Session 19. Post-Trial Obligations in International Health Research Ethics

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Overview

International health research raises many controversial ethical issues, including concerns about fairness, exploitation of subjects or communities, and a lack of clarity over what researchers owe subjects who may have limited access to health care and a lower standard of care. These questions arise with special urgency at the end of a research study given that research funding is typically time-limited, but health care needs may persist long after studies are completed.

This module will explore the ethical issues arising in international health research, focusing on the obligations that arise post-trial. Participants will become aware of what international ethical and policy guidance and laws require of researchers, and the controversy and lack of consensus over what researchers might owe subjects at the end of a research study. Participants will understand what ethical principles do and do not apply to post-trial obligations of researchers. They will also explore questions about trade-offs and how researchers might balance different ethical obligations against each other when resources are limited.

Instructor's Guide

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Case Summary

A researcher plans a trial studying how to prevent vertical transmission of HIV from HIV-positive mothers to their infants during labor and delivery. This trial will be conducted in low-income countries. The study provides antiretroviral therapy (ART) as prophylaxis to the mother during pregnancy and labor and to the child for the duration of breastfeeding. After the infant is delivered, the study stops providing ART to mothers and refers them to the national programs for HIV treatment. The low-income countries where the study is

being conducted only have resources to provide ART to women whose CD4+ T-lymphocyte counts are below 350; other women will have to wait for their health to decline before they will become eligible for treatment.

- What do international ethical, policy and legal standards require of researchers and sponsors in this case?
- Is it ethical for researchers and sponsors to stop providing ART at delivery?
- If not, what should researchers and sponsors do instead?
- What ethical principles support (or do not support) obligations for researchers in advance?
- How should researchers and sponsors balance post-trial care against other competing benefits they could provide, such as providing care for babies born preterm, providing care for others in the community, or conducting other research in the future?

Alternate Cases

1. In a rural community in Venezuela where villagers have extraordinarily high rates of being afflicted with Huntington disease (HD), an American researcher conducted a landmark genetic study nearly 3 decades ago. This study identified the gene that causes HD; there is now a genetic test that can be conducted to determine whether an individual is afflicted with HD. HD is an adult-onset disease that is uniformly fatal. Those who are afflicted have a 50% chance of passing on the gene to their offspring. There is no cure for HD. Today, the villagers in this community do not have access to the genetic test, but the researcher has provided other types of care and improved infrastructure at a local clinic. The researcher is concerned that providing the test without providing access to genetic counseling would lead people to make poor decisions or have information they cannot process appropriately. There are only a handful of genetic counselors in Venezuela, all of whom are in Caracas, which is several hours away from the village. What should the researcher do or have done?

2. Researchers are conducting a phase III trial of third-line ART for people who have developed resistance to first- and second-line therapy. The trial is being conducted in low-income countries where the drugs are not yet approved. Researchers anticipate that it will take anywhere from 2 to 5 years after the trial is complete for national approvals to be granted. In the meantime, there is no way for trial participants to access third-line therapy, and no alternative treatment that will work for them aside for supportive care and treatment for opportunistic infections. What do researchers owe the participants of this trial?

Learning Objectives

1. Understand the controversy over post-trial obligations in international research ethics.
2. Understand the ethical bases for post-trial obligations and the resulting limitations.
3. Understand the competing obligations for researchers studying international health.

Suggested Reading for Instructor

Weijer C, Leblanc GJ. The balm of Gilead: is the provision of treatment to those who seroconvert in HIV prevention trials a matter of moral obligation or moral negotiation? J Law Med Ethics. 2006;34(4):793-808

Shah S, Elmer S, Grady C. Planning for posttrial access to antiretroviral treatment for research participants in developing countries. Am J Public Health. 2009;99(9):1556-1562

Council for International Organizations of Medical Sciences, and World Health Organization. International Ethical Guidelines for Health-Related Research Involving Humans. 2016. Available at: http://cioms.ch/ethical-guidelines-2016/WEB-CIOMS-EthicalGuidelines.pdf

Nuffield Council. The Ethics of Research Related to Healthcare in Developing Countries: A Follow-Up Discussion Paper, Section 4.4. Available at: http://nuffieldbioethics.org/wp-content/uploads/2014/07/HRRDC_Follow-up_Discussion_Paper.pdf

Further Reading

Mastroleo I. Post-trial obligations in the Declaration of Helsinki 2013: classification, reconstruction and interpretation. Dev World Bioeth. 2016;16(2):80-90

Millum J. Post-trial access to antiretrovirals: who owes what to whom? Bioethics. 2011;25(3):145-154

Merritt M, Grady C. Reciprocity and post-trial access for participants in antiretroviral therapy trials. AIDS. 2006;20(14):1791-1794

Case Discussion

What does international ethical and policy guidance and laws require of researchers in this case?

