POSTTRIAL CLINICAL ACCESS: AN EXAMINATION OF THE PRINCIPLES AND
GUIDELINES SUPPORTING THE POSTTRIAL ACCESS FRAMEWORK AND A
DETERMINATION OF WHETHER THE UNITED STATES CAN DEVELOP A GUIDANCE
MANDATING THE PROVISION OF POSTTRIAL ACCESS

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ABSTRACT

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Thesis under the direction of Nancy King, J.D., Professor, Bioethics Program, Department of Social Sciences and Health Policy Faculty Member.

The increased numbers of clinical trials taking place developing countries have raised issues concerning the researcher’s obligation to trial participants, the host community, or the host country at the conclusion of a clinical trial. One of the most controversial obligations is the provision of posttrial access after a clinical research trial. This thesis summarizes the principles and guidelines that suggest or require the inclusion of a posttrial access framework at the conclusion of a clinical research trial in the specific context of HIV antiretroviral clinical trials conducted in developing countries, and determines whether the National Institutes of Health’s existing posttrial access provision adequately addresses the issues related to mandating posttrial access.
The modern research climate has seen a steady increase in the number of clinical trials conducted in both developed and developing countries. Known as multicenter clinical drug trials, these trials enroll a large number of participants and are conducted in multiple countries. The approved drug may eventually become available in the developing world, but will quickly become available for distribution in developed countries, where a pharmaceutical company is likely to profit from drug sales.\(^1\)

The increased number of multicenter clinical trials has resulted in the development of ethical guidelines to address ethical issues and attempt achievement of global justice. One of the ethical issues related to multicenter clinical trials is whether researchers have an ongoing obligation to trial participants, the host community, or the host country at the conclusion of a clinical trial.\(^2\) Some propose that the inclusion of a “posttrial access” provision to a clinical research protocol will satisfy this obligation. Posttrial access is the ethical requirement to make products, proven effective by a regulatory agency, available to trial participants at the conclusion of the trial, until the product is, or should be, reasonably available in the host community or country.\(^3\)

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1. Clinical trials are often discussed because of the inherent ethical issues, but two other types of clinical trials exist: 1) clinical trials that are conducted in developing countries where the intervention will not be made available (or will be too expensive for the host country to obtain), and 2) clinical trials that are conducted in developing countries with the explicit goal of availability within the host country. These two types of trials are not usually discussed in the literature because the first type of trial is the clear definition of exploitation, and the second type of trial is conducted only for the benefit of the individuals in developing countries.

2. Ruth Macklin, "Global Justice, Human Rights, and Health," in *Global Bioethics: Issues of Conscience for the 21st Century*, ed. Ronald M Green, Aine Donovan and Steven A Jauss, 143 (Oxford: Clarendon Press, 2008). Note that the term “posttrial access” (one word) is used as a term of art to describe the specific framework, and “post trial” (two words) is used describe obligations that exist after the end of a clinical trial.

3. I developed this interpretation of posttrial access when it became apparent that other definitions of posttrial access did not provide an adequate explanation of the framework. However, this
This thesis addresses the ethical and policy issues that occur when a research sponsor mandates the inclusion of a posttrial access provision in a research protocol. Specifically, this thesis will address a particular aspect of posttrial access that presents difficult implementation questions—Phase III HIV antiretroviral (ART) multicenter clinical drug trials. The National Institutes of Health’s (NIH) Guidance for Addressing the Provision of Antiretroviral Treatment for Trial Participants Following their Completion of NIH-Funded HIV Antiretroviral Treatment Trials in Developing Countries recommends that researchers address the inclusion of a posttrial access provision in the specific context of HIV antiretroviral clinical trials which will be conducted in developing countries. The last chapter will discuss the specific issues related to this Guidance.

Before analyzing the Guidance,

**Why Choose Posttrial Access as a Thesis Topic?**

*The Constant Gardener* is an Academy Award winning movie about the fraudulent testing of a tuberculosis drug in Africa. The movie’s cinematography and storytelling revealed the issues of exploitation and injustice that still occur in developing countries despite existing domestic and international protections. The movie was based on alleged events in the Kano Trovaflloxacin trial. It was alleged in 1996 that Pfizer violated international law by testing an unapproved drug, Trovan, on children in Kano, Nigeria. According to a panel of Nigerian medical experts, there were “no records documenting that Pfizer had told children or their parents

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that they were part of an experiment.” At the time Pfizer was developing Trovan for release in the United States, where it was expected to gross $1 billion a year. Watching this film and reading about the Kano Trovafloxacin trial helped me realize my interest in the treatment of clinical trial participants in developing countries.

After conducting several months of research on the various issues surrounding multicenter drug trials, I began to focus my research on issues related posttrial benefits—frameworks utilized to protect trial participants after a clinical trial has been completed. I noticed that the NIH enacted a guidance on posttrial access. I questioned why the Guidance only recommended that investigators develop a posttrial access provision instead of mandating a posttrial access provision. This question lead to the decision to write a thesis about the issues related to posttrial access, and the consequences of including a posttrial access provision in research protocols.

**Why is this Question Worth Answering?**

There are two reasons to focus on the NIH Guidance. The first is that the Guidance affects researchers who are performing research on HIV, one of the most devastating and rapidly expanding diseases in the world. Because of its focus on HIV, this Guidance deserves to be scrutinized to ensure that it is as clear and unambiguous as possible. Second, analyzing, evaluating, and rewriting this guidance ensures that the interpretation of posttrial access is clear and an incorrect interpretation of the framework is not included in the NIH Guidance.

While I will focus on HIV ART multicenter drug trials because of the NIH Guidance, which specifically focuses on providing posttrial access for HIV antiretroviral drug trials, the facts on HIV alone warrant specific discussion.

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7 Id.
8 Id.
In 2007 33.2 million people were living with human immunodeficiency virus (“HIV”), and 2.1 people were killed as a result of acquired immunodeficiency syndrome (“AIDS”). The HIV/AIDS pandemic is one that affects people in both developing and developed countries, though nobody argues that the developing world has been hit hardest by this disease. For example, North America had 1.3 million people living with HIV in 2007 (up from 1.1 million in 2001), while Sub-Saharan Africa had 2.25 million (up from 20.0 million).

An enormous amount of worldwide resources have been dedicated to developing treatments and preventions that may combat AIDS. Since 1981, the NIH has recognized HIV/AIDS as an epidemic, and funding for research to combat AIDS has grown to 2.9 billion. Because such a large portion of research funding has been devoted strictly to AIDS, the NIH issued the Guidance and expressed an expectation that “investigators address the provision of antiretroviral treatment to trial participants after their completion of the trial.” In addition, a portion of the literature on posttrial benefits has been dedicated to determining the best way to implement a posttrial provision after the completion of a HIV antiretroviral clinical trial in a developing country. However, the NIH posttrial Guidance and other posttrial literature in this area have been unclear as to the most effective way to implement posttrial access after an antiretroviral trial.

The lack of clarity in the literature also makes this question worth answering. Initially I was concerned that it would be difficult to find a unique approach to evaluating posttrial access. After all, a long-standing debate on posttrial benefits exists, producing a plethora of literature about why and how investigators and sponsors can most effectively address the ethical issues inherent in conducting a clinical trial.

12 NIH “Guidance for addressing the provision of antiretroviral treatment.”
However, after narrowing the thesis to focus on the NIH Guidance that would to guide investigators in their posttrial access obligations, background research on the definition, principles, and issues of the framework began. It became apparent that the research led to unclear explanations of posttrial access. It was difficult to articulate an accurate definition of posttrial access. The definition of posttrial access would change depending on the article, book, or guideline.

The inability to articulate an accurate definition of posttrial access could be attributed to the fact that much of the commentary on the subject gave wide and varied interpretations. It is difficult to read the writings of experts in a field and say, “perhaps they are incorrect in their formulation of this topic.” However, the commentaries written by the well-known scholars in bioethics on the subject of a posttrial access framework usually vague and inconsistent.

**Summary of the Question**

This thesis will consider the issues related to posttrial access, and whether the NIH, the agency of the United States government responsible for biomedical and health related research, has developed a guidance that appropriately directs researchers conducting antiretroviral clinical trials about the best way to include a plan to develop and implement a posttrial access provision within their research protocol.

The question of whether to include a posttrial access provision is often expressed in the following manner: “To what extent are research sponsors and investigators required to ensure that research participants have access to interventions proven effective in clinical trials?”13 The 1964 Declaration of Helsinki was the first international guideline to suggest the posttrial access framework as a way for sponsors and investigators to rectify potential conflicts with ethical principles during the course of their clinical trial. The relevant portion of the Declaration stated: “At the conclusion of the study, every patient entered into the study should be assured access to

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the best proven prophylactic, diagnostic, and therapeutic methods identified by the study."

However, the Declaration’s definition does not adequately describe the requirements of posttrial access. This issue will be discussed in Chapter 2.

Overview of Conclusion

The NIH is responsible for biomedical and health related research, and should be able to develop a policy endorsing the posttrial benefit framework it finds most appropriate. Therefore, the NIH can develop a guidance that requires researchers seeking NIH-funding to include a posttrial access provision within a research protocol. However, by virtue of its statutory mandate, the NIH cannot fund a posttrial access provision.15 Whether posttrial access is required or recommended, funded or not, it is essential that the NIH include the correct definition of posttrial access within their Guidance to enable researchers to correctly incorporate a posttrial access provision.

Description of the Contents

Chapter 2 provides the background information necessary to understand the remaining four chapters of the thesis. Beginning with a short history of the AZT trial, Chapter 2 clarifies the differences between three categories of post trial benefits—posttrial access, reasonable availability, and fair benefits. Because posttrial access is the focus of this thesis, a new interpretation of posttrial access will be described in detail along with a critique of each interpretation. This section will also provide the interpretation of posttrial access which best encompasses the ethical objectives posttrial access. This interpretation is largely based on my own understanding of posttrial access. It is the interpretation of posttrial access that will be used in the remainder of the thesis.

Chapter 3 reviews ethical justifications necessary to support the obligation to provide posttrial access. It begins with a discussion of three ethical principles, beneficence, nonmaleficence and justice, which support the ethical obligation to include posttrial access in a research protocol. Using the aforementioned ethical principles as guidance, it describes three positions that can be taken on posttrial access. Those three positions are a maximal position, a moderate position, or a minimal position. Finally, Chapter 3 analyzes domestic, international, and foreign guidelines or laws related to posttrial access.

While the first three chapters of this thesis will explore nuances necessary to understand the posttrial access framework, this Chapter 4 transitions to focus on the particular aspect of posttrial access that presents difficult implementation questions: HIV ART multicenter drug trials. Chapter 4 refocuses the discussion of HIV antiretroviral treatment by reminding the reader of the question to be answered by this thesis, explaining why this question is important, and will present the reader with the case study that will be used in Chapter 5 to explore the nuances of the NIH Guidance.

