certain conditions are met.⁵⁴ The protections we propose are as follows: (1) participation risks must be minimized, for example through adaptive research designs; (2) the trials must be medically necessary (i.e., previous research should not obviate the need for additional research); (3) the use of placebos must be scientifically necessary to answer the question addressed in the trial; (4) the study must address important health needs for the host community; (5) a fair level of benefit must be conferred on participants; and (6) participants should not be worse off than if the trial had not occurred. The investigator should bear the responsibility of demonstrating that all of these protections are in place in order to use placebos in trials involving epidemic or endemic diseases.

Use of placebos with vulnerable or marginalized groups

The current debate over the Ebola trials highlights not only conflicting views about how to handle pandemics when no proven intervention is available, but also concerns about the use of placebos with vulnerable groups. Clement Adebamowo, for example, has argued that terrified populations cannot be expected to give informed consent in the midst of a raging epidemic, especially if they

are distrustful of health centers and aid workers.⁵⁵ In considering the use of placebos with vulnerable groups, we examine the interpretations of the HRC in General Comment 20 and relevant concluding observations, as well as the report on informed consent from the Special Rapporteur on the right to health. As above, we follow the Special Rapporteur’s lead in recommending heightened protective measures for the use of placebos with vulnerable groups.

Three non-derogable rights are relevant to the use of placebos with vulnerable groups. First, there is the prohibition against subjecting individuals to medical experimentation without their “free consent” under Article 7 of the ICCPR.⁵⁶ Second, there is the core obligation of the right to health that requires States parties to “ensure the right of access to health facilities, goods and services on a non-discriminatory basis, especially for vulnerable or marginalized groups.”⁵⁷ Third, there is the non-derogable prohibition against discrimination based on “race, colour, sex, language, religion, political or other opinion, national or social origin, property, birth or other status,” which appears in both conventions.⁵⁸

The HRC has interpreted “free consent” broadly to take into account the potential for exploitation or coercion. In cases where an individual’s personal characteristics or life situation create a serious risk of exploitation, the HRC has advised exclusion from clinical trials that may be harmful to health. For example, the HRC has indicated that detainees and prisoners “should not be subjected to any medical or scientific experimentation that may be detrimental to their health.”⁵⁹ Similarly, in its Concluding Observations for the Netherlands, the HRC has opined that certain vulnerable populations, including minors and others who cannot give genuine consent, must not be subjected to medical experiments that do not benefit them directly.⁶⁰ The HRC has also expressed concern about the US practice of allowing research to be “conducted on persons vulnerable to coercion or undue influence such as children, prisoners, pregnant women, mentally disabled persons, or economically disadvantaged persons.”⁶¹

Critics of excluding vulnerable groups from

clinical trials contend that doing so risks undue paternalism, and that requiring informed consent with appropriate disclosure techniques and payment of a fair benefit provide adequate protection against exploitation. They further argue that exclusion interferes with obtaining generalizable results, and that “vulnerability” itself is a problematic category that risks over-inclusion of heterogeneous groups.⁶² While these may be valid concerns, the HRC and the Special Rapporteur have already helped define certain vulnerable groups and have made it clear that special protections should apply. We therefore propose permitting the use of placebos on vulnerable groups in developing countries only if heightened protective measures are in place. These measures incorporate, modify, and add to the ones mentioned above in order to take into account concerns regarding vulnerable populations.

Specifically, we incorporate the protections requiring the sponsor to demonstrate that participation risks are minimized, the trials are medically necessary, the use of placebos is scientifically necessary, and the participants are not worse off than if the trial had not been conducted. In addition, drawing on the Special Rapporteur’s report, we propose that the investigators should demonstrate that: (1) no comparably effective alternative research population is available; (2) the study addresses important health needs for the vulnerable groups, not just the host community in general; (3) the benefit provided is fair but incentives are limited to adequate compensation for time, effort, and any adverse consequences of participation; and (4) efforts have been made to involve a representative organization that can assist participants throughout the process.⁶³

We do not go as far as prohibiting the participation of vulnerable groups, as this could be considered discriminatory, both because of the exclusion itself and because such exclusion creates a knowledge gap regarding the efficacy of an intervention for that group. However, differential treatment is permissible under the human rights conventions as long as the justification is compatible with the nature of those conventions and solely for the purpose of promoting the general welfare.⁶⁴ Requiring the

protective measures mentioned above falls within this permissible zone of differential treatment.

