

Exploring Academic and REB Members’ Attitudes Toward Post-trial Access

by

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Abstract

There is currently no international consensus around post-trial obligations toward research participants, community members, and host countries. This literature review and interview-based study investigate arguments and attitudes toward post-trial access. The literature review found that academic discussions focused on the rights of research participants, but offered few practical recommendations. Similarly, there are few regulations or legislation pertaining to post-trial access. Interviews with REB members indicated that respondents understood post-trial access to the intervention as being the role of the state, and many of the views on benefits were shaped by the fact that respondents were based in Canada. Since REB members are uniquely influential as gatekeepers of clinical trials and research, more information on their views and attitudes is particularly important. If regulatory changes are necessary, we need to understand the current arguments, legislation, and REB members' attitudes towards post-trial access and participants, community members, and adolescents.

Keywords: post-trial access; public health; ethics; international research; Canada; adolescents

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Chapter 1.

Introduction

The effects of globalization can be seen in almost all aspects of life and industry, and scientific research is no exception. Increasingly, research and clinical trials are taking place in low-income countries and low-resource regions. However, most of these trials in low-income countries are still conducted and funded by researchers and organizations in high-income countries (Cohen, O'Neill, Joffres, Upshur, & Mills, 2009). This practice requires that additional attention be paid to certain ethical issues, including continued access to the intervention being investigated for participants and community members where research takes place. However, there is currently no strong international consensus around post-trial obligations to participants, communities, or host countries, evidenced by the fact that most trial applications do not make any reference to post-trial benefits (Cohen et al., 2009).

Compounding this issue is the pressing need to develop an HIV vaccine. HIV/AIDS is arguably one of the biggest public health threats globally, and developing a vaccine is a crucial and necessary step in addressing the pandemic. In order to roll out a safe and effective vaccine, human subjects must participate in clinical research trials. To ensure comprehensive and accurate results, trials will likely need to be conducted in HIV-endemic regions on young, HIV-negative participants (McClure, Gray, Rybczyk, & Wright, 2004; Middelkoop et al., 2008). Because of this, there is a pressing need to examine any special requirements around post-trial access issues in this particular context.

1.1. Issues with Post-trial Access: Case Studies

Two well-known and controversial clinical trials have proved instrumental in furthering the ethical discussion around benefits for participants and post-trial access: the 1994 short-course AZT trials, and the 2000 Surfaxin trials. Reflecting on these two cases helps elucidate not only the ethical issues deliberated as a direct result of the trials themselves but also the lasting impact the resulting conversations have had on attitudes and approaches toward post-trial access in the academic and research communities.

Before the short-course AZT trials sparked international controversy, the principal issue in conducting ethical research in low-income countries focused on obtaining informed consent (Annas & Grodin, 1998). While the primary point of contention in the short-course trials focused on whether control groups should be given placebos when known treatments are available, the debate resulting from the AZT trials broadened discussions and increased expectations around what was owed to participants in low-income countries (Annas & Grodin, 1998).

A 1994 US study, conducted in the US and France, demonstrated that mother-to-child transmission of HIV could be reduced from 25% to 8% when AZT – an antiretroviral drug – was administered to the mother during pregnancy and to the newborn baby for a period of six weeks after birth (Annas & Grodin, 1998). Shortly after the conclusion of the study, this AZT regimen was recommended as the standard of care for HIV-positive pregnant women by the US Public Health Service (Annas & Grodin, 1998).

Later that year, several clinical trials in low-income countries in Africa, Asia, and the Caribbean were approved and funded by the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH) (Annas & Grodin, 1998). These trials intended to ascertain whether a simpler and abbreviated AZT regimen, or “short-course,” would also be effective in preventing vertical transmission of HIV (Annas & Grodin, 1998). However, instead of measuring the short-course treatments against the current standard treatment, the control groups were given placebos. The investigators and funding bodies rationalized that since there was little or no access to medical care in the communities in which the trials occurred, no medical care was the standard of care

(Annas & Grodin, 1998). Once this information was made public, a debate raged over whether a lack of access to medical care was justification for a “lower” standard of care in clinical trials. As an aside, it’s worth noting that while the trials in African countries dominated much of the discussion, trials in Thailand and the Dominican Republic were even more troubling: during these clinical trials, ARVs were made available to the general public via national healthcare systems but not to trial participants (Wendland, 2008).

Admittedly, the original US therapeutic regimens were intensive and would have been almost impossible to implement in many HIV-endemic regions (Crouch & Arras, 1998). Crouch and Arras detail the demands of the intervention:

First, the regimen of antenatal, intrapartum, and neonatal AZT requires that women present to the clinic early in their pregnancy for HIV testing and counseling; that they follow the rigorous 076 protocol, which includes five pills per day for at least twelve weeks, and intravenous administration of AZT during delivery; and that the neonates follow a six-week, four-times-per-day, oral AZT regimen, during which time the women are required to abstain from breastfeeding (p. 26).

Wendler, Emanuel, and Lie (2004) acknowledged that although the short-course trials posed serious concerns around exploitation, there was some truth to the argument that it’s necessary to test interventions that can be practically implemented in low-resource regions. In response, Wendler et al. created a framework for determining when it might be ethical to conduct “research that uses less than the ‘worldwide best’ methods, meaning the best methods available anywhere in the world” (p. 923). In short, the framework required:

...(1) scientific necessity: investigators must use less than the worldwide best methods to answer the scientific question posed by the trial; (2) relevance for the host community: answering the scientific question posed by the trial will help address an important health need of the host community; (3) sufficient host community benefit: the trial will produce a fair level of benefit for the host community; and (4) subject and host community nonmaleficence: subjects and the host community will not be made prospectively worse off than they would be in the absence of the trial (p. 927).

Annas and Grodin (1998) argued that while determining the appropriateness of placebo use depending on access to medicines was undoubtedly an important issue, the underlying concern is whether or not researchers should be conducting any trials on populations who have no access to the intervention after the trial is over:

Unless the interventions being tested will actually be made available to the impoverished populations that are being used as research subjects, developed countries are simply exploiting them in order to quickly use the knowledge gained from the clinical trials for the developed countries' own benefit (p. 561).

There is a fine but crucial line between testing simpler methods of treatment on vulnerable populations in an attempt to treat that group versus using vulnerable populations as guinea pigs for products destined only for high-income countries. The litany of complex ethical issues raised by this particular case aside, one issue seems to be unavoidable: intent *does* matter.

The intent of researchers featured heavily in another controversial clinical trial – the Surfaxin trials in Central America. These trials researched a drug that would ease breathing in newborns and infants with pulmonary surfactant deficiencies, a condition that often proves fatal when left untreated (Hawkins & Emanuel, 2008). Although there were already many similar drugs on the market, the pharmaceutical company intended to conduct a randomized control study using a placebo because, they argued, the Latin American communities in which the trials were to be conducted did not have access to any surfactants, making no care the standard of care in these communities (Hawkins & Emanuel, 2008).

Hawkins and Emanuel (2008) highlight three crucial ethical aspects of this trial:

- (1) Placebos were used even though effective treatments already existed and were on the market
- (2) The trial involved researchers from the US conducting trials in low-income countries
- (3) The researchers never expected the product would be available to the community or country in which the trial was being conducted

Further to the second point, the researchers selected these testing sites expressly because the community did not have access to surfactants:

The hospitals selected for this multicenter trial were chosen because they were not able regularly to provide their patients with surfactant therapy. Therefore, those infants in the placebo arm of the trial would not receive worse treatment than that which they would have received otherwise (Snyder, 2012, p. 252).

Not only were participants sought out specifically because the researchers could offer a lower standard of care that would not be acceptable in their home country, there was no formalized agreement that the drug would be made available to the community or country once the trial was completed (Snyder, 2012). Compounding this is the fact that the pharmaceutical company “admitted to the FDA that its new surfactant drug...probably wouldn’t improve upon any of the four surfactants the agency had approved since 1990,” indicating that the researchers were using participants to test a drug that would offer few additional benefits compared to existing products, save for equipping the pharmaceutical company with another profitable product (Shah, 2003, p. 34). Crouch and Arras (1998) summarize the relationship between exploitation, a researcher’s intent, and post-trial access:

...if the results of a clinical trial are not made reasonably available in a timely manner to study participants and other inhabitants of a host country, the researchers might be justly accused of exploiting poor, undereducated subjects for the benefit of more affluent populations of the sponsoring countries...there is the question of whether the organizers of these studies have an exploitative intent. Are they deploying their studies in developing nations primarily to skirt the stricter research ethics environment in North America and gain access to a vast reservoir of uneducated, undemanding, and compliant research subjects? Is their primary intention to obtain answers in the quickest and cheapest possible fashion and then, as critics charge, export them immediately for use in the sponsoring countries (p. 29)?