Chapter 5 applies the NIH Guidance to the Tenofovir gel trial. The goal is to determine whether the Guidance provides adequate information to investigators who are submitting a HIV/AIDS trial research protocol to the NIH in order to identify the weakness and strengths of the Guidance. Chapter 5 also sets forth proposed revisions to the Guidance to include the definition of posttrial access used in this thesis, and then discusses whether the revision would provide investigators with a better Guidance that will allow them to more efficiently address the recommendation of the NIH.
CHAPTER TWO

BACKGROUND INFORMATION:
AZT & POST TRIAL BENEFITS

Understanding the requirements of posttrial access requires a discussion of the background influencing the framework’s development. This chapter provides the background necessary to understand the discussion of posttrial access in the remaining chapters. The AZT trial of the early 90s has largely influenced the discussion about three post trial benefit frameworks—posttrial access, reasonable availability and fair benefits. The three post trial benefit frameworks each has similarities and differences which, if not properly understood and distinguished, can (and has) lead to conflation in the literature. The goal of this chapter is to provide a background that allows the reader to better navigate the criticisms of posttrial access literature discussed in Chapter 3.

History of Posttrial Access: AZT

In 1994, the results of the AIDS Clinical Trial Group (ACTG) Study 076 were published in the New England Journal of Medicine (NEJM). ACTG 076 was groundbreaking because it was the first randomized controlled study in which an intervention was shown to reduce the incidence of HIV infection. The study involved administering an antiretroviral drug, zidovudine (AZT) to pregnant HIV-positive women in the United States and France. The pregnant women would begin an oral regimen during their second trimester, would intravenously receive AZT during labor, and after birth the child’s birth, AZT would subsequently be administered to the

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infants. The drug successfully reduced the incidence of HIV transmission from HIV positive women to infants by two thirds, and the U.S. Public Health Service recommended the 076 regimen become the new standard of care for pregnant women infected with HIV.

The AZT regimen costs upward of $1,000 was considered impossible to implement in the developing world, where the annual health budget can be less than $10 per person, or where a country has little to no health care infrastructure. Nevertheless, with 1,000 HIV-infected babies born each day, it was clear that a solution to maternal-fetal transmission was necessary in developing countries. In June of 1994, the World Health Organization (WHO) convened to discuss beginning a trial to search for a less expensive regimen and concluded, “placebo controlled trials offer the best option for rapid and scientifically valid assessment of alternative antiretroviral drug regimens to prevent perinatal transmission of HIV.” Sixteen AZT versus placebo trials, designed to be randomized controlled trials of shorter and simpler regimens, were funded by the NIH, the Centers for Disease Control (CDC), the Joint United National Program of HIV/AIDS (UNAIDS), and five other governments.

After it became known that the AZT trials would utilize a placebo control, several people came forward to voice their concerns about whether the use of placebos in such trials was ethical. Peter Lurie and Sidney Wolfe published a commentary in the NEJM condemning the trials as unethical. The editor of the NEJM wrote an editorial of support in Lurie and Wolfe, and compared the AZT trials to the Tuskegee trials. The controversy about the trials resulted in two editors of the NEJM resigning because of the editor’s letter of support, the directors of the NIH

18 Ibid.
20 Ibid.
21 Lurie and Wolfe “Unethical Trials in Developing Countries,” 854.
22 Ibid. 853-856.
and CDC writing letters in defense of the trials, and prominent bioethics journals dedicating entire issues to the debate, with all sides of the debate offering their own opinions on the issue.  

It was difficult to distinguish all of the ethical problems involved in the AZT trial. Many ethical issues were identified and discussed, conflated and confused. However, the passage of time has allowed the recognition that the AZT trial primarily raised three ethical issues specific to research conducted in the developing world: 1) what should be considered the correct standard of care and how to design an ethical study, 2) how to properly obtain valid informed consent from trial participants, and 3) whether drugs developed as the result of research must be available to trial participants at the conclusion of the trial. The third ethical issue, the availability of drugs developed as the result of research, raised specific questions such as: what obligations exist once the trial has been concluded, and what criteria must be respected to prevent abusive and exploitative research? Perhaps research conducted in the developing world is inherently “unfair to the study participants in particular and to the host communities in general, since, in many cases, drugs or interventions developed as a result of research will not be available to either group post trial because of prohibitive costs.” One response to remedy this ethical dilemma is to require researchers to provide posttrial benefits to trial participants.

“Post-trial Benefits”

The concept of “post trial benefits” is used to describe any framework that provides a benefit to a specific population after the conclusion of a clinical trial. Posttrial access is one framework that falls under the concept of post trial benefits. Two other post trial frameworks are reasonable availability and fair benefits. The concept of post trial benefits should not be confused

24 Hawkins and Emanuel “Exploitation and Developing Countries,” 3.
25 Ibid., 3-8. Hawkins and Emanuel actually identify the three ethical issues as: standard of care and the ethics of study design, informed consent, and reasonable availability and fair compensation.
with the “fair benefits” framework, which is described in detail later in this chapter. While all three frameworks seek to achieve the same goal—to remedy issues regarding researcher obligations to trial participants after the clinical trial—each framework functions in a different manner. Below, the three post trial frameworks, posttrial access, reasonable availability, and fair benefits, are defined and the issues relevant to each are described.

**Posttrial Access.** Posttrial access can generally be described as the provision of treatment to trial participants after the conclusion of trial. However, descriptions of posttrial access provisions vary because the framework, as it was originally described in the Declaration of Helsinki, did not clarify specific requirements. I suggest that a more explicit definition of posttrial access be adopted in the future. Below are four interpretations of posttrial access, including my own, more explicit interpretation. Because each interpretation potentially leads to a differing explanation of posttrial access requirements, it is important to distinguish each interpretation from others before moving into a discussion of posttrial access guidelines and recommendations.

Long before the AZT trial, the WMA recognized that researchers had an ethical responsibility to research participants and proposed that successful products of research be made available to them. The WMA’s interpretation of posttrial access was the first to suggest that access to interventions proven beneficial should be required after the trial. Paragraph 30 of the 1964 Declaration of Helsinki stated:

> At the conclusion of the study, every patient should be assured of access to the best-proven prophylactic, diagnostic, and therapeutic methods identified by the study.\(^{29}\)

Paragraph 30 has been criticized because of its use of unclear language. The Declaration did not define what it means to reach the “conclusion of the study.” Is the conclusion of the study

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\(^{28}\) Although the fair benefits framework is not technically a post trial framework, because benefits can occur contemporaneously with the trial, most commentators consider it a post trial framework. In order to easily identify the ethical issues that are similar among the three frameworks mentioned (posttrial access, fair benefits, reasonable availability) I will also consider fair benefits under the umbrella of “post trial obligations.”

the point at which the researcher stops collecting data on the drug, or is it after the drug has been approved by a regulatory body? Nor does the Declaration adequately describe what it means to “assure access” for participants. Who is responsible for assuring access? How long does the requirement to assure access continue? Finally, the Declaration does not define what it means for a researcher to provide “the best proven prophylactic, diagnostic, and therapeutic methods.” Will the researcher need to provide access to the intervention tested in the trial? What if the intervention is unsuccessful? In an effort to stem some of the criticism of the Declaration’s posttrial access provision, in 2004 the WMA approved the following note, asserting its continued support of posttrial access:

The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Posttrial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review.\(^{30}\)

However, after reaffirming its commitment to the 1964 interpretation of posttrial access, in 2008 the WMA adopted a second interpretation of posttrial access due to continued criticism of paragraph 30. This interpretation of posttrial access is currently adopted in Paragraph 14 of the 2008 Declaration of Helsinki:

The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.\(^{31}\)

In addition, paragraph 33 reiterates the new paragraph 14 requirements for posttrial access protocols:

At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.\(^{32}\)


\(^{32}\) World Medical Association, Declaration of Helsinki, paragraph 33.
The new interpretation of posttrial access emphasizes the importance of posttrial access to proven interventions and access to other appropriate care. It puts more weight on the requirement to identify arrangements for posttrial access, which is not what the original Declaration emphasized. The newest Declaration seems to both emphasize and deemphasize a requirement to provide posttrial access.

A third interpretation of posttrial access was advanced by Grady in her article “The Challenge of Assuring Continued Post-Trial Access to Beneficial Treatment.” Grady defines posttrial access as the requirement to provide continued access for research participants who benefit from investigational treatments. Her definition identifies the conclusion of the trial as the point when the trial stops collecting data on the participant. Once data collection ends, and it is determined that the drug is beneficial, participants who benefited from the drug would begin to receive it. This access would occur before a regulatory agency approved the efficacy of the intervention. Grady’s definition is flawed because it is unlikely that the WMA intended for drugs unapproved by a regulatory body to be provided to participants. Another shortcoming of Grady’s definition is that it may not provide posttrial access to those in every arm of the trial. Posttrial access could possibly be limited only to participants who received the tested intervention, or could be further limited to those who showed a positive outcome after receiving the intervention.

I believe a fourth interpretation of posttrial access will remedy the deficiencies of the previous descriptions. The requirement to provide posttrial access should read as follows:

Posttrial access is the ethical requirement to make products, proven effective by a regulatory agency, available to trial participants, at the conclusion of the trial, until the product is, or should be, made reasonably available in the host country.

The “ethical requirement” of posttrial access is based on the principles of justice, beneficence, and nonmaleficence, described in further detail in Chapter 3. “Products” include

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34 Ibid., 427.
treatments and preventions. As will be seen in Chapter 5, this distinction is important because recent scientific discoveries necessitate the inclusion of both treatments and preventions in the framework. “Trial participants” are those persons who participated in the trial, regardless of what arm of the trial they were assigned. The statement that only people who participated in the trial receive posttrial access to treatment is important because the inclusion of the host community is a requirement of the reasonable availability framework. “The conclusion of the trial” occurs when a regulatory body has approved the drug because it is efficacious and safe for human use. If a regulatory body has previously approved the product (for example, if the trial is to determine a new use for the drug or to redefine dosing requirements), then the conclusion of the trial occurs when an outside body approves the new use for the intervention or regimen. “Until the product is or should be, made reasonably available in the host country” means when the product is or should be reasonably available to the community, the researchers no longer have an ethical responsibility to provide posttrial access to the intervention.

The goal of this interpretation of posttrial access is to remedy the shortcomings of other interpretations. However, this conception of posttrial access has its own deficiencies. If participants are required to wait for regulatory approval, they could be subject to the harms of withdrawal from therapy identified by Grady. This harm is remedied if investigators, aware of any potential harm from withdrawal, are required to provide continued access until the “conclusion of the trial” even though it has not been approved. If a regulatory body does not approve the intervention, investigators would not be required to make “products proven effective” available posttrial. However, if the intervention is not approved, the reason could be related to a lack of efficacy or safety, it should not be provided to participants anyway.

My interpretation seeks to set clear and definite limits and provide clarity to posttrial access, while providing clarity to the posttrial access provisions. It also attempts to adhere to the Declaration’s original conception of posttrial access. For these reasons, it is the proper
interpretation of posttrial access and will be the interpretation used in the remainder of this thesis to when describing posttrial access requirements and provisions.

Posttrial access is usually implemented after the completion of a Phase III clinical trial. The following is a brief discussion to differentiate between the Phase I, II, and III trials.

Before any clinical trial can begin, an investigational new drug application must be filed with the Food and Drug Administration (FDA). The application contains information from the laboratory tests of the drug.\textsuperscript{35} If the FDA finds the application satisfactory, human testing can begin, starting with a Phase I trial. The Phase I trial tests new drug or agent for the first time in the human body.\textsuperscript{36} Phase I trials are usually small, and do not reveal how effective an agent is at curbing a disease.\textsuperscript{37} Instead, the aim is to learn about the drug’s toxicity, metabolism and other dynamics. A Phase I trial is usually conducted using healthy participants.