Enforcement

One advantage of using human rights norms to set a minimum standard of care in clinical trials is that these norms may be enforceable in developing countries where ethical regulations of such trials are inadequate or nonexistent. Violations of human rights during clinical trials could also be brought before human rights bodies with individual complaint procedures, such as the HRC and CESCR, creating additional avenues for accountability. Of course, in some countries—most notably the US—human rights norms are extremely difficult to enforce. The US does not consider the ICCPR self-executing and has not ratified the ICESCR. In addition, the US Supreme Court held in 2013 that the Alien Tort Claims Act, which had been used to sue corporations for human rights violations abroad, does not apply extraterritorially.⁶⁵ In such situations, effective regulations that prevent human rights violations from happening in the first place are especially critical.

The existence of extensive regulations does not necessarily mean that they effectively prevent exploitation. The detailed regulations issued by the US Food and Drug Administration (FDA), for example, do not require Investigational New Drug (IND) applications for foreign clinical trials.⁶⁶ Although the regulations do generally require evidence that foreign clinical trials conform to “good clinical practice” for the data to be used to support marketing approval or IND applications, the FDA has the authority to waive that requirement, including review and approval by an independent ethics committee.⁶⁷ Furthermore, the regulations describing the requirements for obtaining marketing approval based solely on foreign clinical data provide that “FDA will apply this policy in a flexible manner,” again permitting deviation from the standards.⁶⁸ Making matters worse, while the FDA is allowed to perform on-site inspections for foreign trials, it rarely does so.⁶⁹ In fact, a study by the Office of the Inspector General found that the

FDA inspected less than one percent of foreign clinical trial sites in 2008.⁷⁰

Oversight and accountability could be improved across the board through the creation of an international body that could review controversial protocols for clinical trials before they begin, as well as hear complaints that arise during or after a trial. This body should include experts in both bioethics and human rights, thereby developing complementary standards. Among other things, such a mechanism could explore how the international obligation to provide assistance under human rights treaties relates to the standard of care in clinical trials. Like the duty to provide a benefit in bioethics, the obligation to assist under human rights law need not be limited to paying for a treatment but could also include paying royalties generated from the sale of a drug or a fixed amount based on the principle of proportionality.⁷¹ By applying human rights norms to specific situations in biomedical research, an international body would also help develop the content of core obligations.

Conclusion

Bioethics and human rights are both predicated upon the desire to protect individual freedoms, promote justice, prohibit exploitation, and ensure human dignity. The notion of drawing on human rights norms to analyze the appropriate standard of care in clinical trials should not, therefore, be surprising. The real surprise is how little human rights bodies have thus far engaged dilemmas in clinical research aside from informed consent. The framework we propose here of applying non-derogable rights, including the core obligations of the right to health, to establish a minimum standard of care for clinical trials represents an initial step in that direction. Certainly, neither bioethics nor human rights has resolved internal tensions about universality versus relativity. Furthermore, some may dispute the usefulness of core obligations or disagree about the particular protective measures proposed here. Such critiques are vital to the discussion and will help deepen our thinking about concepts in both fields.

While this article primarily addresses the standard of care debate, the promise of collaboration between the two disciplines extends much further. In order to make a meaningful difference in the protection of all human subjects, bioethics must strive to prevent the conditions in which individuals are systematically made vulnerable to exploitation. Adopting a human rights perspective is consistent with developments in public health ethics and global health ethics, which seek to address the larger social, political, and economic forces behind the increasing inequities in global health—perhaps the greatest ethical dilemma of all.