The controversies around these two clinical trials are microcosms of the larger debate around post-trial access. While these case studies touch briefly on the academic debate surrounding post-trial access, Chapter 2 of this paper explores academic views and attitudes in a more in-depth manner, along with investigating international laws and regulations.

1.2. Ethical Obligations for Post-trial Access

Post-trial access raises issues around who should benefit, what benefits should be received, and how these benefits should be distributed. In its broadest definition, post-trial access is access to the pharmaceutical, therapy, or intervention under investigation, after the study period is over, for those individuals involved with or impacted by the research. Who, precisely, constitutes the individuals involved with or impacted by research is one of many contentious aspects of this issue. As explored through the literature in Chapter 2 of this thesis, many academics assume that the only parties who may have a claim to post-trial benefits are those who are direct participants of research and clinical trials. This assumption neglects to recognize the impact large-scale research can have on a region, community, or country. While the focus of post-trial access debates often leans towards the rights and entitlements of participants, there is still a substantial body of literature investigating benefits owed to the broader community and host country (Ballantyne, 2010; Dainesi & Goldbaum, 2012; Gbadegesin & Wendler, 2006; Hyder, Krubiner, Bloom, & Bhuiya, 2012; Macklin, 2010; Pace et al., 2006; Phillips, 2011).

While the concept of “benefits” in the post-trial benefits context is often limited to a focus on access to the intervention being studied, some argue that this notion is unnecessarily restrictive and benefits outside of access to the intervention can be an ethical and, in some cases, more appropriate choice (The Hastings Center, 2004). In a 2004 paper, the participants of the 2001 Conference on Ethical Aspects of Research in Developing Countries, led by Ezekial Emanuel, argued that post-trial benefits should not be limited to the intervention being studied or even to broader healthcare benefits, depending on the communities’ needs (The Hastings Center, 2004). They propose a fair benefits framework as “a more reliable and justifiable way to avoid exploitation” that includes financial rewards and investments in infrastructure as appropriate compensation for participants and community members (The Hastings Center, 2004, p. 17). Their justification is that “exploitation is about ‘how much,’ not ‘what,’ each party receives. The key issue is fairness in the level of benefits” (The Hastings Center, 2004, p. 19).

One trait commonly absent from academic papers on post-trial access is a lack of attention paid to the actual implementation and monitoring of post-trial access benefits. There are few suggestions or frameworks for how post-trial access should be provided and who should be responsible for enforcing or overseeing these disbursements. Discussion around precisely *who* should be responsible for funding and providing post-trial access is similarly scarce.

1.3. Legislating Post-trial Access

There is very little in the way of national – or even regional – legislation governing post-trial access. While there is no international consensus around the specifics of post-trial access, there are several influential guidelines that inform international norms. Perhaps the most well-known guideline pertaining to post-trial access is the 2000 edition of The Declaration of Helsinki, which stated, “At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study” (World Medical Association, 2000, p. 29). As an indication of just how controversial the issue of post-trial access can be, a “note of clarification” was added in 2004 that appeared to soften the previous edition’s statements:

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. 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 (World Medical Association, 2004, p. 29).

The Council for International Organizations of Medical Sciences (CIOMS) address post-trial access in a similarly influential, and at times controversial, document – the International Ethical Guidelines for Biomedical Research Involving Human Subjects. Guideline 10 of this document recommends that “any intervention or product developed, or knowledge generated, will be made reasonably available for the benefit of that population or community” (Council for International Organizations of Medical Sciences & World Health Organization, 2002, p. 51). While this may seem like a clear show of

support for post-trial access for community members, it raises more issues than it addresses. Crouch and Arras (1998) explain:

... there is the question of the scope of 'reasonable availability.' Must new pharmaceuticals be made available merely to former research or to the social groups they (loosely) represent...? Or does the scope of this requirement also include the entire town, city, region, or nation in which the study was performed? Although recent commentary appears to favor the notion of a commitment to the country in which a study is done... this gloss raises important questions about the moral relevance of political boundaries...will it give pharmaceutical companies a powerful incentive to conduct studies in smaller, less populated developing nations in order to avoid higher costs elsewhere? Questions can also be raised about the content of 'reasonable availability.' Exactly how much access for how many people are we talking about (p. 30)?

1.4. Investigating Research Ethics Board Members' Perspectives

There has been some interest in investigating post-trial access through the lens of various stakeholders. Within the academic and research communities, there is one group that is involved with the issue in a uniquely influential way. Research Ethics Boards (REBs) serve as gatekeepers between researchers and participants, making the views of their members particularly informative. While several studies have questioned patients, researchers, or healthcare staff, few have looked at the views of REB members specifically (Dainesi & Goldbaum, 2012; Pace et al., 2006). REBs are a key step in evaluating the ethical requirements of human subject research, but little is known about their views towards benefits for participants, especially adolescents and other community members.

One of the first attempts to investigate the views of ethics board members was by Pace et al., who used telephone and self-administered surveys to study attitudes towards post-trial access (2006). This study specifically investigated access to IL-2 treatment for HIV/AIDS, and found that the majority of ethics committee members questioned believed that access to this beneficial drug should be guaranteed for all people in the country where the research was being conducted (Pace et al., 2006). Interestingly, Pace et al. also reported, "IRB/REC chairs from Europe and South America

were more likely to endorse providing drugs free of charge, whereas respondents from the United States, Australia, and Thailand said drugs should be provided at a price the average person can afford” (2006, pp. 840-841).

More recently, Dainesi and Goldbaum (2012) used an e-survey to investigate the views of major stakeholders in Brazil around post-trial access, including clinical investigators and ethics committee members. The majority of ethics committee members questioned believed, “all patients with the disease should receive the medication after trial if a benefit had been demonstrated in the study” (Dainesi & Goldbaum, 2012, p. 760).

1.5. Adolescents and Post-trial Access

An important and related area that has garnered little attention thus far is REB members’ attitudes towards post-trial access with a focus on adolescent participants. When viewed in the context of the pressing need for HIV vaccine testing, this issue is particularly pressing. While the rate of new HIV infections continues to fall globally, adolescents are still disproportionately affected by the epidemic (UN Joint Programme on HIV/AIDS (UNAIDS), 2013). Between 2001 and 2012, adolescents are the only demographic in which AIDS deaths increased – all other demographics saw a decrease (UN Joint Programme on HIV/AIDS (UNAIDS), 2013). In 2012, approximately 2.1 million adolescents aged ten to 19 years in low- and middle-income countries were living with HIV (UN Joint Programme on HIV/AIDS (UNAIDS), 2013). Targeting this demographic for an HIV vaccine roll-out could have significant implications, curbing the rate of new infections and potentially stemming the global epidemic (McClure et al., 2004; Middelkoop et al., 2008). Therefore, it is essential to determine in advance when and how vaccine testing on this group will be ethical in order to facilitate testing when and if a vaccine candidate appropriate for this population is available.

One crucial element of this is that in order to administer an approved vaccine to adolescents, it must first be tested on adolescents to verify safety and efficacy in this particular demographic (de Bruyn, Skhosana, Robertson, McIntyre, & Gray, 2008; Jaspan et al., 2008). While it is likely that adult and adolescent biological responses to

an HIV vaccine will be very similar, there is some concern that immune responses, particularly in younger adolescents, may differ from those of adults (Jaspan et al., 2008). In terms of technical challenges associated with testing vaccines on adolescents, there may need to be multiple groups of adolescents of varying age demographics, and careful attention paid to national regulations regarding minors and clinical research in the country where the trials are conducted (Jaspan et al., 2008; Slack, Strode, Grant, & Milford, 2005).

Social and ethical issues in testing an HIV vaccine on a vulnerable adolescent population may prove to be more of a challenge (Jaspan et al., 2008). Jaspan et al. (2008) describe three “critical next steps” in rolling out HIV vaccine trials involving adolescents:

- (1) Connect with the community, including the creation of community advisory boards
- (2) Prepare for vaccine trials by assessing logistics related to recruitment, follow-up, feasibility, and ethical and legal requirements
- (3) Develop assessments conducted in step two into protocols, keeping the needs of adolescents and the community front and centre.

Jaspan et al. stress the importance of communicating and connecting with not just the adolescents themselves, but with the parents, guardians, and broader community. Numerous studies have been conducted in regions likely to be used as HIV vaccine testing sites in an attempt to ascertain how acceptable adolescent participation would be to prospective participants and the community (de Bruyn et al., 2008; Kiwanuka et al., 2004; Middelkoop et al., 2008; Webb, Zimet, Mays, & Fortenberry, 1999). While willingness to participate is largely dependent on individual communities' attitudes and beliefs, generally adolescents and parents were more likely to indicate an interest in involvement if the predicted efficacy of the vaccine was high (Webb et al., 1999; Zimet, Blythe, & Fortenberry, 2000). Interestingly, one study found that access to health services such as counselling, testing, and current information were very important to individuals when determining willingness to participate (de Bruyn et al., 2008). This could indicate that clearly established post-trial access for participants and community members could be an effective way of addressing not only ethical issues, but issues of participation and retention.