The Phase II trial also is concerned with understanding the safety and side effects of the agent.\textsuperscript{38} However Phase II trial the agent will specifically determine the drug’s efficacy.\textsuperscript{39} In Phase II information is gathered about the drug’s affects in comparison with either an approved treatment or a placebo.\textsuperscript{40} In order to reduce the possibility of bias when interpreting trial results, most studies are double-blind, meaning that both those conducting and taking part in the trial are not told how is receiving which treatment.\textsuperscript{41}

If the drug is found to be effective in Phase II study, the drug will move to Phase III testing. Phase III study is the largest Phase, and could enroll thousands of subjects and can take

\begin{footnotes}
\item[37] Ibid.
\item[38] Ibid.
\item[39] Ibid.
\item[40] Jeffereys, "Clinical Trials," 136.
\item[41] Ibid, 136-137.
\end{footnotes}
several years to complete.\textsuperscript{42} Phase III aims to prove that the drug is safe and effective for the majority of people taking it. This phase requires collecting information on the incidence of illness and the rare side effects of the people taking the drug.\textsuperscript{43} As in Phase II, there is usually a comparison of treatment or placebo, and the study is double blind. The implementation of posttrial access occurs after the conclusion of a Phase III study.\textsuperscript{44}

\textbf{Reasonable Availability.} The ethical framework most likely to be confused with posttrial access is reasonable availability. Reasonable availability is a term coined in the Council for International Organizations of Medical Sciences (CIOMS) \textit{International Ethical Guidelines for Biomedical Research Involving Human Subjects}.\textsuperscript{45} Guideline 10 states:

As a general rule, the sponsoring agency should agree in advance of the research that any product developed through such research will be made \textit{reasonably available} to the inhabitants of the host community or country at the completion of successful testing.\textsuperscript{46}

The reasonable availability framework requires investigators or sponsors to provide the host community with reasonable access to the fruits of research, which in the case of a clinical trial would be the proven intervention.\textsuperscript{47} The “host community” is the city and/or country where the research has been conducted. Supporters of this framework believe that in order for research to be ethically conducted it must offer the potential of actual benefit to the inhabitants of the developed country.\textsuperscript{48} This framework is based on the potential violations of justice inherent in

\textsuperscript{42} Ibid, 137.  
\textsuperscript{43} Ibid.  
\textsuperscript{44} Ibid.  
\textsuperscript{46} Ibid., Further discussion of CIOMS Guideline 10 occurs in Chapter 3.  
\textsuperscript{48} Participants in the 2001 Conference on Ethical Aspects of Research in Developing Countries, "Moral Standards for Research in Developing Countries: From "Reasonable Availability" to "Fair Benefits",\textquotedblright \textit{Hastings Center Report} 34, no. 3 (2004): 17-27, 18.
every research trial, because it is possible to exploit individual participants as well as the communities that host the research.

Posttrial access and reasonable availability are two frameworks easily merged and integrated with one another because both use the same ethical principles to justify their implementation into a research protocol and both require investigators and sponsors to provide the intervention to a population after it has been proven effective in the clinical trial. Both frameworks are implemented after the completion of a Phase III clinical trial. Neither framework requires the investigator or the sponsor to provide any type of benefit beyond the intervention that has been proven beneficial. Despite the similarities, it is easy to distinguish reasonable availability from posttrial access by discerning two important elements, the target population, and timing. If the framework requires the sponsor or investigator to provide the proven intervention to a community, rather than a trial participant, it is reasonable availability. If the framework requires the sponsor to provide the intervention immediately after it has been approved, the framework is posttrial access. By clarifying whom the drug goes to (participant versus community) and when the drug should be available (immediately after approval versus after a period of time) it is less difficult to determine where the boundaries exist between posttrial access and where the reasonable availability.

**Fair Benefits.** The fair benefits framework grew out of the belief that the posttrial access and reasonable availability was not the most advantageous way to provide benefits to participants or the host community because the drugs tested in clinical trials were not always proven beneficial, leaving no way for investigators or sponsors to provide a benefit to the participants or community. Critics have argued:

The fundamental problem with the reasonable availability standard is that it guarantees a benefit—the proven intervention—but not a *fair level* of benefits, and therefore it does not necessarily prevent exploitation. Reasonable availability
focuses on what—the products of research—but exploitation requires addressing how much—the level of benefit.”

Supporters of the fair benefits framework propose that communities in developing countries should be given the ability to choose the benefit that would be best suited to their needs. This framework is distinguished from reasonable availability by three principles. The first principle, “fair benefits,” asserts that there should be a comprehensive delineation of tangible benefits to the research participants and the population from both the conduct and the results of the research. The second principle, “collaborative partnership,” asserts that the population being asked to participate in the trial should determine whether a particular array of benefits is sufficient and fair. The third principle, “transparency,” asserts that fairness is relative, since it is determined by comparisons with similar interactions. Therefore a developing country should have access to a repository of prior “fair benefits” agreements, to allow independent comparisons and assessment.

Critics of the fair benefits framework question its contractual focus and ask whether an agreement should be considered fair simply because the host community accepts it. Critics also take issue with the transparency principle because it is unknown how the repository will ensure that agreements are fair. The fair benefits framework differs from posttrial access and reasonable availability because it does not focus on providing the tested drug to participants or the community, but instead seeks to provide any agreed upon benefit—something with social value (such as building hospitals or schools)—to the community.

49 Ibid., 20.
50 Ibid., 22.
51 Ibid.
52 Ibid., 23.
55 Ibid., at 37.
Differentiating between the three post trial frameworks—posttrial access, reasonable availability, and fair benefits—allows the reader to recognize when they are not clearly applied as distinct frameworks. The ability to identify when this has occurred is especially important in Chapter 3 and 4, which will discuss the literature and critique how the three frameworks have been so grossly misapplied so that the current literature no longer distinguishes between the three frameworks.
CHAPTER THREE

REVIEW OF THE ETHICAL JUSTIFICATIONS FOR POSTTRIAL ACCESS

Every bioethics discussion should begin with the identification of the ethical principles supporting the adoption of an ethical requirement. Chapter 3 will identify three ethical principles—beneficence, nonmaleficence and justice—which support the inclusion of a posttrial access provision into a research protocol. These ethical principles lead to the adoption of three positions on whether a researcher should be required to include a posttrial access provision in their protocol. These positions are identified as the maximum, moderate, and minimal positions.56 Guidelines that include a posttrial access provision implicitly endorse the moderate position. The goal of this chapter is to introduce the reader to the way that posttrial access has gone from an idea based on theoretical justifications to one that is endorsed by international organizations, governments and is applied to actual research trials.

Ethical Principles

Posttrial access addresses the ethical concerns related to multicenter clinical research trials. International guidelines and developing countries have long suggested that posttrial access provisions should be included in research protocols. Advocates of posttrial access apply the principles of beneficence, nonmaleficence and justice to justify mandating posttrial access provision into a research protocol.

Despite the ethical justifications supporting posttrial access, critics of the framework do not believe posttrial access should be required. Jeff Blackmer and Henry Haddad have detailed some objections:

56 Richard Ashcroft, After the trial is over: what are the sponsor’s obligations, May 1, 2005, http://www.scidev.net/en/science-and-innovation-policy/policy-briefs/after-a-trial-is-over-the-ethical-issues-1.html (accessed July 23, 2010). According to their website SciDev.net—the Science and Development Network—project set up by the news staff at the journal Nature, and is committed to providing constructive dialogue on science and technology related issues. It is unclear whether Ashcroft’s article is peer reviewed.
Opponents of posttrial access argue that it is the responsibility of local health care systems, not the study sponsors, to provide access to ongoing health care, and that, in any case, the infrastructure in developing countries does not always exist to enable study sponsors to ensure this access. They also feel that the financial burden on research sponsors as a result of providing ongoing treatment would be overwhelming and would prevent many companies from conducting studies in developing countries, thus impeding the collection of data on effective treatment delivery in vulnerable populations and adding a further obstacle to the development of drugs for the neglected diseases of the world's poor. Ethically, there is the issue of the responsibilities of physicians to study participants, particularly those who have benefited from the trial medication or intervention and may suffer once it is removed. As a great majority of these trials are run by physician investigators, we must examine not just the responsibilities of study sponsors but of physician collaborators as well. The needs of trial participants may be quite different in a North American or Western context than in the developing world. In Western countries, most patients will have access to needed treatment on the completion of a trial through their local health care system. This is not the case in many developing nations.

As these objections show, the ethical principles supporting posttrial access do not convince critics that posttrial access is justified in practice. While I acknowledge these objections exist, this discussion continues under the assumption that the ethical justifications are valid, and lead to the necessary inclusion of a posttrial access provision.

The achievement of global justice is the basis for an obligation to provide successful interventions to trial participants. Beauchamp and Childress, in *Principles of Biomedical Ethics*, as define the principle of justice as:

Fair, equitable, and appropriate treatment in light of what is due or owed to persons. Standards of justice are needed whenever persons are due benefits or burdens because of their particular properties or circumstances, such as being productive or having been harmed by another persons’ acts. A holder of a valid claim based in justice has a right, and therefore is due something.

While the concept of justice generally supports the theory that certain obligations exist once the trial has concluded, the particular conception of justice relevant to posttrial access is

justice as reciprocity in the recognition of the relationship between researcher and participant.

The National Bioethics Advisory Commission (NBAC) explained that justice as reciprocity:

Is concerned with what people deserve as a function of what they have contributed to an enterprise or to society. In the context of clinical trials, justice as reciprocity could mean that something is owed to research participants even after their participation in a trial has ended, because it is only through their acceptance of risk and inconvenience that researcher are able to generate findings necessary to advance knowledge and develop new medical interventions.\(^{60}\)

Because participants accept some risk for the good of society and the advancement of science certain things are owed to them in return.\(^{61}\) Subject participation allows researchers to obtain and develop new treatments and there is a corresponding responsibility of sponsors or investigators to likewise benefit the participants.\(^{62}\) People who participate in antiretroviral treatment trials are contributing to the eventual social good that the trial could produce, and therefore it is just for investigators to offer participants posttrial access to the successful antiretroviral treatment.\(^{63}\)

However, some question the use of justice as reciprocity to substantiate offering posttrial access to trial participants. Maria Merritt and Christine Grady “question the reciprocity based justification for offering priority access to antiretroviral treatment trial participants when antiretroviral treatment must be rationed.”\(^{64}\) They offer the following conclusion about policies requiring posttrial access:

Whether reciprocity justifies such a policy depends on several variables, including the quantity of antiretroviral treatment available, the number of people in the country who need antiretroviral treatment, and whether the country’s concurrent allocation policy selects specific subpopulations (such as HIV-infected mothers of young children) for priority. We conclude that only under some circumstances, at best, does reciprocity justify giving antiretroviral

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\(^{60}\) National Bioethics Advisory Commission (NBAC), *Ethical Policy Issues in International Research: Clinical Trials in Developing Countries*, (National Bioethics Advisory Commission, 2001), 74.

\(^{61}\) Ibid., 58.


\(^{63}\) Ibid.