There is very limited international consensus on this issue. The World Medical

Association's Declaration of Helsinki (2013 version) requires that: "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." Guidance from the National Institutes of Health (NIH) on posttrial access to antiretroviral therapy indicates that, "[f]or antiretroviral treatment trials conducted in developing countries, the NIH expects investigators/contractors to address the provision of antiretroviral treatment to trial participants after their completion of the trial," but also indicates that NIH funds cannot be used to provide treatment post-trial.

The Council for International Organizations of Medical Sciences has new guidance (as of 2016) that requires the following: "Especially in the context of clinical trials, researchers and sponsors must make adequate provisions for addressing participants' health needs during research and, if necessary, for the transition of participants to care when the research is concluded. The obligation to care for participants' health needs is influenced, among other things, by the extent to which participants need assistance and established effective care is available locally." Some countries, like Brazil, require that study drugs be provided post-trial, but do not specify who has the duty to provide them—the Brazilian government, researchers, or pharmaceutical companies? Notably, however, many countries lack laws on this issue, and some ethicists argue that post-trial access is not obligatory.[1]

At a minimum, among the countries and documents that address post-trial access, it appears that there is agreement that researchers should address the participants' post-trial needs in the protocol and informed consent.[2,3] This suggests that the plan to transition participants to the national program appears to be at least sufficient. However, expecting women to transition successfully days after giving birth seems unrealistic. A reasonable transition plan might include the provision of treatment through the study for a few weeks or months after birth. Some might argue that the researchers should do more, particularly for the women who will not qualify for treatment through the national program, but it is not clear how the researchers would pay for this. Moreover, once treatment is provided, the women may not ever become eligible for treatment through the national program, because their CD4+ T- lymphocyte counts will remain stable, which means that the researchers would have to enter into a lifelong commitment.

What ethical principles support (or do not support) obligations for researchers and sponsors after trials conclude?

The ethical principles of nonmaleficence and beneficence may support post-trial obligations, particularly if stopping care temporarily causes harm to the former participant. Participants might be harmed if stopping therapy after a trial causes resistance to ART or sends message that treatment adherence is not important. Although it is generally agreed that researchers have obligations of beneficence that may include participants, it is worth noting that these obligations could be fulfilled in multiple ways (eg, payment, provision of other kinds of ancillary care, provision of care to members of the community, improving health care infrastructure in the community).

The ethical principle of reciprocity—the idea that someone who has received a benefit from someone else owes something in return—likely does not support post-trial obligations. This principle is intended to ensure that if participants give something to researchers, they receive something in return. What counts as a fair reciprocal arrangement may also vary on the basis of cultural context. However, these participants have already received substantial benefits during the trial, and this benefit may be sufficient to satisfy the principle of reciprocity.[4]

How might researchers and sponsors plan to address post-trial obligations in advance?
As alluded to previously, many guidance documents counsel researchers and sponsors to make anticipatory plans with local governments, international aid organizations, and other stakeholders to ensure that participants continue to receive care they need. Unfortunately, grant funding rarely extends after a trial is over or to cover treatment that is unrelated to/not necessary for the conduct of research. It may make sense for researchers to plan for a reasonable transition to another source of care, and what counts as reasonable is an open question. One study has found that some researchers engage in short-term provision of ART or other care to facilitate a successful transition post-trial.[3]

How should researchers and sponsors balance post-trial care against other competing obligations to research participants, or against their obligation to conduct other research in the future?
To the extent that researchers are obligated to provide post-trial access to prevent harm from the research itself, there may not be other competing obligations. To the extent that researchers are obligated to provide post-trial access through the principle of beneficence, there are other benefits they could provide to their participants, such as by providing care for infants born preterm or if complications occur that are not related to the trial. However, as researchers, they are first and foremost trained and obligated to conduct research. One way to resolve this potential conflict of duties is for researchers to determine what resources they can spare without compromising their primary duties of conducting research, and plan in advance the best way to allocate these resources amongst these competing options to do the most good.

Conclusions and Suggestions

It is important to emphasize to students that although their instincts may suggest that researchers should do as much good for these participants as possible, there are many competing ways to do good, and researchers have primary obligations to conduct research. Additionally, this case is a useful way to point out that ethical and legal guidance is often a starting point for discussion, and does not often clearly resolve complex ethical issues. Finally, the idea of achieving a successful transition post-trial is intuitively attractive and supported by recent guidance, but is still undertheorized in terms of the ethical principles that support it and may be best justified when failing to assist individuals in a post-trial transition may cause them to be harmed.

References

1. Millum J. Post-trial access to antiretrovirals: who owes what to whom? Bioethics. 2011;25(3):145-154

2. Council for International Organizations of Medical Sciences, and World Health Organization. International Ethical Guidelines for Health-Related Research Involving Humans. 2016. Available at: http://cioms.ch/ethical-guidelines-2016/WEB-CIOMS-EthicalGuidelines.pdf

3. Shah S, Elmer S, Grady C. Planning for posttrial access to antiretroviral treatment for research participants in developing countries. Am J Public Health. 2009;99(9):1556-1562

4. Merritt M, Grady C. Reciprocity and post-trial access for participants in antiretroviral therapy trials. AIDS. 2006;20(14):1791-1794

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