1.6. Thesis Overview

While there has been some valuable research conducted investigating post-trial access, the views of REB members, and considerations around adolescents, further attention is needed to better understand the intersection of these issues. To investigate these issues more thoroughly we must first understand the current state of international, national, and regional legislation and guidelines, in addition to exploring the arguments currently occupying academic discussions on post-trial access. Chapter 2 of this paper includes a scan of existing legislation and guidelines, along with a broad literature review on the academic views around post-trial access. Since REB members are uniquely influential as gatekeepers of clinical trials and research, more information on their views and attitudes is particularly important. Chapter 3 of this paper includes qualitative interviews with REB members from across Canada and investigates their views on post-trial access, with particular attention paid to special requirements involving adolescents. As most studies conducted in low-income countries still do not even address the issue of post-trial access, clearly more needs to be done to protect the interests of participants, community members, and host countries (Cohen et al., 2009). If we want to push forward regulatory changes we need to understand the current arguments, legislation, and REB members' attitudes towards post-trial access and participants, community members, and adolescents.

Chapter 2.

Post-trial Access Literature Review

2.1. Background

Healthcare is increasingly dependent on biomedical interventions, but before pharmaceuticals or treatments are approved for use they must pass extensive and expensive clinical trials. While the health and safety of research participants is of primary concern during a clinical trial, an investigator's obligation to endeavour to improve the health of participants often ends with the completion of the trial. In instances when a trial treatment improves a participant's health or quality of life, a participant's continued access to beneficial treatments is of particular concern. While continued access to beneficial treatments may not be a critical issue for residents of countries with comprehensive and affordable healthcare systems, this is not the case for all trial participants, particularly those who do not have access to pharmaceuticals through public programs or at affordable prices. As the world becomes progressively more interconnected and globalized, interactions between the developed and developing world are more and more commonplace, often highlighting stark imbalances between developed and developing countries. Medical research is not immune to the effects of globalization, leading to the advent of the globalization of clinical trials (Dainesi & Goldbaum, 2011). This aspect of the investigator-participant relationship presents several ethical challenges. While participants and communities in poor regions or developing countries often shoulder the risks of research, the benefits may be disproportionately afforded to companies and consumers in the developed world if participants do not have ongoing access to trial treatments.

Post-trial access, when a study participant is afforded access to beneficial pharmaceuticals or treatments after the study has been completed, is seen by some as

being a moral imperative in ethical research. Some parties argue that in lieu of post-trial access, investments in health infrastructure or similar expenditures on community well-being could be equally valuable for participants. Researchers and organizations that advocate for post-trial access often cite exploitation and fairness as rationales for post-trial access and other benefits (The Hastings Center, 2004). However, determining whether participants are entitled to additional benefits is only the first of several challenging questions: what specific benefits accrued to participants would make the researcher-participant relationship less exploitative and problematic? Who should be reimbursed for participation – only direct participants or the broader community and country? And if stakeholders agree that participants are owed certain benefits, which parties should be held responsible for providing these benefits?

In order to address the degrees of consensus and contention around these questions, we present the findings of a review of existing guidelines, legislation, and academic arguments pertaining to post-trial access. We also explore the rationales given in the academic literature supporting post-trial access in order to assess the presence or lack of consensus over the motivation for post-trial access.

2.2. Methods

The research team set out to identify existing national and international legislation and guidelines addressing post-trial access to pharmaceuticals and medical therapies, as well as reviewing current academic literature on post-trial access. The following section describes the literature review, inclusion and exclusion criteria, and categorization of the literature review results.

The academic literature review was not an attempt to conduct an exhaustive categorization, but to analyze a representative sample of the existing discussions and research being conducted around issues related to post-trial access. Adequate post-trial access is largely dependent on the situation, as treatments for chronic diseases likely require different post-trial access considerations than cures or vaccines. Furthermore, levels of risk can vary considerably between studies and treatments. For the purposes of this review, the research team aimed to reflect a global perspective on post-trial access

by casting a wide net in terms of included resources, and have not differentiated resources based on the type of treatment or disease under investigation. It's also important to note that some issues related to post-trial access, such as negative health consequences associated with trial participation and continued access to treatment after participation in unsuccessful trials, are ultimately outside the scope of this review. The focus of this review is to consider existing approaches and views on post-trial access to pharmaceuticals and therapies following a successful trial.

In consultation with a Health Sciences librarian, Web of Science was selected as the primary search database as it provided a wide variety of sources and was comprehensive enough to return a large number of results. The search was conducted based on the research team's knowledge of post-trial access and related issues, and search terms were chosen based on the research team's familiarity with the literature. Search parameters included English language sources using the search terms outlined in Table B1.

The search was conducted in June of 2013 over a period of a few days and ultimately returned 46 results. All academic papers that discussed post-trial access were included, resulting in 26 articles (see Appendix A).

The two members of the research team each reviewed the academic literature independently, assessing the results of these papers and identifying their themes. It was decided that each resource should be classified in two ways: by the type of action concerning post-trial benefits recommended and by the underlying ethical rationale for the recommendation. After identifying common themes, each reviewer independently classified all results into several categories. After jointly reviewing and discussing each research team member's categories, some of the categories were collapsed. The final categories were:

- Policy and guideline action categories
 - Post-trial access involving research participants
 - Post-trial access involving communities
 - Indirect benefits and fair benefits involving research participants
 - Indirect benefits and fair benefits involving communities
 - Procedural actions

- Rationale categories
 - Fiduciary relationship
 - Reciprocity
 - Beneficence
 - Justice
 - Fairness
 - Exploitation

These categories were applied to each of the 26 articles. Articles were assigned multiple categories when they covered multiple actions or rationales.

The literature review of existing legislation and guidelines was intended to be more exhaustive and comprehensive than the academic literature review. The research team relied on its own familiarity with these guidelines, on recommendations from experts and researchers familiar with issues around post-trial access, and on results of searches using Google and Google Scholar. Furthermore, references and discussions from the academic literature review identified several additional pieces of legislation and guidelines.

Based on the categories identified in the academic literature review, each member of the research team individually reviewed and categorized the legislation and guidelines. While the research team had initially intended to include rationale categories as with the academic literature, few rationales were given for legislation and guidelines and so these categories were eliminated. Ultimately, the action categories were:

- Policy and guideline action categories
 - Post-trial access involving research participants
 - Post-trial access involving communities
 - Indirect benefits and fair benefits involving research participants
 - Indirect benefits and fair benefits involving communities
 - Procedural actions

2.3. Findings

Table B2 illustrates the counts for action categories in the academic literature. “Post-trial access involving research participants” and “Procedural actions” have the highest counts, with 15 and 13, respectively. There were six references to “Indirect benefits and fair benefits involving communities,” four references to “Post-trial access involving communities,” and one reference to “Indirect benefits and fair benefits involving research participants.”

Table B3 examines six rationale categories in the academic literature. “Fairness” and “Exploitation” were the most frequently cited rationales, with ten and nine references, respectively. “Beneficence” was cited four times, “Fiduciary relationship” was cited three times, and “Reciprocity” and “Justice” were each cited twice.

Table B4 illustrates the counts for action categories in the legislation resources. “Procedural actions” had the highest count with three references; “Post-trial access involving research participants” and “Indirect benefits and fair benefits involving communities” were each referenced twice; and “Post-trial access involving communities” and “Indirect benefits and fair benefits involving research participants” were each referenced once.

Table B5 shows the number of references to action categories in the guidelines analyzed. “Post-trial access involving research participants” and “Procedural actions” had the highest counts, at nine and eight references, respectively. “Post-trial access involving communities” was referenced six times; “Indirect benefits and fair benefits

involving communities” was referenced four times; and “Indirect benefits and fair benefits involving research participants” was referenced once.

2.3.1. Actions from Academic Literature

The academic literature review returned 46 results, 26 of which were included in the analysis (see Appendix A). Each resource was classified into action categories, as described previously. Not all resources prescribed an action, while some resources recommended more than one action. As outlined in Table B2, “Post-trial access involving research participants” and “Procedural” changes were the dominant actions. The other three actions were only mentioned a handful of times in the academic literature.

These action categories highlight clear delineations in the post-trial access discussion. In this literature there was a marked distinction between providing post-trial access to the drug or therapy that was tested on participants and providing other types of indirect benefits.