\(^{64}\) Maria Merritt and Christine Grady, "Reciprocity and post-trial access for participants in antiretroviral therapy trials," *AIDS* 20 (2006): 1791-1794, 1791.
treatment trial participants priority over equally needy HIV-infected compatriots.\(^{65}\)

Merritt and Grady acknowledge that reciprocity has intuitive appeal, and can be used to justify application of guidelines encouraging posttrial access provisions, they simply caution against the blanket use of posttrial access provisions without considering the potential increase in burdens on people who did not participate in the trial. Despite their hesitancy to endorse a blanket requirement to provide posttrial access, they do not condemn the use of posttrial access provisions.

The principles of beneficence and nonmaleficence provide another source for the obligation to provide the successful products of research to trial participants.\(^{66}\) Beauchamp and Childress define the principle beneficence as: “an obligation to help others further their important and legitimate interests,”\(^{67}\) and the principle of nonmaleficence is defined as “an obligation not to inflict ham on others.”\(^{68}\)

The NBAC explained that the principles of beneficence and nonmaleficence support the inclusion a posttrial access because:

It is clear that participation in a clinical trial resembles treatment because the health status of participants may be altered by their participation. Consequently, if all intervention by the research team ends when the trial is over, participants may experience a loss and feel that the researchers in their clinical role have abandoned them. This sense of loss can take several forms. The starkest form arises when participants in a clinical trial are worse off at the conclusion of the trial than they were before it began. Being worse off does not mean that they were harmed by the research. It can simply mean that their medical condition has deteriorated because they were in the less advantageous arm of the protocol. Such an outcome—particularly when participants are worse off than they would have been had they received standard treatment or if they had been in the other arm of the trial—underlines the extent to which any research project can depart from the Hippocratic goal of “do no harm,” despite the best intentions and efforts of all concerned. When such a result occurs, efforts to restore participants to at least their pretrial status could be regarded as attempts to reverse a result that

\(^{65}\) Ibid., 1791.
\(^{66}\) Macklin, "Global Justice, Human Rights, and Health," 147.
\(^{67}\) Beauchamp, Principles of Biomedical Ethics, 113.
\(^{68}\) Ibid., 166.
would otherwise be at odds with the ethical principles of nonmaleficence and beneficence.\textsuperscript{69}

According to the NBAC, several conditions occur at the conclusion of a trial that harm participants. Participants may experience a loss when the trial is over, because they no longer have access to the researchers who have played the role of clinicians. The sense of loss can range from being physically worse off because their medical condition has deteriorated, mental to the feeling of abandonment because of the lack of access to treatment.

Grady also believes the principles of beneficence and nonmaleficence support posttrial access because of the harm that occurs at the conclusion of the trial, but offers an alternate description of the harm facing participants:

\begin{quote}
If a participant is deriving clinical benefit from an investigational therapy, withdrawing that therapy can be harmful. For many diseases, especially those requiring chronic treatment, exacerbation of symptoms or disease can occur if treatment is stopped. In accord with the principles of nonmaleficence and beneficence, patients, including those who are being treated as participants in research, should continue to receive a treatment they need as long as they are benefiting from it.\textsuperscript{70}
\end{quote}

Zhiyong Zong offers a similar account of harm facing participants:

\begin{quote}
Once the investigators withdraw beneficial treatments or prophylactic measures after the study is over, participants who still require these interventions will probably suffer deterioration in their health and experience feelings of frustration and helplessness. In my opinion such withdrawal is not in accordance with the “do not harm” rule. Instead, posttrial supply of beneficial interventions is an important assurance to maximize possible benefits and minimize potential harm for trial participants.\textsuperscript{71}
\end{quote}

Grady and Zong are primarily concerned with the potential for physical harm directly related to the exacerbation of symptoms or disease that occur if treatment is suddenly stopped at the conclusion of the trial, while the NBAC is primarily concerned with the harm related to the lack of access to treatment. The NBAC and Grady emphasize different aspects of the ethical dilemma, which lead to differing views of the ethically correct interpretation of posttrial access.

\textsuperscript{69} NBAC, \textit{Ethical Policy Issues in International Research}, 58.
\textsuperscript{70} Grady, "The Challenge of Assuring Continued Post-Trial," 430.
\textsuperscript{71} Zhiyong Zong, "Should post-trial provision of beneficial experimental interventions be mandatory in developing countries?,” \textit{Journal of Medical Ethics} 34 (2008): 188-192, 188.
The version of posttrial access I set forth in Chapter 3 cannot be applied to the harm identified by Grady, because the harm related to the exacerbation of symptoms will not be addressed by my definition (the requirement to provide posttrial access would not begin until after the drug is approved, not immediately after data collection ends.)

Therefore, the principles of beneficence and nonmaleficence, as conceived by the NBAC, provide support for posttrial access. However, the principle of justice, specifically justice as reciprocity, establishes the most convincing justification of posttrial access.

Positions Based on the Ethical Principles

The principles of justice, beneficence and nonmaleficence generate three positions on the degree of responsibility an investigator or sponsor may have to provide posttrial access. These three positions have been adopted from an article by Richard Ashcroft, “After the trial is over: what are the sponsors obligations?” Ashcroft presumes that an investigator or sponsor owes trial participants either a maximum amount of responsibility, a moderate amount of responsibility, or a minimal amount of responsibility. Ashcroft presents the maximal and minimal positions as a strawman to demonstrate his belief that moderate responsibility is the correct amount of responsibility for researchers. It is unclear whether Ashcroft meant for this framework of responsibility to be applied specifically to posttrial access, or to another type of posttrial benefit. Regardless, it is a helpful discussion to show the different positions one can take on the responsibility to provide posttrial access. The greater the responsibility, the more the investigator or sponsor owes to participants. The lower the responsibility, the less the investigator owes to participants.

If an investigator owes a maximum amount of responsibility to trial participants, then the investigator must provide posttrial access. Three arguments are used to support this position. First, one can apply the principle justice as reciprocity and assert that research participants have an

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72 As noted in Chapter 3, this harm is best remedied if researchers are required to continue providing a drug until approval if they believe withdraw will prove harmful to trial participants.

73 Ashcroft, After the trial is over: what are the sponsors obligations.
absolute right to share in the benefits of research: “They contribute significantly to researchers objectives and commercial sponsors make a lot of money from the results of successful research.” Second, the principles of beneficence and nonmaleficence assert that participants inherently assume a number of risks by participating in researcher, and deserve to be compensated for taking on these risks. Third, the principles of beneficence and nonmaleficence assert that the researcher has taken on a duty of care, which cannot be cancelled unilaterally, by enrolling participants in a trial. The strict application of the ethical principles to these arguments connotes that researchers do, in fact, have an obligation to research participants. Responsibilities are “created by virtue of the fact that researchers have entered into a relationship with participants and the host community that cannot be waived away because it is inconvenient.” These responsibilities extend beyond the research period because researchers have developed ethical responsibilities to the research participants.

The moderate position would give the investigator less responsibility to provide posttrial access to trial participants. The moderate position states that any posttrial provision should be determined by 1) rationality, 2) limited responsibility, and 3) concerns of justice. Implementation of a posttrial access provision would be rationally justifiable and not arbitrary. Any decision should account for the situation in the developing country: whether there are scarce resources, intense medical need and competing alternatives for investment in posttrial access. An investigator could also consider society’s limited responsibility for the situation in developing

74 Ibid., Position two: researchers’ obligations are maximal.
75 Ibid.
76 Ibid.
77 Ibid.
78 Ibid. Ashcroft seems to set up the maximal position as a straw man to show that the position cannot be applied in clinical trials.
79 Ibid., Toward a more nuanced response.
80 Ibid.
countries. While developed countries may bear some responsibility for the blight in developing countries, there should be a limit of what is expected from investigators and sponsors.\(^{81}\)

Those who believe that investigators should have a minimal role in providing posttrial access believe that the investigators who are conducting the trial are required to only provide a treatment during the duration of the trial. The ethical principles of beneficence, nonmaleficence and justice as reciprocity are not violated as long as, during the period of the trial, the researchers are withholding normally effective treatments and are not violating the ethical principles.\(^{82}\) Any higher standard of access is supererogatory, is morally praiseworthy but not obligatory, and could actually hurt those it tries to help because it diverts money away from research and toward interventions and healthcare.\(^{83}\)

**Posttrial Access Guidance**

*Domestic.* In 2005 the NIH issued a document titled *Guidance for Addressing the Provision of Antiretroviral Treatment for Trial Participants Following Their Completion of NIH-funded Antiretroviral Treatment Trials in Developing Countries.*\(^{84}\) This Guidance states that the NIH expects researchers and sponsors who apply for funding to “address the provision of antiretroviral treatment to research participants following their completion of the trial.”\(^{85}\) The summary of this document states:

It is important that individuals who volunteer to participate in NIH-supported/funded HIV antiretroviral treatment trials have the option to continue to receive antiretroviral treatment following the completion of the treatment trial. For 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. The NIH recommends investigators/contractors work with host countries’ authorities and other stakeholders to identify available sources of antiretroviral treatment.\(^{86}\)

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\(^{81}\) Ibid.  
\(^{82}\) Ibid.  
\(^{83}\) Ibid.  
\(^{84}\) NIH, *Guidance for Addressing the Provision of Antiretroviral Treatment.*  
\(^{85}\) Ibid.  
\(^{86}\) Ibid.
Under the “Background” section of this Guidance, the NIH recognizes that it plays a pivotal role in setting the standard of care in conducting and supporting studies that assess antiretroviral regimens, and that: “it is important that trial participants who receive antiretroviral treatment in NIH supported/funded antiretroviral treatment trials have the option to continue to receive antiretroviral treatment following their completion of the trial.”\textsuperscript{87} Despite the NIH’s strong statement on the importance of access to antiretroviral treatment after the trial, the statutory mandate is limits the ability to fund posttrial access provisions, and therefore only recommends the inclusion of a provision, rather than mandating a provision. U.S. Code 42 § 284 (b)(1)(A)\textsuperscript{88} does not allow the NIH to support or provide services after the trial has been completed.\textsuperscript{89} The relevant portion of the statutory mandate, Directors of National Research institutes—duties and authority, grants, contracts and cooperative agreements, states:

In carrying out the purposes of section 241 of this title with respect to human diseases or disorders or other aspects of human health for which the national research institutes were established, the Secretary, acting through the Director of each national research institute--

(A) Shall encourage and support research, investigations, experiments, demonstrations, and studies in the health sciences related to--

(i) The maintenance of health,
(ii) The detection, diagnosis, treatment, and prevention of human diseases and disorders,
(iii) The rehabilitation of individuals with human diseases, disorders, and disabilities, and
(iv) The expansion of knowledge of the processes underlying human diseases, disorders, and disabilities, the processes underlying the normal and pathological functioning of the body and its organ systems, and the processes underlying the interactions between the human organism and the environment.\textsuperscript{90}

\textsuperscript{87} Ibid.
\textsuperscript{88} Directors of National Research Institutes, U.S. Code 42 § 284(b)(1)(A). (January 3, 2007)
\textsuperscript{90} Directors of National Research Institutes, U.S.Code 42 § 284(b). Section 241 is about research and investigations in general.
This mandate explicitly states which powers Congress has conferred on the NIH, from which it can be inferred that those powers not listed are beyond the NIH’s statutory mandate. Because the power to fund posttrial benefits is not included in the statutory mandate, “the NIH’s authority to ‘encourage and support research’ does not extend to providing treatment following the completion of that research.” 91 Therefore, the NIH cannot fund the provision of posttrial access treatments, and can only recommend that NIH-funded investigators work with sponsors or host countries to identify other sources of posttrial funding.