References

1. C. Terwindt, "Health rights litigation pushes for accountability in clinical trials in India," *Health and Human Rights Journal* 16/2 (2014), pp. 86-87.
2. S. Glickman et al., "Ethical and scientific implications of the globalization of clinical trials," *New England Journal of Medicine* 360/8 (2009), pp. 816-823; S. Nundy and C.M. Gulhati, "A new colonialism? Conducting clinical trials in India," *New England Journal of Medicine* 352 (2005), pp.1633-1636; Terwindt (see note 1), p.86.
3. D. Sharma, "Outsourcing big pharma," *Health Affairs* 29(3) (2010), pp. 563-564.
4. World Medical Association, Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects, G.A. Res. (adopted 1964, last amended 2013), para. 33. Available at <http://www.wma.net/en/30publications/10policies/b3/> [hereinafter Declaration of Helsinki].
5. For discussions of both sides of this debate, see P. Marshall, *Ethical challenges in study designs and informed consent for health-research in resource-poor settings* (Geneva: WHO, 2007), pp. 19-22. Available at http://whqlibdoc.who.int/publications/2007/9789241563383_eng.pdf; Nuffield Council on Bioethics, *The ethics of research related to healthcare in developing countries* (London: Nuffield Council on Bioethics, 2005), pp. 25-33. Available at http://nuffieldbioethics.org/wp-content/uploads/2014/07/HRRDC_Follow-up_Discussion_Paper.pdf.
6. J. Cohen and T. Ezer, "Human rights in patient care: A theoretical and practical framework," *Health and Human Rights Journal* 15/2 (2013), p. 16.
7. S. Marks, "The new partnership of health and human rights," *Human Rights Dialogue* (New York: Carnegie Council for Ethics in International Affairs, Spring/Summer 2001), pp. 21-22. Available at https://www.carnegiecouncil.org/publications/archive/dialogue/2_06/articles/650.html.
8. S. Lingnou, "The 'standard of care' debate and global

justice in research,” *Research Ethics* 7(1) (2011), pp. 5-12.

9. P. Lurie and S.M. Wolf, “Unethical trials of interventions to reduce perinatal transmission of the human immunodeficiency virus in developing countries,” *New England Journal of Medicine* 337 (1997), pp. 853-855.

10. Lingnou (see note 8).

11. The Council for International Organizations of Medical Sciences, *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (3rd ed. 2002), guideline 11, p. 54. Available at http://www.cioms.ch/publications/layout_guide2002.pdf.

12. *Ibid.*, pp. 56-57.

13. U. Schuklenk, “The standard of care debate: Against the myth of an ‘international consensus opinion,’” *Journal of Medical Ethics* 30 (2004), p. 196.

14. Declaration of Helsinki (see note 4), para. 33.

15. *Ibid.*

16. See R. Lie et al., “The standard of care debate: The Declaration of Helsinki versus the international consensus opinion,” *Journal of Medical Ethics* 30(2) (2004), pp. 190-193; Schuklenk (see note 13), p. 196.

17. H. Ehni, “The definition of adequate care in externally sponsored clinical trials: The terminological controversy about the concept ‘standard of care,’” *Science and Engineering Ethics* 12 (2006), pp. 123-130; U. Schuklenk, “Protecting the vulnerable: Testing times for clinical research ethics,” *Social Science and Medicine* 51 (2000), pp. 969-977.

18. International Conference for Harmonization, *Guidance for Industry, E10 Choice of Control Group and Related Issues in Clinical Trials* (2001). Available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073139.pdf>.

19. *Ibid.*, para. 2.1.3.

20. *Ibid.*

21. *Ibid.*

22. *Ibid.*, paras. 2.1.5.2, 2.1.5.2.1, 2.1.5.2.2, 2.1.5.2.3.