Post-trial access for patients who directly participated in a study was generally discussed as being distinctly different from the issue of post-trial access for larger communities. Most sources indicated that the two groups should not necessarily be compensated in identical ways, with only three advocating for post-trial access by community members. One study highlighted the different attitudes toward the two groups: *“The greater part of the research participants (60%), and of the EC members (35%), answered that all patients (study participants as well as non-participants) should receive it. Of the clinical investigators, 43% responded that the medication should be given to study participants; the other 40% only to those subjects who benefited from the study treatment”* (Dainesi & Goldbaum, 2012, p. 759). While suggested benefits for trial participants tended to take the form of post-trial access to the therapy being tested, benefits to the community focused on indirect benefits, such as general healthcare and health infrastructure. With respect to community benefits, one paper explained, *“target populations in developing countries often lack access to regular health care, political power, and an understanding of research. They may be exposed to the risks of*

research, while access to the benefits of new, effective drugs and vaccines goes predominantly to people in developed countries and the profits go to the biopharmaceutical industry. This situation fails to provide fair benefits and thus constitutes the paradigm of exploitation” (Participants in the 2001 Conference on Ethical Aspects of Research in Developing Countries, 2002, p. 2133).

Beyond recommending post-trial access as an action, there was much discussion around which actors are responsible for providing post-trial access, with donors, researchers, and state governments held up as potentially responsible. In one case, *“There is no clear definition about who should eventually be responsible for post-trial access in Brazil — the State or the research sponsor. According to current case law, whoever is the respondent in a lawsuit will be held to have open-ended responsibility for the provision of post-trial treatment”* (Wang & Ferraz, 2012, p. 194).

There were also many recommendations that focused largely on strengthening ethics review board and clinical trial procedures without offering specific recommendations on post-trial access to medical interventions: *“It was felt that institutional guidelines could help develop agreed, consistent and rational approaches and explanations on benefits and payments for the main types of study conducted, minimize differences between similar projects, and thereby reduce perceived unfairness”* (Molyneux, Mulupi, Mbaabu, & Marsh, 2012, p. 12).

2.3.2. Rationales from Academic Literature

While not all academic sources included a detailed discussion of the rationale behind their post-trial access action recommendations, those that did discussed a range of rationales that were categorized into six broad themes: fairness (ten references), exploitation (nine), beneficence (four), fiduciary relationship (three), reciprocity (two), and justice (two).

Fairness and exploitation were referenced most frequently in the academic literature as reasons for providing some type of post-trial access. Some of the references to fairness and exploitation were made merely in passing and with little contextual discussion – some researchers seemed to assume that fairness and

exploitation were well-known and widely accepted justifications for providing post-trial access. Fairness and exploitation were often discussed concurrently and as being inherently related: *“Preventing exploitation in human subjects research requires a benchmark of fairness against which to judge the distribution of the benefits and burdens of a trial”* (Phillips, 2011, p. 79). Emanuel et al.’s “fair benefits framework” was referenced frequently, with researchers variably agreeing with or critiquing the framework: *“Emanuel et al.’s account of fairness provides a framework for objecting only to transactions that occur without the fully informed consent of the weaker party. As a result, a debate about exploitation collapses into a debate about consent. This is problematic because, as the proponents of the fair benefits framework acknowledge, neither the trial participants’ consent nor the host community’s consent preclude exploitation”* (Ballantyne, 2008, p. 239).

The remaining four themes were referenced with relatively similar frequency. Beneficence and reciprocity both appeared as rationales in one study investigating researchers attitudes towards benefits for research participants: *“It became clear over the course of the audit and workshop that research staff generally approach benefits and payments deliberations in two ways: a) focusing on ensuring that participants do not incur overall costs, with their overall approach being one of research being based on good will and partnership between researchers and research participants or communities, underpinned by a concern about moving away from this type of relationship towards a more commercial one; or b) aiming to maximise benefits as far as possible to participants, given the relative wealth of the institution and poverty of many community members/research participants”* (Molyneux et al., 2012, p. 12).

Justice was often referenced in conjunction with other rationales: *“...owing to the dedication of participants, researchers can acquire useful knowledge and develop new interventions to benefit the society as a whole. Thus, based on the principle of justice as reciprocity, since participants have contributed to others and society, they should be rewarded. It is obvious that their contribution does not end with the completion of their involvement in trials. Therefore, those who participate in a trial should have the opportunity to benefit from findings of the trial”* (Zong, 2008, p. 188).

Some academics cited the fiduciary relationship between researcher and participant as being fundamentally different from other relationships and rationales: *“The nature of post-trial obligations, therefore, cannot be considered the same in all situations and contexts; however, the relationship created between researchers and patients during a clinical trial should always be terminated with responsibility and respect”* (Dainesi & Goldbaum, 2011, p. 696).

2.3.3. Actions from Legislation and Regulations

The study identified six pieces of legislation that mentioned or impacted post-trial access, originating from the United States, Canada, the European Union, South Africa, and Brazil. While none of these included rationales, they can be categorized in the same action categories as the academic literature, based on the type of action recommended. While it’s difficult to identify common themes with only six sources, there was a clear distinction between those sources that explicitly recommended post-trial access, and those that recommended other indirect benefits.

Only one of the sources explicitly recommend post-trial access, while one other source had a proposed revision that addressed post-trial access: *“Post-trial access should be considered at individual and population level. Even if sponsors and researchers cannot be expected to solve the problem of access to care in resource-poor countries, a realistic plan for future access should always be proposed...”* (Institute of Tropical Medicine Antwerp, 2011, p. 4).

Similarly, Brazil’s Resolution 196 aims, *“to ensure the research subjects will receive the benefits resulting from the project, either in terms of social return, access to procedures, products or investigation agents”* (Brazil). While this resolution is not legislation per se, it has been legally enforced by Brazilian courts: *“...Brazilian courts in some cases have considered that the guidance for clinical trials, as well as the research protocols and the terms of informed consent based on the protocol, can be judicially enforced against pharmaceutical companies. According to some Brazilian courts, therefore, there is not only an ethical duty to provide post-trial access, but also a legally*

enforceable right of patients who participated in the trials” (Wang & Ferraz, 2012, p. 188).

References to indirect benefits – those not explicitly mentioning post-trial access – generally prescribe somewhat vague indirect benefits for research participants and communities in which research is being conducted: research should “...*be relevant both to the overall health and developmental needs of the people of the Republic and the individual needs of those who suffer from the disease and or concerns of the study*” (South African National Health Research Ethics Council, 2007).

“Procedural changes” was the most frequently cited category in the legislation resources, which generally pertained to establishing clear post-trial commitments to participants and communities at the outset of any clinical or research trial: “*The Common Rule in the Code of Federal Regulations requires that investigators inform participants in advance of any interventions or compensation that will be provided if a research participant is injured during trial participation, but it offers no guidance regarding [post-trial access]*” (Grady, 2005, p. 426).

2.3.4. Actions from Guidelines

There were ten national and international guidelines identified that mentioned or impacted post-trial access. As no universally accepted guidelines currently exist, guidelines and legislation varied considerably by region. As with the review of legislation, sources were categorized based on the actions they recommended, with few rationales listed.

Interestingly, the guidelines reviewed focused more on post-trial access than indirect benefits, which is in contrast to the actions presented in the legislation section. Another point of interest is that while post-trial access for participants is the primary focus, there are also several mentions of post-trial access for communities: “*Research proposals submitted to ethics review committees should include an explanation of how new interventions that are proven to be effective from the research will become available to some or all of the host country population beyond the research participants themselves*” (National Bioethics Advisory Commission, 2001, p. 74).

Again, we see that indirect benefit recommendations are generally broad: *“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”* (Indian Council of Medical Research, 2006, p. 30).

As with the legislation action recommendations, procedural recommendations for guidelines were relatively frequent and, again, primarily aimed at ensuring the post-trial benefits be distributed. The National Bioethics Advisory Commission (2001) recommends, *“Wherever possible, preceding the start of research, agreements should be negotiated by the relevant parties to make the effective intervention or other research benefits available to the host country after the study is completed”* (p. x).

2.4. Discussion

When we combine the three action categories for the academic literature, guidelines, and legislation and summarize the totals across all three groups, we see that overall “Post-trial access involving research participants” was referenced the most, with 26 mentions; “Procedural actions” was a close second with 24 references; “Indirect benefits and fair benefits involving communities” was referenced 12 times; “Post-trial access involving communities” was referenced 11 times; and “Indirect benefits and fair benefits involving research participants” was mentioned only three times.

Unsurprisingly, we see that the most frequently cited action category when exploring post-trial access literature is “Post-trial access involving research participants.” Interestingly, the second-most cited category is not related to indirect benefits or community access, but “Procedural actions.” This reflects a general trend in the academic literature, guidelines, and legislation to refrain from citing specific solutions to post-trial issues and instead making general recommendations, such as strengthening ethics review board practices and formalizing research relationships through written memorandums. While these types of procedural actions are undoubtedly very important, at times they seemed to mask the underlying challenges by providing cosmetic improvements to existing practices. With the exception of Brazil, the legislation

resources in particular made vague recommendations around strengthening procedural actions. The academic literature provided a much broader range of more radical solutions than the guidelines or legislation, including frameworks for global tax systems and international pharmaceutical access mechanisms. Even in the academic literature – which would theoretically provide a freer space for discussion than either the guidelines or legislation – procedural actions are one of the most frequently cited areas of suggested action.