Despite the NIH’s acknowledgment on the constitutional limitations of their ability to mandate a posttrial access provision, the Guidance endorses the ethical principles of justice, beneficence, and nonmaleficence. Question 5 of the Questions and Answers website states:

Now that the NIH has increased its support of HIV antiretroviral treatment trials in developing countries, issues regarding post-trial treatment for individuals who participate in these trials must be addressed. Discontinuation of antiretroviral treatment when a trial ends could have negative health effects, which include the increased risk of mortality. To help prevent the possibility of such adverse effects, the NIH developed this Guidance. 92

This is an endorsement of the principles of beneficence and nonmaleficence, because one of the principle reasons for the NIH Guidance is to protect against any harm that withdrawing treatment after completion of the trial could cause the participant. The NIH also endorses the principles of beneficence and nonmaleficence, in Question 1 of the Questions and Answers website:

It is important to develop a plan so that participants in developing countries who volunteer to participate in an HIV antiretroviral treatment trial have the option to continue to receive antiretroviral treatment following their completion of the trial. Without such a plan, there is an increased possibility that trial participants may not receive post-trial antiretroviral treatment. 93

In 2005, two months after the NIH issued its guidance, the Division of AIDS (DAIDS) at the National Institute of Allergy and Infectious Diseases provided a template of “suggested language” indicating that “for studies of drugs or agents, posttrial access is to be discussed with

91 NIH. Guidance for Addressing the Provision of Antiretroviral Treatment.
92 NIH. Questions and Answers Regarding Guidance.
93 Ibid.
participants who are benefiting from the study intervention.” Inclusion of such language is part of the informed consent documents that support the ethical principal of patient autonomy, because participants, who sign choose to participate in NIH funded research that include the NIH Guidance in its protocols, have agreed that they will participate with the knowledge that the potential to continue to receive drugs at the completion of the trial will be “discussed” but not promised to participants.

The NIH has chosen to limit its Guidance and DIADS subsequent template only to ART, and does not open the possibility of the discussion of posttrial access to other effective treatment or prevention of harmful diseases, such as malaria or tuberculosis, although the NIH acknowledges “there may be other situations where guidance is needed,” There has been no other guidance issued that supports the provision of posttrial access to treatments proven effective or preventive interventions for other types of diseases commonly faced by those in developing countries.

There are several major issues with the NIH Guidance. The first is that adopts an unclear interpretation of posttrial access from the Declaration of Helsinki, Paragraph 14. As shown in Chapter 2, there are four versions of posttrial access, and except for the one I believe should be used, the other three have serious deficiencies. Another issue is that this Guidance does not recommend the length of time investigators are required to provide posttrial access to trial participants. This could be problematic for those researchers who are attempting to gauge the expectations of the NIH. The NIH Guidance places the responsibility of implementing posttrial access provisions on the investigator.

Despite the lack of clarity regarding the details of the NIH Guidance, Shah, Elmer and Grady’s article, “Planning for Posttrial Access to Antiretroviral Treatment for Research

95 NIH, Questions and Answers Regarding Guidance., Question 5.
Participants in Developing Countries” found that 18 of the HIV studies subject to the NIH Guidance addressed the issue of posttrial access for participants.96 However, the article notes: “Consistent with this Guidance, no studies guaranteed NIH funding for posttrial access to ART. The majority of the studies identified external funding mechanisms available in developing countries, rather than funding from sponsors or the NIH. Although one study guaranteed two month transitional access, no study guaranteed long-term posttrial access.”97 Shah et. al. suggest four conclusions that will improve future posttrial access policies:

Our data suggest 4 conclusions that may help inform the development of future posttrial access policies: (1) plans for posttrial access in part reflected variation in local contexts and resources, (2) most studies partnered with external funding sources and institutions, (3) some investigators went beyond what the guidance required, and (4) plans for posttrial access were affected by the uncertainty of predicting long term local conditions.98

Along with some of the issues identified above, these four conclusions can be considerations when developing a stronger posttrial access guidance. Before attempting to develop a stronger guidance, it may be helpful to look at the guidelines and laws from international organizations and developing countries. These guidelines can serve as valuable input for what are believed to be important considerations for the implementation of a posttrial access framework.

International Organizations. There are several international guidelines that support the obligation to provide of posttrial access. The two most often cited statements are from the Declaration of Helsinki and the Council for International Organizations of Medical Sciences (CIOMS). The 2008 version of the Declaration of Helsinki, Paragraph 14 states:

The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the

97 Ibid.,1559.
98 Ibid.
research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.\textsuperscript{99}

As mentioned in Chapter 1 \\& 2, the Declaration of Helsinki was the first guideline to suggest posttrial access a way to address the issues of justice faced in multicenter clinical trials. Originally, the guideline only suggested that posttrial access should be offered to “the best proven prophylactic, diagnostic, and therapeutic methods identified by the study.”\textsuperscript{100} However, after facing some criticism for adopting the posttrial access framework, the WMA adopted new language including the phrases “post-study access by study subjects” and “access to other appropriate care or benefits.” Regardless of recent changes, this framework still endorses the inclusion of posttrial access provisions.

The Council for International Organizations of Medical Sciences (CIOMS) also makes a strong statement mandating post trial obligations after a trial, stating in Guideline 10 of the “International Ethical Guidelines for Biomedical Research Involving Human Subjects”:

\textit{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 responsible 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}\textsuperscript{101} (Emphasis Added)

Other international organizations do not take such a strong stance on post trial obligations as the WMA and CIOMS has done. Instead some suggest that sponsors or investigators only discuss the inclusion of post trial obligations, but do not require formal, prior agreements.\textsuperscript{102} For example, in the comments of Guideline Point 2, the Joint National Program on HIV/AIDS states,

\textit{Attention needs to be given immediately to how a successful vaccine, and other benefits resulting from the research, will be made readily and affordably available to the communities where the vaccine is tested, as}

\textsuperscript{100} World Medical Association, "Declaration of Helsinki," 1964.
\textsuperscript{102} Participants in the 2001 Conference, "Moral Standards for Research in Developing Countries,”18.
well as to other communities and countries at high risk for HIV infection. This process of discussion and negotiation should start as soon as possible and should be carried on through the course of the research.103

The UNAIDS guideline endorses both the fair benefits and reasonable availability framework. The fair benefits framework is endorsed because the guideline specifically mentions “other benefits from the research.” The reasonable availability framework is endorsed because the guideline mentions providing a successful vaccine to the community, and not only the participants.

The WMA, CIOMS, and UNAIDS each endorse a different post trial obligation, making it clear that different organizations believe that certain frameworks are preferable methods to alleviate issues of justice. In addition, organizations disagree on whether a formal agreement on post trial obligations should exist in the research protocol. However, there appears to be a general consensus that post trial benefits are necessary to avoid some of the issues raised in the aftermath of the AZT trial.

Foreign. Like the International guidelines in the section above, many of the foreign documents relating to post-trial access mix, confuse, or replace the meaning of “posttrial access” with other post trial benefit frameworks. Still these guidelines are helpful to understand why it is necessary to be clear about any posttrial access framework adopted for use in a research protocol.

The Indian Council of Medical Research (IMCR) issued its Ethical Guidelines for Biomedical Research on Human Research.104 Chapter III, entitled “General Ethical Issues” begins by describing the four basic ethical principles (autonomy, beneficence, nonmaleficence and justice) and states “the guidelines which follow are directed at application of these basic principles.”105 In Part VIII of this chapter, on Post-Trial Access, the Indian Council states:

The Declaration of the WMA in 2004 reaffirmed “its position that it is necessary

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104 Indian Council of Medical Research, Ethical Guidelines for Biomedical Research on Human Subjects, 34 (New Delhi: Indian Council of Medical Research, 2006).
105 Ibid. 21.
during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review.” Whenever possible, an EC should consider such an arrangement in the a priori agreement. Sometimes more than the benefit to the participant, the community may be given benefit in indirect way through improving their living conditions, establishing counseling centers, clinics or schools, and giving education on maintaining good health practices. For smaller scale or student projects post trial benefit to the participants may not be feasible but keeping in mind the post trial responsibility conscious efforts should be made by the guides and the institution to initiate steps to continue to support and give better care to the participants.  

While a portion of this chapter is titled “Post-Trial Access,” it seems as though India is actually endorsing a fair benefits framework for the trials that have the money to provide such an arrangement and for smaller trials a posttrial access framework. Therefore, even the last portion of this guidance does not endorse a purely posttrial access provision. Note that this guideline asks the ethics committee to “consider” an arrangement, suggesting that any posttrial arrangement is permissive and not mandatory.

The National Health Council of Brazil, *Resolution No. 196/96 on Research Involving Human Subjects* 107 is cites on several international declarations and guidelines and meets the requirements of Brazilian constitutional and legislative provisions. Like the IMCR guidelines in India, *Resolution No. 196/96* is based on the 4 ethical principles, however this resolution attempts to balance the rights of three entities that may at times have competing interests (the scientific community, the research subjects, and Brazil).108 In addressing the issue of posttrial access, Brazil takes a clearer position on posttrial access than India, simply stating in section III.3.P,

Research involving human subjects, regardless of the field of knowledge, must comply with the following requirements: to ensure the research subjects the benefits resulting from the research project, in terms of social return, access to procedures, products or research agents.

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106 Ibid. 30.
108 Ibid., 1.
Brazil clearly states that it would like to ensure subjects access to procedures, products, or research agents. This resolution states that researchers “must” comply with its requirements, indicating that implementation of the posttrial access provision is mandatory rather than permissive.

Given that a large amount of HIV research is done in Africa, two other guidance documents from South Africa and Uganda are discussed below.

The South African Clinical Trial Working Groups of the South Africa Department of Health\textsuperscript{109} states in section 9.3.5:

Many patients who participate in HIV/AIDS treatment trials have no alternative access to drug therapy. Where a patient has a therapeutic response to a study drug, that patient should be offered ongoing treatment. In designing studies, consideration should be given to the costs of long term provision of study drugs and of clinical monitoring, including the costs of medical staff. The duration of drug therapy in a study should be clearly stated in the patient information section of the informed consent document.\textsuperscript{110}

The first section of the South African guideline, which states that patients should be offered ongoing treatment if they have a therapeutic response seems to endorse the version of posttrial access endorsed by Grady. This version of posttrial access would greatly reduce the number of participants that would potentially need to be provided posttrial access as compared to the Brazilian or Indian resolution and guideline on posttrial access. This guidance might appear to be beneficial to sponsors seeking to conduct a clinical trial in South Africa because the guideline implicitly reduces the number of participants that would receive any type of posttrial benefit.