23. D. Garde, *Report: Indian clinical trials fell 93% last year* (January 27, 2014). Available at <http://www.fercecro.com/story/report-indian-clinical-trials-fell-93-last-year/2014-01-27>.

24. Anand Grover, UN Special Rapporteur on the right of everyone to the enjoyment of the highest attainable standard of physical and mental health, Report of the Special Rapporteur on the Right of Everyone to the Enjoyment of the Highest Attainable Standard of Physical and Mental Health, UN Doc. No. A/64/272 (2009). Available at <http://www.un.org/en/ga/third/64/documentslist.shtml>.

25. *Ibid.*, para. 40.

26. *Ibid.*, para. 40.

27. Committee on Economic, Social and Cultural Rights, General Comment No. 14, *The Right to the Highest Attainable Standard of Health*, UN Doc. No. E/C.12/2000/4 (2000), paras. 9, 47. Available at <http://www1.umn.edu/humanrts/gencomm/escgencom14.htm> [hereinafter “General

Comment No. 14”].

28. K. Frank, “The minimum core of economic and social rights: A concept in search of content,” *Yale Journal of International Law* 33 (2008), pp. 154-156.

29. M. Hall and D. Weiss, “Human rights and remedial equilibration: Equilibrating socio-economic rights,” *Brooklyn Journal of International Law* 36 (2011), p. 469.

30. General Comment No. 14 (see note 27), para. 39.

31. *Ibid.*, para. 51.

32. *Ibid.*, para. 48.

33. *Ibid.*, para. 43.

34. Resolution WHO 28.66, *Official Records of the WHO*, 1975, No. 226, pp.35-36.

35. M. Reich, “Essential drugs: Economics and politics in international health,” *Health Policy* 8 (1987), pp. 41, 49. Available at http://www.hsph.harvard.edu/wp-content/uploads/sites/480/2013/01/essential_drugs.pdf.

36. General Comment No. 14 (see note 27), para. 63.

37. See, for example, B. Meier, “Employing health rights for global justice: The promise of public health in response to the insalubrious ramifications of globalization,” *Cornell International Law Journal* 39 (2006), pp. 735-736.

38. Anand Grover, Special Rapporteur on the right of everyone to the enjoyment of the highest attainable standard of physical and mental health, Report of the Special Rapporteur on the Right of Everyone to the Enjoyment of the Highest Attainable Standard of Physical and Mental Health, UN Doc. No. A/65/255 (2010), para. 40. Available at <http://daccess-dds-ny.un.org/doc/UNDOC/GEN/N10/477/91/PDF/N1047791.pdf?OpenElement>.

39. *Ibid.*, at para. 40.

40. General Comment No. 14 (see note 27), para. 45; Frank (see note 28), p. 156.

41. General Comment No. 14 (see note 27), para. 39 (emphasis added).

42. European Group on Ethics in Science and New Technologies, Opinion No. 17, *Ethical Aspects of Clinical Research in Developing Countries* (2003), para. 2.12; Medical Research Council of South Africa, *Guidelines on Ethics for Medical Research*, Book 5: HIV Preventive Vaccine Research (2003), paras. 1.4.4, 16.1, 16.4.1, 16.4.4. Available at <http://www.mrc.ac.za/ethics/ethicsbook5.pdf>.

43. General Comment No. 14 (see note 27), para. 64.

44. World Health Organization, *The use of essential drugs: Seventh report of the WHO expert committee* (Geneva: WHO, 1997). Available at http://apps.who.int/iris/bitstream/10665/41938/1/WHO_TRS_867.pdf.

45. UN Human Rights Committee, General Comment No. 6, Article 6 (Right to Life), UN Doc. HRI/GEN/1/Rev.6 at 127 (2003), para. 1.

46. See C. Coleman, “The ethics of using placebo controls in Ebola clinical trials,” *Health Reform Watch* (November 25, 2014). Available at <http://www.healthreformwatch.com/2014/11/25/the-ethics-of-using-placebo>

bo-controls-in-ebola-clinical-trials/.