Overall, much more attention was paid to post-trial access for research participants than broader communities or countries, with many sources refraining from mentioning groups outside of direct research participants altogether. At times, some sources seemed to assume that research participants would be the only group that would have a claim to post-trial access or compensation. Similarly, less attention was paid to indirect and fair benefits for all groups, with most of the discussions focusing on post-trial access to the drugs or therapies being investigated in clinical trials.

Turning our attention to the rationale categories for the academic literature, we see that the most frequently cited rationales are “Fairness” and “Exploitation.” While these rationales were routinely cited as grounds for post-trial access, they were rarely explicitly defined. At times these rationales were only mentioned in passing, with some authors seeming to assume that these rationales were already well understood and widely accepted. This is a problematic assumption as there is likely to be wide disagreement around the use of these terms.

There were no explicitly stated rationales given in the guidelines or legislation literature and most statements simply outlined what researchers “should” do with regards to post-trial access and concluding a study. However, at times the language used hinted at underlying rationales. For example, Brazil’s Resolution 196 states that researchers should, “ensure the return of benefits gained through researches to individuals and the communities in which they are carried out,” perhaps attempting to address concerns around reciprocity (Brazil). Another recurring theme in the guidelines and legislation was around the relevance of research to trial participants, host

communities, and countries. This may be in response to concerns around fairness, exploitation, and beneficence.

The two main points of contention in the academic literature, guidelines, and legislation were *what* resources and therapies should be shared and *who* should have access to these resources. While some academic sources advocated that post-trial access be limited to the pharmaceuticals and therapies being tested on research participants, most sources accepted other indirect benefits to participants or communities as being equally – or more – appropriate. Appropriate indirect benefits included investments in healthcare infrastructure, technology, education, intellectual property, or social goods. A key point of import is that most sources advocating for indirect benefits stipulated that the appropriateness of benefits should be determined by the participants or host community. There was disagreement around whether or not direct cash payments to participants were preferred or even appropriate, with most sources advocating for broader investments in health.

There was discrepancy in the academic literature regarding who was entitled to post-trial access or indirect benefits. Some sources that advocated for benefits to groups beyond research participants struggled to define “community” or delineate between communities and countries. A significant number of sources – particularly amongst the legislation literature – focused solely on benefits for research participants without noting the potential claims of other parties. While the majority of the legislation neglected to mention groups outside of research participants, the majority of the guidelines reviewed referenced researcher responsibilities to broader groups, such as host communities and countries.

An important but less predominant issue was concern around who should be responsible for providing post-trial access or indirect benefits. Few sources discussed this issue at length, beyond mentioning that it was a point of concern. Of sources that did touch on this issue, the consensus seemed to be that those groups profiting from the research should be responsible for providing post-trial access or indirect benefits.

An outlier of note that spans issues of both *what* and *who* were sources that focused on access to healthcare and inequalities between countries as being the

primary issue, not just inequalities in clinical trials specifically. In response, some authors proposed mechanisms to help reduce these inequalities, some of which could be funded by researchers or those profiting from research.

An overriding element in the *what/who* discussion was the issue of practical implementation. For example, some sources dismissed providing benefits to host countries solely on the basis of feasibility. While this may be expected in the legislation literature, even in discussions that focused on the ethics of post-trial access in the academic literature, some authors cite practical implementation as an important consideration, blurring the line between what should be done from an ethics standpoint, and what can reasonably be achieved. Despite the fact that the authors of legislation, guidelines, and academic literature can be very different groups with different constituencies, a lack of real discussion on implementation was evident in all three categories.

For example, controversy around post-trial access language in The World Medical Association's Declaration of Helsinki illustrated concerns around mandating implementation of post-trial access. The Declaration of Helsinki is arguably one of the most influential and widely referenced guidelines of ethical principles in medical research. In 2000, the Declaration of Helsinki recommended that, "*at the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study*" (World Medical Association, 2000). This statement was so controversial that in 2004 a footnote was added: "*Note of clarification: 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. 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*" (World Medical Association, 2004). Some argued that it was unreasonable and impractical to recommend that all patients receive post-trial access, but others wondered whether researchers and organizations were unable or unwilling.

While implementation was referenced as a primary concern by many authors, few offered insight into how to address this issue. This is particularly evident in the “Procedural actions” category, where sources often advised that researchers and communities agree on post-trial access and compensation issues before the start of the trial, but provide no real framework for accomplishing this.

Despite some similarities, when comparing the legislation and guidelines literature we see significant discrepancies in their directives and recommendations. Overall, the guideline literature pushed for more aggressive action than the legislation literature, including post-trial access or indirect benefits for communities. This likely reflects differences in the actors and stakeholders who were responsible for drafting legislation versus those writing guidelines. Since the guidelines were often written by individuals or groups from the research or medical communities, the resulting guidelines reflect an expertise and intimate knowledge of post-trial access issues. Additionally, the fact that guidelines are not binding likely gave authors more latitude in their recommendations.

Federal and regional policymakers drafting legislation that could impact post-trial access have issues of enforceability and regulation to consider, as well as additional pressure from interested stakeholders such as research institutions and corporations. Ultimately, the legislation literature rarely went beyond vague “Procedural actions,” with the notable exception of Brazil: *“The ethical guidance for clinical trials in Brazil is arguably one of the clearest in the world in attributing to research sponsors the responsibility for providing post-trial drugs to patients who participated in their experiments. What is more, Brazilian courts in some cases have considered that the guidance for clinical trials, as well as the research protocols and the terms of informed consent based on the protocol, can be judicially enforced against pharmaceutical companies. According to some Brazilian courts, therefore, there is not only an ethical duty to provide post-trial access, but also a legally enforceable right of patients who participated in the trials”* (Wang & Ferraz, 2012, p. 188).

2.5. Conclusion

Given that the frequency of clinical trials conducted in low-income countries will likely increase in our progressively globalized world, there is an urgent need for consideration of post-trial benefits for participants, communities, and citizens of host countries. While this issue may not be as pressing in countries where participants have access to healthcare and medicines through public schemes, it is particularly important in regions where this may not be available.

This literature review found that there was keen awareness around issues of fairness and justice, but many researchers and academics were reluctant to make recommendations around possible solutions or improvements. Interestingly, many of the recommended actions were procedural in nature, but generally only vaguely alluded to stricter regulations and improved oversight. Similarly, there was little in the way of legislation that directly addressed post-trial access. When post-trial access was addressed in legislation or guidelines it was much more likely to focus on research participants than on community members and citizens of host countries. Moving forward, more attention needs to be paid to benefits for communities and citizens, and there needs to be more discussion around concrete ways to guarantee post-trial access to beneficial interventions.

Chapter 3.

Examining Attitudes Toward Post-trial Access

3.1. Background

HIV/AIDS is one of the biggest public health challenges of our time, and developing a vaccine to protect against HIV infection is arguably a crucial step in addressing the pandemic. HIV vaccine testing among human subjects often takes place where HIV is endemic, which may include populations who are economically disadvantaged and vulnerable to exploitation. Given the importance of and urgent need for HIV vaccine research, it is important to balance the need to facilitate vaccine development with the requirement to ethically test HIV vaccines with special consideration for avoiding exploitation. While exploitation in biomedical research is a complicated concept with many different interpretations, special concern with research on vulnerable populations has focused on the extent of benefits conferred on the trial participants and their communities, including provisions for ensuring access to any treatments developed through the research and demonstration that the research will meet the host community's health needs (UN Joint Programme on HIV/AIDS (UNAIDS), 2007).

Before a vaccine or pharmaceutical can be judged effective it must pass rigorous clinical trials, which hinge on the participation of human subjects. While there are strict requirements relating to the treatment of human participants during research trials there are few requirements around a researcher's obligation to participants once the trial ends (Cohen et al., 2009). In the case of pharmaceuticals and other intervention-based therapies, this could mean access to a potentially beneficial treatment would end when the trial ends.