\textsuperscript{110} Ibid., 9.3.5.
The Guidelines for the Conduct of Health Research Involving Human Subjects in Uganda

issued by the Uganda National Council for Science and Technology,\textsuperscript{111} provides for a stronger and farther-reaching posttrial requirement. The guideline state:

Research should aim at improving the well being of research participants and their communities. This can be attained through: (a) Provision of health care beyond research related care; (b) Optimization of collateral benefits to the research communities; (c) Provision of good client care during study investigations and procedures; (d) Taking measures to ensure easy access by the community to the test drug/device, if proven beneficial.\textsuperscript{112} Emphasis added

Instead of a posttrial access or fair framework, Uganda appears to adopt the reasonable availability framework, because sponsors should provide community access to the tested drug, rather than only the participants. Uganda restates this position:

Where factors relating to vulnerability are an aspect of the research project, research should specify how that particular vulnerability would be addressed. In particular Institutional Review Committee must ensure that: (a) Selection of the particular communities is justified by the research goals; (b) Research is relevant to needs and priorities of the community in which it is to be conducted; (c) Research is beneficial to that community; (d) the community can access the products of the research.\textsuperscript{113} Emphasis added.

Uganda, like Brazil, seems to take a stronger stance on whether the post trial benefit should be permissive or mandatory. Despite the fact that Uganda calls its protocol a “Guideline” its use of the word “ensure” suggests that Uganda is taking a more mandatory than permissive stance on its guideline.

These international guidelines and foreign laws demonstrate the various approaches to addressing the ethical issues about clinical trials identified in Chapter 2. However analyzing these laws and guidelines also demonstrate the lack of clarity used in literature related to posttrial access. The following points should be considered when adopting a guidance related to the provision of post trial benefits: first, and most important, clarify the which post trial framework is

\textsuperscript{112} Ibid., 3.
\textsuperscript{113} Ibid., 32.
being adopted in the law or guideline. Second, be sure to clarify whether the guideline is permissive or mandatory.
CHAPTER 4

STATEMENT OF THE QUESTION

As stated in Chapter 1, this thesis addresses the ethical and policy issues presented by implementing a framework requiring posttrial access to beneficial interventions. The first three chapters of this thesis were dedicated to exploring the nuances necessary to understand the posttrial access framework. The last three chapters will focus on one particular aspect of posttrial access that presents difficult implementation questions: HIV ART multicenter clinical drug trials, where the research is primarily conducted in a developing country, but will be made available for distribution in both the developing country and other markets. The NIH Guidance discussed in Chapter 3 is the reason for the focus on HIV ART. This chapter refocuses the discussion of HIV antiretroviral treatment by reminding the reader of the question to be answered by this thesis, explaining why this question is important, and presenting the reader with the case study that will be used in Chapter 5 to explore the nuances of the NIH Guidance.

The Question

Can and should the NIH implement a stronger and clearer Guidance addressing the provision of posttrial access for participants in NIH-funded HIV ART trials in developing countries? Chapter 3 identified a number of problems with the current NIH Guidance for Addressing the Provision of Antiretroviral Treatment for Trial Participants. These problems included: 1) the inability to determine which form of posttrial access the NIH adopts, 2) abstaining from detailing the length of time the required to provide posttrial access, 3) putting the responsibility of implementing the posttrial provision solely on the investigator. These issues should be discussed while considering the following four conclusions identified by Shah, Elmer, and Grady:

(1) plans for posttrial access in part reflected variation in local contexts and resources, (2) most studies partnered with external funding sources and
institutions, (3) some investigators went beyond what the guidance required, and (4) plans for posttrial access were affected by the uncertainty of predicting long term local conditions.\textsuperscript{114}

The remainder of this thesis will determine whether the NIH can and should implement a stronger Guidance requiring the inclusion of a posttrial access provision in research protocols. I propose rewriting the current NIH Guidance in Chapter 5, with a focus on correcting and strengthening the current Guidance using the issues and conclusions identified above. I will then apply the rewritten Guidance to the Tenofovir case study to identify what issues still exist with the revised protocol.

Issues of Clarity in the Literature

The following papers provide an example of how imprecise language on the posttrial access framework can cause an author engage in a sometimes inaccurate and confusing discussion of posttrial access that can mislead readers in their understanding of posttrial access.

One example is a result differing definitions of posttrial access. Grady begins her article “The Challenge of Assuring Continued Post-Trial Access” with the story of Sam, a participant in a clinical trial testing an experimental drug as a treatment for his chronic disease:

Soon after Sam begins to take the drug, he reports feeling better and the level of disease marker in his blood is significantly lower at each study interval. The study reaches its predetermined endpoint, is stopped as planned, and the sponsor submits an application to a regulatory agency to license the drug for this indication. It is clear that Sam would clinically benefit from continuing to take the drug.\textsuperscript{115}

Grady asks whether the investigator has a responsibility, to continue providing Sam with the treatment shown to be clinically beneficial.

Is it the responsibility of the investigator or the research sponsor to ensure that Sam and other participants in this study continue to receive the drug or even to provide it to them after a study ends?\textsuperscript{116}

\textsuperscript{114} Shah, Elmer, Grady. “Planning for Posttrial Access to Antiretroviral Treatment,” 1557.


\textsuperscript{116} Ibid.
Grady would define posttrial access as the requirement to provide continued access for research participants who benefit from investigational treatments.\footnote{Ibid., 433.} However, posttrial access should be defined as the ethical requirement to make products, proven effective by a regulatory agency, available to trial participants at the conclusion of the trial, until the product is, or should be, reasonably available in the host community or country. While both definitions seem similar, each leads to a different interpretation of posttrial access. Grady’s definition would require sponsors to provide the drug only to those participants who benefit during the trial. Therefore, those who receive the placebo drug would not receive posttrial access to the drug, as they would not have had the opportunity to show they benefited from the drug. While Grady’s definition addresses some of the harms related to clinical research, it is not the definition of posttrial access traditionally used and therefore is not the definition that should be adopted in the literature.

Another example of ambiguity in the literature comes from Zong’s article “Should Post-trial Provision of Beneficial Experimental Interventions be Mandatory in Developing Countries?”\footnote{Zong, “Should post-trial provision be mandatory in developing countries?,” 188-192.} Confusion begins with the title because it is unclear what “post-trial provision” Zong intends to focus on because the term has been used to describe various post trial frameworks. Zong actually discusses posttrial access in this article, but throughout her paper, she fails to distinguish between the term “posttrial access” as its own framework and other “post-trial provisions.” For example when discussing the guidelines that support the inclusion of posttrial provisions, Zong states:

Some international or national guidelines support mandatory post-trial provision of beneficial drugs, vaccines, proven prophylactic and therapeutic methods, or products for trials participants. Among these guidelines, two clearly state that post-trial provision should be free of charge and two definitely require that the provision should be available for all participants.\footnote{Ibid., 189.}
Zong cites seven different guidelines that she says support “posttrial provisions.” These guidelines support posttrial provisions, however not all support a posttrial access provision, which is the provision she advances in her article. Failing to distinguish between the provisions is another common way that authors who write about posttrial access confuse the framework.

These two articles provide the common examples of how authors have conflated the literature, making it difficult to determine where one framework begins, and where another ends. For the purpose of the NIH Guidance, recognizing the existing conflation will allow me to propose a guideline that is explicit, unambiguous, and uncomplicated so that the investigators who follow its recommendations understand the requirements.

Case Study: Tenofovir

To assist in answering the question above, a case study on the ART Tenofovir gel trial is helpful to explore why posttrial access has been such a difficult framework to apply to an ART protocol. This case study will be used to demonstrate whether and how the U.S. can effectively implement a posttrial access provision in the protocol for an ART trial. It will allow me to explore the issues that could be faced when an investigator funded by the NIH attempts to follow the existing guideline. It will also allow me to explore the limits of what the NIH Guidance can mandate investigators include as part of their research protocol. This analysis will be part of the last chapter. First, the reader should have some background on the Tenofovir gel clinical trials.

In order to reduce transmission of sexually transmitted infections, microbicides are products that can be applied to the vagina or rectum with the intention of reducing the acquisition of a virus such as HIV. There have been 11 trials testing several different microbicides, but none have been successful in protecting against HIV. However, it was the drug Tenofovir that was recognized for its effectiveness in suppressing replication of the HIV virus, and was

120 Ibid.  
122 Ibid.
determined to be an ideal choice as the first antiretroviral to be successfully formulated as a microbicide gel.\textsuperscript{123} Tenofovir is an antiretroviral drug that has already been shown to be effective in treating the HIV virus. The FDA approved it in 2001 for oral use in the 3-drug oral combination tenofovir disoproxil fumarate (Viread), used to treat HIV/AIDS.\textsuperscript{124} When Tenofovir was tested as a vaginal microbicidal gel the trial showed that women who used the microbicide were less likely to contract HIV than those who used a placebo gel.\textsuperscript{125}

The study was sponsored by the Center for the AIDS Program of Research in South Africa (“CAPRISA”), and is called the CAPRISA 004 trial. It was conducted as a Phase II randomized, double-blind, placebo-controlled study.\textsuperscript{126} The 889 participants included in the analysis of the data were enrolled at an urban and rural clinic in KwaZulu-Natal, South Africa. The trial was conducted in the KwaZulu-Natal urban and rural sites based on a feasibility study, which showed the city had a HIV incidence rate of 15.6 percent (in the urban areas) and 11.2 percent (in the rural areas) and anal sex rates were substantially lower.\textsuperscript{127} The women enrolled were HIV-negative, 18-40 years old, and sexually active (having engaged in vaginal sex at least twice in the 30 days before screening), not pregnant, and using a nonbarrier form of contraceptive.\textsuperscript{128} Roughly half of the participants were assigned to the Tenofovir gel, and the other half was provided the placebo gel (the placebo gel is the “universal” placebo gel, shown to have minimal anti-HIV activity).\textsuperscript{129}

Women were instructed to insert a single-use applicator of the Tenofovir gel or placebo up to 12 hours before vaginal intercourse and again as soon as possible after sex, with a

\begin{flushright}
\textsuperscript{123} Ibid.  \\
\textsuperscript{124} Ibid.  \\
\textsuperscript{126} Daniel M. Keller, Tenofovir Vaginal Gel First Microbicide to Prevent HIV, HSV Infections, 21 July 2010, October 2010 <http://www.medscape.com/viewarticle/725583>.  \\
\textsuperscript{127} Karim, et al., "Effectiveness and Safety of Tenofovir Gel,” 1168.  \\
\textsuperscript{128} Ibid.  \\
\textsuperscript{129} Ibid., 1169.
\end{flushright}
maximum of 2 doses in 24-hours. Participation in the study lasted for at least 1 year and up to 2.5 years. All women were provided with monthly HIV risk-reduction counseling, condoms, treatment for sexually transmitted infections and were tested for HIV infection. The results of the trial showed that women using the tenofovir gel before and after sexual intercourse had a 39% lower risk of being infected with HIV as compared with women using the placebo. During the course of the trial, 38 women in the tenofovir group and 60 women in the placebo group became HIV-positive. Women who used Tenofovir gel in more than 80% of their sex acts had a 54% reduction in HIV infections, a 38% reduction if they used it 50% to 80% of the times they had sex, and a 28% reduction if they used it in less than half of their sex acts.

This thesis addresses posttrial access that is relevant only after the conclusion of Phase III trials. Although this trial is only in Phase II testing, it can be useful to attempt to anticipate the issues faced by investigators when they begin Phase III trials and if they implement a posttrial access provision in the next phase of trials. These issues will be discussed in Chapter 5.