47. E. Cox et al., “Evaluating Ebola therapies—the case for RCTs,” *New England Journal of Medicine* 371 (2014), pp. 2350-2351. Available at <http://www.nejm.org/doi/full/10.1056/NEJMp1414145>.

48. S. Kanters, “Evaluating Ebola interventions: adaptive designs should be commonplace,” *The Lancet Global Health Blog* (Oct. 10, 2014). Available at <http://globalhealth.thelancet.com/2014/10/10/evaluating-ebola-interventions-adaptive-designs-should-be-commonplace>.

49. General Comment No. 14 (see note 27), para. 44.

50. *Ibid.*, para. 43(f).

51. *Dictionary of epidemiology, 5th edition* (New York: Oxford University Press, 2008), pp. 78-70 (entries of “endemic” and “epidemic”).

52. *Encyclopedia Britannica* (2015) (entry for “endemic disease”). Available at <http://www.britannica.com/EB-checked/topic/186790/endemic-disease>.

53. Grover (see note 24), para. 36.

54. D. Wendler et al., “The standard of care debate: Can research in developing countries be both ethical and responsive to those countries’ health needs?” *American Journal of Public Health* 94 (2004), pp. 923-928.

55. C. Adebamowo et al., “Randomized controlled trials for Ebola: Practical and ethical issues,” *The Lancet* 384 (9962) (2014), pp. 1423-1424.

56. International Convention on Civil and Political Rights (ICCPR), G.A. Res. 2200A (XXI) (1966), Art. 7. Available at <http://www2.ohchr.org/english/law/ccpr.htm>. [Hereinafter ICCPR].

57. General Comment No. 14 (see note 27), para. 43(a).

58. ICCPR (see note 57), Art. 2(1), Art. 4(1).

59. UN Human Rights Committee, General Comment No. 20, Article 7, U.N. Doc. HRI/GEN/1/Rev.1 at 30 (1994), para. 7.

60. UN Human Rights Committee, Concluding Observations on the Netherlands, UN Doc. CCPR/CO/72/NET (2001), para. 7.

61. UN Human Rights Committee, Concluding Observations on the United States, UN Doc. CCPR/C/USA/CO/3 (2006), para. 31.

62. See, for example, C. Denny and C. Grady, “Clinical research with economically disadvantaged populations,” *Journal of Medical Ethics* 33 (2007), pp. 382-385.

63. Grover (see note 24), paras. 36-38, 40-41.

64. UN Human Rights Committee, General Comment No. 20, Article 7, U.N. Doc. HRI/GEN/1/Rev.1 at 30 (1994), para. 13l.

65. *Kiobel v. Royal Dutch Petroleum*, 133 S.Ct. 1659 (2013).

66. US Department of Health and Human Services, Food and Drug Administration, Code of Federal Regulations - Title 21 - Food and Drugs (2008), § 312.120; US Department of Health and Human Services, Food and Drug Administration, Code of Federal Regulations - Title 21 - Food and

Drugs (1990), § 314.106; US Department of Health and Human Services, Food and Drug Administration, Code of Federal Regulations - Title 21 - Food and Drugs (2002), § 312.23. Available at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Databases/ucm135680.htm>.

67. *Ibid.*, § 312.120(c).

68. *Ibid.*, (1990), § 314.106.

69. *Ibid.*, (2008), § 312.120(a)(i).

70. US Department of Health and Human Services, Office of the Inspector General, Challenges to FDA’s Ability to Monitor and Inspect Foreign Clinical Trials (2010), p. 15. Available at <http://oig.hhs.gov/oei/reports/oei-01-08-00510.pdf>.

71. D. Orentlicher, “Universality and its limits: When research ethics can reflect local circumstances,” *Journal of Law, Medicine and Ethics* 30 (2002), pp. 403-410.