Post-trial access, when a research participant is provided with access to the pharmaceutical, therapy, or intervention under investigation after the study period, can be overlooked as an ethical issue for researchers. While post-trial access may not be a pressing issue for participants in high-income countries with access to universal healthcare systems, participants in other parts of the world may lose access to beneficial treatments at the end of a trial. For example, researchers conducting short-course AZT trials in South Africa in the late 1990's chose to use a placebo group when effective medicines were already available on the market because the community being studied did not have access to these medicines (Wendland, 2008). The researchers argued that the only treatment option available to these participants was no treatment, and thus a placebo group should not receive any medicines. These actions were widely criticized for exploiting a lack of access to medicines in South Africa as justification for failing to provide treatment, and eventually led to more stringent international ethics guidelines (Wendland, 2008). After the trials were over, participants and community members lost access to the pharmaceuticals being studied (Wendland, 2008).

A similar and related concern exists around benefits for community members, particularly in low-income communities and countries. Community members may shoulder some of the burdens of research trials, such as supporting friends and family or being affected by new infrastructure, even if they are not directly participating in the research. If researchers or drug companies are profiting from the results of research conducted in low-income communities, do they also have an obligation to the larger community? If so, what is the best way to define the boundaries of a community? Following the short-course AZT trials, not a single African government was following short-course AZT protocol because it was still too expensive (Wendland, 2008).

A potential target population for testing HIV vaccines is adolescents in HIV-endemic regions, likely outside of high-income countries where the HIV burden is higher (Bekker, Jansen, McIntyre, Wood, & Gray, 2005). Adolescents are particularly good candidates for HIV vaccine trials as they are "at high risk of infection due to sexual activity, lack of access to HIV prevention education and means, and engagement in injecting drug use" (UN Joint Programme on HIV/AIDS (UNAIDS), 2007, p. 36). Much has been published in the academic literature on ethical issues associated with post-trial

benefits (Sofaer & Strech, 2011), but less has been said about adolescents as a special population. Adolescents are a particularly vulnerable population, and as such may be deserving of special attentions or protections to avoid exploitation of this group (Bekker et al., 2005).

REBs are a key group in evaluating the ethical requirements of human subject research, but little is known about their views towards benefits for participants, especially adolescents, and other community members. This paper seeks to better understand the attitudes of REB members regarding what benefits are owed to research participants and their communities and the ethical rationale for requiring these benefits. The REB members interviewed in this paper are all based in Canada, a high-income country that is and will continue to be a “funder” country for HIV vaccine research in low-income countries and therefore serve as an initial gatekeeper via research ethics review of studies that would take place amongst vulnerable populations. By better understanding the attitudes of these REB members, we will be able to understand what benefits Canadian REBs are likely to require from future HIV vaccine trials, what additional benefits participants and communities may be owed, and why, ethically, REB members feel they are owed these benefits. This information will be helpful for understanding whether current research ethics protections are sufficient for avoiding exploitation of future HIV vaccine participants, including adolescents.

3.2. Methods

The purpose of this qualitative study was to explore attitudes of REB members regarding benefits owed to research participants and communities. To address this, phone interviews with REB members were conducted in the spring of 2014.

3.2.1. Recruitment

The researchers identified all Canadian universities with associated medical schools, and used information on the universities’ websites to identify REB members associated with the medical school or other health research REBs at the university. Participant recruitment started after approval for this study was received from the

Research Ethics Board at Simon Fraser University. Using only publicly accessible information on university websites, REB members were contacted via email. The email contained information about the study, contact details of the researchers, and offered a \$50 honorarium. All participants were current or recent REB members. Where information was available, the researchers contacted members of biomedical, health sciences, and health social sciences REBs.

3.2.2. Data Collection

In total, 23 phone interviews were completed, each lasting approximately 45 minutes and conducted by one researcher. Participants had varying experiences with the subject matter being discussed in the interviews, and had varying research and academic backgrounds, resulting in a wide variety of views on the subject matter.

As the researchers were trying to capture a broad array of views on the subject matter, certain terms used in the interviews were kept intentionally general. “Research participants” were defined as those directly participating in research, while “community members” were defined as those not directly participating in research, but who may be impacted by the research in some way. “Benefits” could be any positive impact of research, be it tangible or intangible. “Adolescents” were defined as those between 12 and 18 years of age.

3.2.3. Analysis

All interviews were digitally recorded and transcribed verbatim. The transcripts were uploaded into NVivo and reviewed by the investigators. A coding scheme was created and applied to the transcripts in NVivo. After coding, the coded data was analyzed by both researchers to identify central themes and topics. Themes were identified, and application of the themes was confirmed by both authors.

3.3. Results

3.3.1. Benefits for Participants

Respondents indicated that they were familiar with the challenges and issues around providing benefits for participants, and most explained that they had considered these issues through their role as REB members. The interviews first explored benefits for those directly participating in research as subjects. The main themes investigated were what benefits, if any, were required by the REBs; what the respondents themselves feel is morally required regardless of REB requirements; and why they feel certain benefits are morally required.

Most respondents indicated that Canadian law does not require benefits for research participants (see Table C1), although there was some confusion around “legal” requirements versus common practices. Several respondents specified that their role as an REB member was to ensure protection from harm, but that this did not involve ensuring benefits for participants. As one respondent explained, *“The ultimate goal of an ethics committee is to maximize the safety of a person who volunteers to participate in a study. There is absolutely no guarantee of benefit and that’s supposed to be stated on virtually all consent forms.”* Another common concern was that while no benefits are required, it is crucially important that researchers clearly communicate this to participants during the consent process.

Generally, there was some confusion around what was explicitly required by the REBs and what was common practice. As one respondent noted, *“I think the requirements are a little fuzzy... Rather than being direct in stating what is expected or what is required. I think that speaks to the different funding arrangements and the different policy frameworks, of course it comes down to who’s funding the research and therefore what...do they allow in terms of benefits to participants...”* Over the course of the interviews, several participants singled out funders as having some control over benefits for participants, or dictating benefits in some way.

A key recurring theme throughout almost all of the interviews was a concern around undue inducement to participate in a study. One REB member stated, *“...it’s*

pretty unclear as to what...is defined as an appropriate amount of compensation for folks, when does something become more coercive than others. I mean I think this is where there is a lot of gray area cause it's not exactly clear and people define it a little bit differently of course." Approximately one third of respondents took a broad view of benefits for participants and indicated that while no direct benefits were required by the REBs, all research had to have some expected benefit for society as a whole such as contributing to new advances in technology or to societal knowledge in general. There was an expectation that there be some potential societal benefit from the research for it to meet REB requirements. One respondent explained, *"Well I, I would assume there is in the area of health research, that you can't just go around sticking pins into people and drawing their blood unless there's at least a legitimate intent to you know provide a cure for something or to understand a disease."*

A few respondents specified that the potential benefits to participants be proportional to the risk they experienced through their participation in the research, with some respondents indicating that this is often a difficult balance to strike: *"My understanding is that we're always looking at proportionality, that we want to be sure that what is required in contributing to the research that there is some kind of balance for that in terms of what the person will get, either directly or indirectly."*

When respondents were asked what they themselves thought was morally required in terms of benefits to participants, regardless of existing legal requirements or norms, the answers were markedly different from those around legal requirements. The two most common responses had to do with compensating participants for their time and expenses and for increasing knowledge (see Table C2). Compensation for participants' expenses included reimbursing them for parking, gas, and bus fare, as well as providing financial compensation for their time. Several participants made a clear distinction between "benefits" for participants and "compensation" for time and expenses: *"I get quite grumpy if people put in there that we have no money and therefore people will be paying for the privilege of being involved in the research, so definitely the out-of-pocket expenses, I believe is a bare minimum."* Others considered compensation to be an impermissible benefit.

Again, undue inducement was mentioned several times as a key consideration when compensating participants. One researcher described this dilemma in the context of their own research: *“...what I offer to do in my own research is pay any sort of transit or transportation costs and then I have a small honorarium that sort of represents the hour that they’ve given for an interview that I’ll be doing. But I think that’s very different than paying someone \$500 to do an interview.”*

Increasing knowledge was the second common theme around morally required benefits for participants. For some, this meant a commitment to research that will further our collective understanding of a disease or therapy, while others included self-knowledge and understanding gained through the research process. Multiple respondents described access to study results as the “minimum” for ethical research. For one respondent, increasing knowledge comprised several areas: *“...I think they need to learn something from the process...I think they need to learn their own medical results and...I think that they have a right to know what the trial accomplished.”* A few respondents stressed that participants should have access to their personal results, not just the anonymized study results.