Note that the Tenofovir microbicidal gel trials shows that Tenofovir is effective as a preventative against contracting HIV rather than as a treatment used to combat HIV in those already affected. The difference between drugs tested for use as preventives and treatments should be recognized, because the differences could have implications for how a posttrial access provision might be implemented. In Chapter 5, when I use the Tenofovir trial to demonstrate posttrial issues, I will distinguish any potential issues that are presented by implementing a

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130 Ibid.
131 Ibid.
132 Ibid., 1171.
133 Ibid., 1172.
posttrial access provision which involves a drug tested for prevention and a drug tested for treatment.
CHAPTER FIVE

APPLICATION OF THE NIH GUIDANCE TO THE TENOFOVIR GEL TRIAL

The investigators who conducted the Phase II Tenofovir gel trial are ready to begin the Phase III trial. The results from the Phase II trial were groundbreaking, and the numbers from the first trial indicate that Phase III will also be successful. Investigators plan to enroll up to 3,000 participants, and are applying to the NIH for funding. One part of this application requires investigators to address posttrial access as part of their research protocol. This requirement is part of the NIH Guidance for Addressing the Provision of Antiretroviral Treatment for Trial Participants Following their Completion of NIH-Funded HIV Antiretroviral Treatment Trials in Developing Countries. The summary of the Guidance states:

It is important that individuals who volunteer to participate in NIH-supported/funded HIV antiretroviral treatment trials have the option to continue to receive antiretroviral treatment following the completion of the treatment trial. For 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. The NIH recommends investigators/contractors work with host countries’ authorities and other stakeholders to identify available sources of antiretroviral treatment.135

After reading the summary, the remainder of the Guidance, and the Questions and Answers webpage, the investigators understand that the NIH recommends they address whether they can provide trial participants with the option to receive antiretroviral treatment following the completion of the trial. They also understand that the NIH would like them to work with the host country and other stakeholders to identify the best method for the provision of antiretroviral treatment. However, some of the information in the Guidance is ambiguous, and the investigators

135 The Guidance is specifically applicable to HIV/AIDS trials that have been conducted by the resource-rich United States in resource-poor countries. This Guidance will not be revised to expand the original scope of the Guidance to include other types of diseases, or trials that occur only within resource-rich countries. It will merely address the issues that occur within the limitations of an HIV/AIDS already identified as important by the NIH.
have questions that will need to be answered before they decide whether it is necessary to include a posttrial access provision into their research protocol.

The purpose of this chapter is to address and demonstrate the application of the NIH Guidance, as it is currently written, to the Tenofovir gel trial. It will identify issues and problems inherent in the Guidance. After identifying these issues, the second section will revise the language to include the definition of posttrial access used in this thesis and address the issues identified in the Chapter 2 and 3. The last section of this chapter will re-apply the Tenofovir gel trial to the revised language to determine if the issues identified still exist, and to determine whether the revised language creates new problems.

**Application of the Current NIH Guidance to the Tenofovir Gel Trial**

What are some of the issues and questions faced by investigators of the Tenofovir gel trial who attempt to follow the current NIH Guidance? The first two issues impact whether the investigators are required to include any posttrial provision within the trial protocol they present to the NIH. The first issue is whether the NIH Guidance applies to their trial. The title of the NIH Guidance is “Guidance for Addressing the Provision of Antiretroviral Treatment for Trial Participants Following their Completion of NIH-Funded HIV Antiretroviral Treatment Trials in Developing Countries.” The Guidance only uses the words “antiretroviral treatment” and does not include the words “antiretroviral prevention.” However, Tenofovir gel will be tested for use as an antiretroviral that will prevent the transmission of HIV, not as a treatment for HIV. Therefore, the first question that should be asked by the investigators is whether, under the NIH Guidance, the Tenofovir gel trial is required to address the inclusion of a posttrial access provision, because it is an antiretroviral preventative drug and not an antiretroviral treatment drug.

The second issue is what it means for the investigators to “address” the provision of posttrial access. The use of the word “address” is nebulous, and the remaining Guidance and Questions and Answers webpage does not provide additional explanation of the term. By addressing the provision of posttrial access, should the investigators go only so far as to “identify
sources available in the countries for the provision of antiretroviral treatment to trial participants,” or will they be required to actually implement the posttrial access provision after the trial?\textsuperscript{136}

Other important issues relate to the clarity of the language within the document. For example, what does it mean for participants to “continue to receive antiretroviral treatment.”\textsuperscript{137} This is an important question, and the answer will determine what provision investigators should plan to fund and how they should provide funding once the trial is complete. Should the investigators provide Tenofovir gel as the prevention that will be included in the posttrial access provision? If the Phase III trial does not produce the positive results expected, should the investigators be prepared to provide another type of prevention that is currently recognized as the standard of care for HIV? This question raises serious issues for the investigators because if the Tenofovir gel does not produce the positive results that would allow it to be approved by a regulatory agency, there is no other effective microbicide gel that is considered the standard of care for HIV prevention. Tenofovir gel is the first successful vaginal microbicide. The existing standard of care for HIV prevention would be offering condoms, teaching abstinence and safe sex practices, and perhaps providing money to girls.\textsuperscript{138} Whether the NIH Guidance would accept these alternative forms of posttrial access is not clear, and this ambiguity should be of concern to investigators seeking to meet the recommendations of the Guidance.

Assuming the trial is successful, another question is when investigators should be required to begin posttrial access to the Tenofovir gel or other type of preventives. One of the issues identified with the current definitions of posttrial access is they are all silent on

\begin{itemize}
  \item \textsuperscript{136} NIH, \textit{Questions and Answers Regarding Guidance.}, Question 1.
  \item \textsuperscript{137} The question of the “treatment” language is addressed in the next section of this chapter. The remaining issues will be addressed on the assumption that the investigators will include the posttrial access provision despite the use of the word “treatment” in the guidance.
  \item \textsuperscript{138} Story from NYT article \textit{Studies give African Women Hope in HIV Fight}. This article explained that that giving adolescent girls money was even more successful than the Tenofovir gel at reducing transmission because many families in sub-Saharan Africa are so impoverished that trading sex for money is a standard income source for some young girls. Celia W Dugger, "African Studies Give Women Hope in H.I.V. Fight," \textit{New York Times}, July 20, 2010, http://www.nytimes.com/2010/07/20/world/africa/20africa.html?_r=4 (accessed September 2010).
\end{itemize}
identification of or clarification of the time period when the investigator should begin provision of the posttrial treatment. As it is currently written the Guidance makes it possible for investigators to begin posttrial provision of Tenofovir gel at several different points. Provision of the gel could begin right after the clinical trial ends, but before the investigators know whether the Phase III trial has been successful. Investigators could provide the gel after the investigators know that the clinical trial results have been successful, but before the gel has been approved by the appropriate regulatory agency or investigators could provide the gel after the drug has been approved. Provision of the gel could begin after the clinical trial ends, and continue until a participant has died or is no longer at risk of sexually transmitted HIV. Once posttrial access begins, it is also unclear when the investigators’ responsibility to provide the Tenofovir gel would end. The Guidance also does not explicate when the responsibility would end. Therefore, investigators would be required to make a guess as to the appropriate time period in which they should provide Tenofovir gel or other prevention.

Other questions relate to identifying available sources of antiretroviral interventions. Who should identify these sources? The Guidance directs investigators to work with “host countries’ authorities and other stakeholders” but does not provide any further specificity on potential resources. Who is the NIH describing as the “other stakeholder?” Are the investigators required to determine these stakeholders on their own, or could the NIH provide further guidance to identify potential resources? What if the host country or stakeholders cannot or will not provide posttrial access to the participants? What responsibility would the investigator then have to persist in securing other stakeholders and sources of funding for posttrial access? 139 The NIH Guidance could and should provide researchers with answers to some of these questions. In the

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139 One issue that is not a posttrial access question, but that may be important to investigators is what treatment participants should receive if the Tenofovir gel was not effective in preventing them from contracting HIV during the trial. These participants may not want or need to receive the Tenofovir gel because they are more concerned about treatment of the disease.
next section will address as many of these questions as possible by changing or clarifying some of the information in the current Guidance.

Addressing Issues with the NIH Guidance

The NIH Guidance is a two-page document supplemented by a webpage dedicated to answering questions a researcher may have about the Guidance. My revision focuses on improving the elements that could present problems for implementing a posttrial access provision. The summary of the Guidance states:

It is important that individuals who volunteer to participate in NIH-supported/funded HIV antiretroviral treatment trials have the option to continue to receive antiretroviral treatment following the completion of the treatment trial. For 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. The NIH recommends investigators/contractors work with host countries’ authorities and other stakeholders to identify available sources of antiretroviral treatment.\(^\text{140}\)

As previously stated in Chapter 3, the principle problems identified in this Guidance are that 1) it is not clear what form of posttrial access the NIH Guidance adopts, 2) the Guidance is silent on the length of time investigators are required to provide posttrial access, and 3) the Guidance places total responsibility of posttrial access on the investigator an provides little guidance about who should assist the investigator in

Revising the Guidance requires the incorporation and consideration of the various issues listed above. However, the biggest issue with the NIH Guidance is that the NIH’s statutory mandate will not allow it to fund the provision of posttrial antiretroviral treatment after research has been completed. Because the NIH is attempting to do exactly that with this Guidance, it is limited to “recommending” rather than “mandating” posttrial access. This limitation cannot be

\(^{140}\) The Guidance is specifically applicable to HIV/AIDS trials that have been conducted by the resource-rich United States in resource-poor countries. This Guidance will not be revised to expand the original scope of the Guidance to include other types of diseases, or trials that occur only within resource-rich countries. It will merely address the issues that occur within the limitations of an HIV/AIDS already identified as important by the NIH.
changed without Congress expanding the NIH’s power to “encourage and support research.” Consequently, any changes to the Guidance must be made with this limitation in mind.

Despite the legislatively imposed limitations, the first change that the NIH should make to its Guidance is to include the term antiretroviral prevention trials within the scope of the Guidance. This would mean the title of the Guidance should change to “Guidance for Addressing the Provision of Antiretroviral Prevention or Treatment for Trial Participants Following their Completion of NIH-Funded HIV Antiretroviral Prevention or Treatment Trials in Developing Countries.” It is important to distinguish between the terms “treatment” and “prevention” because the terms have two different meanings. In the context of HIV/AIDS research, treatment is “the management of care of a patient for the purpose of combating disease or disorder,” and a preventive “seeks to avert the occurrence of” a disease.\textsuperscript{141} Despite the differing definitions of the two terms, in the Questions and Answers webpage, the NIH defined “HIV antiretroviral treatment trials” as follows:

\begin{quote}
HIV antiretroviral treatment trials that are subject to the provisions outlined in this document are defined as clinical trials conducted in developing countries where antiretroviral medications are provided to enrolled subjects in order to assess the safety and efficacy of HIV antiretroviral treatment regimens.\textsuperscript{142}
\end{quote}

This definition expands the definition of treatment to include any “medication.” Medication means “a drug or medicine”, and the definition of drug is “a chemical or substance that affects the processes of the mind or body.”\textsuperscript{143} Therefore, as long as the preventative is a drug, it is applicable to the NIH Guidance. It is unlikely that the NIH intentionally excluded prevention trials from the original Guidance. Tenofovir gel is the first antiretroviral shown to be effective in preventing the transmission of HIV. The exclusion of prevention trials is likely the result of the need for the law to be updated with current science. Therefore, because the NIH expands the definition of antiretroviral treatment trials, to include antiretroviral medications anywhere the

\begin{footnotes}
\begin{enumerate}
\item\textsuperscript{141} Dorland’s Illustrated Medical Dictionary, 26th (Philadelphia: Saunders, 2003).
\item\textsuperscript{142} NIH, Questions and Answers Regarding Guidance., Question 5.
\item\textsuperscript{143} Dorland’s Illustrated Medical Dictionary, 26th (Philadelphia: Saunders, 2003).
\end{enumerate}
\end{footnotes}
term “antiretroviral treatment” is used in the Guidance, the term “antiretroviral preventive” should be added.144

Another major change that can be made to the Guidance is to clarify the type of posttrial access provision to be included in applications. The current language states:

It is important that trial participants who receive antiretroviral treatment in NIH-supported/funded antiretroviral treatment trials have the option to continue to receive antiretroviral treatment following their completion of the trial.