Interestingly, several respondents focused not on the specific benefits that participants should receive, but on the transparency of the consent process. These respondents felt that participants are entitled to whatever was specified in the consent form, and stressed that true consent from participants was more important than the precise benefits offered. Generally, these responses emphasized the need for informed consent and the ability of participants to choose to participate without undue inducement or coercion. One researcher described this view as being “a pretty typical one,” while another explained, *“...I’m comfortable with the current status where there’s no requirement and the requirement is really to make it clear what benefits are including, including in many cases none.”*

A final recurring theme was continued access to an intervention or therapy as a moral requirement of research. Some felt that this should be a requirement for all research, while others specified that access to the intervention being studied should only be extended past the end of the study if no other alternatives are available: *“...if it’s truly*

a unique medication for a unique problem then there should be some way in which they can get privileged access.” Several respondents indicated that while they supported continued access to an intervention, they had reservations about the practical implementation of such a requirement: *“...I mean in a utopian world I think that would be great, but if you’re going to say well you know what these benefits have to keep going after the research I think there’s going to be a lot of research, that will stop because of the money issue.”*

When asked *why* they believe certain benefits are morally required, some participants provided rationales for *not* providing benefits, such as: it is not the role of researchers to offer benefits; cost prevents researchers from offering benefits; offering anything would be coercive; and transparency, including honouring consent forms (see Table C3). One respondent explained that researchers are *“not out there to continue to treat, they’re actually there to do the research and provide the knowledge,”* and that *“it’s up to the...country and the provinces to decide what they want to actually provide.”* Another respondent explained that, *“funding is difficult to come by”* and requiring certain benefits would limit unfunded research conducted by students and professors. Several respondents believed that providing any benefits at all could be coercive and unethical. These respondents stressed the “voluntary” and “non-obligatory” aspects of research participation. Again, several respondents stressed that as long as participants freely agree to participate in research, no additional benefits are morally required.

The rationales for providing benefits focused almost exclusively on fairness and reciprocity. Many respondents cited proportionality as a consideration within fairness, with one respondent explaining, *“...people are giving up their time, in some cases they’re taking risks and while those may be motivated by altruistic motives and...it’s definitely ethically desirable that participants receive some benefit from participating in a trial that is related to the risks that they’re assuming and the time that they’re putting in as research subjects.”* Other respondents emphasized knowledge exchange and a “quid pro quo” approach to research.

A few participants indicated confusion around ethical rationales for moral requirements, while others indicated that they were unsure of their own opinions on the subject or chose not to offer an opinion.

3.3.2. Benefits for Community Members

While questions relating to benefits elicited clear responses from participants, they seemed to struggle with specifying benefits for community members, with several participants explaining that they had never considered benefits for community members in their role as an REB member. The definition of “community” was left intentionally broad, as to include a wide variety of opinions and approaches, which caused some confusion in respondents. The most common responses were that community members were either owed nothing or were entitled to generalizable knowledge gained through the study (see Table C4). One respondent cited a *“vague notion that the research is good for everybody”* while another explained that research *“has to have some kind of outcome that the larger society could draw on and build...on.”* Several respondents also stressed the need for communicating study results as *“an obligation to make your findings public.”*

As with the preceding section, respondents were asked what benefits they believed community members should receive, regardless of existing REB requirements or legislation. These responses fell into three categories: no benefits; access to information about the results (including broader societal impacts of the information generated from the study such as new technologies or policies); and access to the intervention being researched (see Table C5). Well over half of respondents cited access to information generated by the study as a requirement for conducting ethical research, but benefiting from the knowledge gained through research clearly varied in definition between respondents. Some felt this was limited to having access to the final study results, while others believed that this knowledge should be translated into improvements in the community, such as policy changes or improvements in health and medical treatments and procedures. One respondent voiced that researchers don’t value communication with communities and stakeholders as much as publication in peer-reviewed publications.

A few respondents felt that community members should also have access to the therapy or intervention under investigation if it demonstrated a benefit to participants. One respondent explained that since pharmaceutical companies were profiting from tax breaks, “...therefore the obligation should be that they are contributing to the health and well-being of the community...” Another respondent explained, “...ethically there absolutely is an obligation on the sponsor in this case to make efforts to ensure that the intervention is available and to contribute to addressing problems that might frustrate that intervention from being available.”

When asked for an ethical rationale as to why community members should benefit from research, respondents generally struggled to define a specific rationale. Some respondents indicated that benefits and an ethical rationale were dependent on a specific definition of community, such as within certain geographic boundaries or defined by some common connection. Several respondents evaded the question, while again referring to vague benefits, such as knowledge exchange. Interestingly, several respondents cited an ethical obligation to taxpayers as a rationale for providing benefits to community members: “...if Canadians are paying for research...there should be benefits for, for Canadian communities.”

3.3.3. Adolescent Participants

Participants were also asked about ethical issues concerning adolescents as research participants, and how this population impacts legal and ethical requirements for benefits for participants and community members. When asked if adolescent participation in research raised any special legal or ethical requirements around benefits, most respondents focused on issues of consent and vulnerability. Many respondents indicated that adolescent participation did not have any impact on benefits for participants, but involved a special requirement that you take the limited decision-making capability of an adolescent into account. Those responses that did note changes in benefits for adolescent participants could be grouped into three categories: adolescent participation resulted in a shift in proportionality; adolescent participants should receive fewer benefits to avoid coercion; and benefits required extra creativity to ensure relevance (see Table C6). Several respondents highlighted the importance of making

benefits relevant to adolescents. As one REB member explained, *“I think the consent process have to be particularly strong, but they also have to consider that when you look at benefits, what’s appropriate for the adolescent, what’s appropriate for the family in that case.”* Other common concerns were around proportionality, with one REB member describing how *“the risk/benefit ratio has to get tipped a little bit”* when involving adolescents, and taking extra care to avoid coercion by paying special attention to benefits: *“...where it might be appropriate to give I don’t know fifty dollars for a, somebody to participate in a research study, the amount might be different for a teenager...”*

When asked about benefits for parents or caregivers of adolescent participants, respondents continued to note issues around consent and coercion, but were less willing to give strong opinions on the matter. Some respondents felt that caregivers who may be responsible for transportation of the adolescent participant or involved in helping the adolescent to participate should be compensated in some way, but most also expressed concern that inducing caregivers to participate could potentially be harmful to adolescent participants. There was more concern around undue inducement and coercion when caregivers were considered for benefits than when discussing benefits for adolescent participants alone. One respondent explained that benefits for guardians should be contingent on who provides consent, *“If the young person is consenting then I think it is more appropriate to have benefits that can flow to other people involved in the research, but if other people are consenting on the young person’s behalf then I think it gets really tricky and I would be concerned about coercion.”*

When asked if adolescent participation created any special requirements around benefits for community members, few respondents felt that it did. Those that felt it was a moral requirement to provide benefits for community members of adult participants largely believed that this was still applicable, but no respondents explicitly stated that an adolescent participant raised issues around special benefits for community members. One respondent explained, *“I don’t feel strongly or even have an inkling of what should be different, I can’t say, but I, but I definitely think you know it has to be, you know the benefits have to be different for a participant versus a community member versus a parent. It just seems logical to me I guess.”*

3.4. Discussion

Our analysis of the interviews identified three challenges when considering benefits for research participants, communities, and adolescents. Many REB members understood benefits in the form of access to the intervention as being the role of the state, not the role of the researcher. Similarly, many of the views on benefits were shaped by the fact that REB members were based in Canada, and expected the state to fulfill certain health obligations. The interviews also highlighted that more consideration, awareness, and research is needed around benefits for participants and communities.

3.4.1. Identifying Roles

The Canadian REB members we spoke to identified researchers and the state as having distinctly different roles with respect to health research and healthcare provision. Respondents generally referred to the role of researchers as being solely focused on research – not with providing healthcare or therapies. At times, even when respondents indicated that research participants should not receive any benefits, they later went on to explain that it was extremely important that participants, community members, and citizens all have access to a beneficial intervention through the healthcare system. Those respondents who did not believe any benefits were necessary were largely still concerned with access to medicines, but did not feel that providing this access was the responsibility of researchers. While some respondents stressed the importance of access to medicines, this was often expressed as being an issue unrelated to ethical research. Similarly, most felt it is not the role of REBs to compel researchers to provide healthcare.

There was a concern from some respondents that researchers were not doing enough to provide benefits for participants, or that researchers were not even considering benefits for participants and communities in ethics applications. However, with respect to addressing this issue, few respondents supported requiring researchers to include specific considerations around benefits. This response mirrors the belief that researchers and the state have distinct roles with respect to providing access to pharmaceuticals and healthcare. Several respondents expressed a desire for

researchers to be more aware and proactive in choosing to provide benefits for participants, but shied away from recommending legislation or requirements forcing researchers to provide certain benefits. The rationale for this was the fact that every study is different, and there was a reluctance to mandate the same requirements for all types of research. Thus, REB members might be seen as understanding the provision of these benefits to be a supererogatory act of charity, morally praiseworthy but not required of these researchers. This view may also be influenced by the fact that often funders, not researchers, own the therapy under investigation, limiting the ability of researchers to require certain benefits.