The NIH uses the WMA’s Paragraph 14’s definition of posttrial access. However, as noted in Chapter 2, the WMA Paragraph 14 definition is lacking clarity of some of the terms. The same is true here. It is unclear what type antiretroviral treatment participants should receive (should it be the treatment tested in the trial or the treatment considered to be the standard of care) and it is unclear what is meant by the phrase “completion of the trial.” To remedy this nebulous explanation of posttrial access, NIH should replace this language with the following:

It is important that after the trial, participants in NIH-supported/funded treatment or prevention trials have access to products proven effective in research and approved by the appropriate regulatory agency.

This change incorporates the clarity that is offered as part of the definition of the NIH Guidance. This language explains that the investigator’s responsibility is one that does not exist until the intervention they have tested is approved. This new explanation of posttrial access includes both treatment and prevention trials, otherwise a trial such as the Tenofovir gel trial, which involves a preventative antiretroviral, would not be covered by the posttrial access provision of the Guidance.

The revised section above references “products proven effective.” However, many HIV treatment trials investigate a regimen of already approved treatments to determine whether a certain combination is more effective than another.145 This means that no new product will be

144 With the caveat that the preventive should be a drug and not another form of prevention, such as condoms.
145 The revised section includes the term “prevention.” Because there are no currently approved antiretroviral prevention drugs on the market, we do not know if investigators will initiate
proven effective, and regulatory approval may not be sought. So should investigators still be required to provide posttrial access to the product or regimen? The revised policy indicates the answer would be no, investigators would not be required to provide posttrial access to the combination treatment even if it is shown to be effective, because the policy limits the posttrial access provision to new treatment or preventions approved by the appropriate regulatory agency. This result seems unfair to the trial participants taking part in this type of trial. However, consider that international organizations, such as the World Health Organization, may mitigate this result by requiring or providing the more effective antiretroviral regimen so that it is reasonably available to the population. Therefore moral responsibility to make effective products reasonably available would protect the participants and community who participated in the trial of a treatment that was not going to be approved by a regulatory agency.

Another issue is the length of time the investigator would be required to provide posttrial access to treatment or prevention to the trial participants. This is an issue common to many Guidance documents and commentary advocating posttrial benefits. Concerns exist about the wisdom of mandating posttrial access (or any posttrial benefit) because pharmaceutical companies might shy away from funding research if they know that they will be required to fund the provision of some treatment or benefit for an unspecified period of time. Also, ethical concerns might dictate a reluctance to set time limits on when a posttrial benefit should end. Regardless of these concerns, it is important that the investigators know how long they will need to secure funding for the posttrial access provision. Instead of the NIH setting time limits using increments of months or years, the Guidance should explain when the posttrial access framework begins and ends. A clear explanation of the framework’s boundaries would make it unnecessary to explain time limits in terms of “months” and “years.” The following language helps to explain the limits of the requirement to provide posttrial access:

prevention trials for the purpose of investigating whether certain combinations of drugs will be more or less effective at prevention. Still this is an important provision to clarify with antiretroviral drugs used for either treatment or prevention.
Investigators should address the provision of access to the approved treatment until the treatment or provision is or should be made reasonably available in the country. If and when it becomes apparent that the intervention cannot or will not be made reasonably available, the obligation to provide the intervention ends.

This language limits the time that posttrial access will be offered to trial participants. Once the product can or should be reasonably available to the community, the ethical obligation to provide access ends. The wording “is or should be” also addresses the possibility that the host country or the pharmaceutical company might not fulfill its responsibility to make the beneficial intervention reasonably available.\footnote{146}

The last issue identified was the responsibility conferred on the investigators to identify the best manner in which to secure funding from host countries or stakeholders. Investigators are the principal actors in the clinical trial, and should have part of the responsibility of determining the process of supplying access to trial participants. Investigators should know the “stakeholders” who can assist to identify funding sources. However, these stakeholders may have some responsibility to work with the investigators to determine how to get funding. As stated earlier, the responsibility is on the investigator because the NIH has no jurisdiction over pharmaceutical companies or host countries. It only seems fair, however, that the eventual sponsors of the antiretroviral prevention or treatment has partial responsibility to develop a plan for funding posttrial access provisions. Again, because of its statutory mandate, the NIH cannot require that pharmaceutical or private companies assist in developing (or funding) a posttrial access provision. Therefore, it seems that the NIH cannot do more than require investigators to be the sole source for identifying available sources of antiretroviral treatment or preventives.

In addition to the issues identified above as problematic, in Planning for Posttrial Access, Shah, Elmer & Grady supply some conclusions that would help with the development of future posttrial access policies:

\footnote{146 When the investigator’s obligation to address the provision of posttrial access ends, it does not mean that all moral obligation to provide posttrial benefits ends. The obligation to make products reasonably available belongs to the host country in collaboration with the pharmaceutical industry and other stakeholders.}
(1) Plans for posttrial access in part reflected variation in local contexts and resources, (2) most studies partnered with external funding sources and institutions, (3) some investigators went beyond what the guidance required, and (4) plans for posttrial access were affected by the uncertainty of predicting long term local conditions.147

These conclusions are useful for developing additional guidance that investigators can use when they develop a posttrial access provision. The NIH may want to include the following language into the Guidance or Questions and Answers webpage:

1) Planning for posttrial access should reflect the variation in local contexts and resources, 2) in the past, studies have partnered with external funding sources and institutions. These sources may be appropriate for investigators to contact to help secure funding sources, 3) investigators should not limit themselves to what the guidance requires, and 4) be aware that plans for posttrial access are can be affected by the uncertainty of predicting long term conditions.

Such language is a way to provide investigators with some context of what type of posttrial access provision the NIH would like included in a funding application.

Application of the Revised NIH Guidance to the Tenofovir Gel Trial

Now that the NIH Guidance has been revised, will the investigators seeking NIH approval for funding the Tenofovir gel trial have an easier time developing a posttrial access provision that will be approved by the NIH? Do problems still exist in the revised Guidance? Can the Guidance be amended by adding language that is generally applicable to any treatment or prevention trial seeking funding from the NIH, or will some ambiguities continue to exist by virtue of the fact that the Guidance must be made generally applicable to all HIV/AIDS antiretroviral treatment or prevention trials?

The main issue that would be identified by investigators attempting to implement a posttrial access provision is whether the language of the original Guidance requires a posttrial access provision. The revised language would require investigators to provide posttrial access in prevention trials.

147 Shah, Elmer, Grady. “Planning for Posttrial Access to Antiretroviral Treatment,” 1556.
Another issue faced by investigators when they attempt to fulfill the requirements of the original Guidance, would be what it means for participants to “continue to receive antiretroviral treatment.” The revised language requires investigators to provide only the intervention tested in the trial to participants. This makes the process of creating a protocol much simpler for investigators. Therefore the investigators would not be expected to provide Tenofovir gel or any other type of antiretroviral intervention if the trial has proven unsuccessful or if a regulatory body or international public health agency did not approve the intervention. As stated above this is an inherent limitation of the definition of posttrial access.

Additional questions faced by the investigators relate to when investigators should begin and end provision of the Tenofovir gel (assuming that the test has been successful) or other type of care. This question is can also be answered by the revised Guidance. The Tenofovir gel posttrial access provision would begin after the drug was approved by the appropriate regulatory agency. The provision would end once the Tenofovir gel should or could be made reasonably available to the community or host country.

The last questions relate to identifying available sources of antiretroviral treatments. Who should provide funding of a posttrial access provision? The Guidance already suggests that the host country, or other stakeholder should play this role. Can the NIH provide any Guidance to assist in the identification of who the “other stakeholder” is? What if the host country or stakeholder cannot or will not provide the treatment to a participant posttrial? The revisions could not make changes to the Guidance based on these questions, largely because of the limitations of the NIH’s statutory mandate. Without changing the mandate, it could be difficult for the NIH to provide any guidance that the Tenofovir gel investigators might require. Therefore, the Guidance’s language will remain the same so that the NIH does not violate its mandate. Still, the Tenofovir gel investigators should informally partner with the NIH to identify appropriate forms of funding.

Conclusion
It is wonderful that the United States has recognized its position as a leader on HIV/AIDS research and is one of the developed countries has made an effort to achieve social responsibility in its global research. The NIH Guidance is concrete evidence that the United States has recognized an ethical requirement to address the issues of justice created by conducting research in developing countries. Unfortunately, the Guidance that addresses the provision of posttrial access is inadequate and does not actually require investigators to implement posttrial access to beneficial interventions at the conclusion of a clinical trial.

Because the NIH is responsible for biomedical and health related research, it should be able to develop a policy endorsing the posttrial benefit framework it chooses. Therefore the NIH should develop a guidance that requires researchers seeking NIH-funding to include a posttrial access provision within the research protocol. However, the NIH cannot require such provisions because it is statutorily limited to recommending that investigators include a posttrial access provision. Whether posttrial access guidance is required or recommended, it is essential that the NIH include the correct definition of posttrial access within their protocol to enable researchers to correctly incorporate a posttrial access provision.

Some of the shortfalls of the NIH Guidance can be blamed on other guidance documents and literature that existed before the 2005 Guidance was implemented. The outcome of the AZT trials resulted in discussion that something is owed to trial participants in developing countries. However, when commentators began to write on the topic of post trial benefits they were not careful to distinguish between posttrial access, reasonable availability, and fair benefits. The authors of post trial literature began to neglect its responsibility to clarify the nuances of the various positions, and some publications cited to other publications that were unclear, and the result was a confusion of information that no one has yet untangled.

Beginning with an enhanced definition and explanation of posttrial access, and continuing with an examination of the existing literature on posttrial access, this thesis should provide investigators with a clearer understanding of the posttrial access framework. However,
even with a clear description of posttrial access more needs to be done to provide investigators with better guidelines. It is up to those who are writing international, foreign, and domestic guidelines to make sure that they carefully craft the specifics of their document. Questions such as “when the requirement to provide posttrial access end” and “who should we ask to help us identify or provide funding” will be important to investigators seeking to comply with any posttrial access provision.

Overall, the literature on posttrial access deserves to be better developed. The framework is one that is particularly important to those who participate in antiretroviral research, but may not receive the fruits of research once the clinical trial has concluded. Future research on this subject should be dedicated to the further investigation of the history of posttrial access, better development of the ethical principles that support its implementation, and development of better and clearer guidelines to help investigators with implementing the framework.
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WORKS CONSULTED


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