Several respondents made statements that indicated pharmaceutical companies were inherently different than the “average” researcher, and that different requirements might apply to them. There seemed to be a general attitude that the “average” researcher is a university-based academic, professor or otherwise, and several respondents cited pharmaceutical companies as being a different case entirely, facing correspondingly different ethical requirements. Because these companies are presumed to be making substantial financial gains based on the results of the study, REB members may have felt that their obligations to participants are stronger and more stringent. This raises issues around whether who is conducting or funding the research creates special requirements around who benefits and what benefits they should receive, and also around whether or not financial gain creates special requirements and obligations around benefits. This also raises broader concerns around addressing inequalities and power imbalances in research, particularly in low-income settings where participants may be more vulnerable.

3.4.2. Research Ethics Board Members' Context

The basic assumption that the role of the researcher is fundamentally different from that of the state in terms of access to medicines and healthcare is likely rooted in the fact that all of the researchers interviewed are based in Canada, a country with a comprehensive national healthcare system. Their context of a high-income country with a well-functioning healthcare system likely shapes their assumptions and focus. The assumption that the state is responsible for – and will provide – access to needed

medical care frees researchers to focus on research, and to trust that advances will be accessible to the general population. It's worth noting that even in the Canadian context, access to affordable pharmaceuticals is not guaranteed. Several respondents also noted that the lag between clinical trials and access to the approved drug could be a health issue for many trial participants.

With respect to individual participants, respondents were more concerned with obtaining informed consent and freedom from undue inducement than with ensuring participants had access to the intervention being studied. Assuming individuals will eventually have access to healthcare through the state limits the benefits discussion to compensation rather than benefit. Applying these assumptions to research in low-income countries and resource-limited areas introduces issues of exploitation.

With respect to community members, there was a general sense of confusion around *why* community members should benefit, possibly due to existing community access to healthcare, and a lack of concern around exploitation and venue shopping in Canada. The fact that "community" is a difficult concept to define and the definition was left intentionally broad in the interviews likely also contributed to the confusion. The same issues around assuming eventual access to pharmaceuticals and healthcare for participants applies to community members. The same assumptions around access to healthcare will likely not apply in all communities in all countries, where research is often being conducted by researchers and companies in high-income countries. This leads to issues around whether or not conducting research in low-resource settings affects the role of researchers, perhaps requiring them to accept greater responsibility for access to healthcare and the intervention being studied. It also indicates that it may be important to have ethical approval from the country where the trial is being conducted as well as the country conducting the investigations, as REBs in the host country will be more attuned to the context of the research on participants.

3.4.3. Need for More Research and Awareness

Based on the conversations around adolescent participants, it is clear that there needs to be more awareness and research around not only adolescent consent, but also

whether the increased risks to this population require increased benefits. There's also a need for more awareness around additional considerations for researchers when they're conducting research outside of high-income settings, and a stronger discourse amongst researchers and REB members around benefits for adolescent and non-adolescent participants. Additionally, more research investigating the perspective of prospective research participants, including adolescents in low-income countries, could be very useful.

There is also a need for further research and awareness on the tension between fairness or proportionality and consent. This is especially pertinent for adolescent research and participants. There was general confusion on how to address balancing benefits with undue inducement, and the presumption that national healthcare schemes will provide certain benefits limits discussions around benefits in high-income countries. Again, more research on the perspective of research participants, particularly adolescents, in regions where research is being conducted would help to clarify needs around fairness and proportionality in health research.

3.5. Limitations

Since some universities do not publish REB members' names or their contact information on their websites, the researchers were unable to contact REB members from all medical schools. There was no publicly accessible information for schools in Quebec and Eastern Canada, thus these REB members from these regions are not represented in this study. The phone interview methodology limited our understanding of respondents' views, as we were unable to observe body language and emotional displays. Also, there is likely self-selection bias present, as those REB members with a particular interest in the subject matter may have been more likely to participate.

3.6. Conclusion

Addressing the HIV/AIDS pandemic demands new medicines and vaccines, inevitably requiring clinical trials in endemic regions. The discovery of a vaccine could

have profound impacts on the health and well-being of people worldwide. However, testing a vaccine and other medicines could have potentially negative impacts on the participants and communities involved, particularly if these groups lack access to the medicines after they're developed. As most endemic regions are in low-income countries, and since vaccine testing would benefit from having adolescent participants, it is likely that a clinical trial will be comprised of uniquely vulnerable participants, both in terms of age and socio-economic status. Compounding this is the fact that many of the researchers and companies currently investigating an HIV vaccine are located in high-income countries, introducing issues of wealth and power imbalances, along with differences in cultural and political contexts between investigators and participants.

Our discussions with REB members based in Canada highlighted assumptions around access to healthcare and the role of the researcher that may not translate ethically to other countries and communities. In the Canadian context, investigators can focus on conducting research, while trusting that the state will provide access to beneficial health innovations. This may simply not be the reality in some HIV-endemic regions. Our interviews also indicated that more consideration is needed around benefits for adolescents, particularly those in low-income countries. While the primary concern around adolescents in our interviews concerned consent and undue inducement, access to medicines maybe a much more pressing issue in participant populations. Above all, our research highlights a need for continued discussion and awareness around these issues and the need for further investigation.

Chapter 4.

Conclusion

The literature review in Chapter 2 presented the major themes and discussions currently underway in the academic community. There is concern amongst ethicists that a lack of post-trial benefits for participants and community members may constitute exploitation. While there is frequent reference to procedural changes and increased oversight, there is scant discussion around how best to make this happen. Outside of Brazil, there are few national laws or regulations directly addressing post-trial access, and only slightly more in the way of non-enforceable guidelines.

The qualitative interviews in Chapter 3 investigated REB members' views on post-trial access for participants and community members, and whether adolescent participation entails any special requirements around benefits. While most respondents supported post-trial benefits and were more or less familiar with the issue in relation to participants, there was less knowledge and support of benefits for community members. With respect to adolescents, most of the discussion focused on obtaining informed consent. One interesting theme in the REB member interviews was a focus on consent as a rationale for a lack of benefits. In a 2008 paper, Ballantyne warns against conflating consent too closely with benefits (Ballantyne, 2008). She specifically refers to the fair benefits framework proposed by Emanuel et al., but her arguments apply to many post-trial access discussions:

Emanuel et al.'s account of fairness provides a framework for objecting only to transactions that occur without the fully informed consent of the weaker party. As a result, a debate about exploitation collapses into a debate about consent. This is problematic because, as the proponents of the fair benefits framework acknowledge, neither the trial participants' consent nor the host community's consent preclude exploitation (Ballantyne, 2008, p. 239).

In the interviews with Canadian REB members, many of the questions about benefits quickly became discussions about consent. It's important to be wary that informed consent is not used as a crutch to avoid a critical analysis of post-trial benefits.

There are several important issues to note that are outside the scope of Chapters 2 and 3. One critical point is that post-trial access discussions are apt to create a false dichotomy between low-income countries that do not have access and high-income countries that do have access to pharmaceuticals and therapies. Indeed, this paper has specifically focused on the needs of participants in low-income countries. Increasingly, we're seeing that this clear delineation simply isn't the case. Needed pharmaceuticals are often out of reach for citizens of high-income countries, largely due to a lack of coverage and provision by state governments. In Canada, the government pays for less than 40% of drug expenditures, with the remainder financed through private insurance and out-of-pocket payments (Morgan, Thomson, Daw, Friesen, & Dijkstra, 2012). Compare this to approximately 80% in Australia and New Zealand (Morgan et al., 2012). Even when new medicines are provided by the state, the gap between successful clinical trial and access to the drug on the market could cause unnecessary suffering for participants. Unless policy changes in pharmaceutical coverage are enacted, many new medications could remain out of reach.

Another area of concern is the advent of contract research organizations in commercial pharmaceutical research. The interviews in Chapter 3 only involved REB members evaluating university-based academic research, so the issue of contract research organization involvement was not addressed. However, the growing presence of contract research organizations could have a significant impact on both participants and researchers.

Commercial contract research organizations are independent businesses that conduct research and clinical trials for pharmaceutical and medical device companies (Lenzer, 2008). Their market size of \$24 billion in 2010 is a testament to their growing importance and influence in the medical research industry (Masri, Ramirez, Popescu, & Reggie, 2012). Contract research organizations claim to be a boon to the advancement of ethical research, as they create distance between the drug sponsor and the drug's

performance and ultimate approval. However, working with contract research organizations poses inherent conflicts of interest: the companies that hire them still have a vested interest in positive results – if the research organization fails to deliver these results, they could lose clients (Lenzer, 2008). Pharmaceutical companies distancing themselves from research also frees them of many of their traditional obligations, including obligations to participants. In a government-mandated quarterly report filed by Gilead Sciences, the biotechnology company explicitly stated the role of contract research organizations in its research and clinical trials:

Due to our reliance on third-party contract research organizations to conduct our clinical trials, we are unable to directly control the timing, conduct, expense and quality of our clinical trials. We extensively outsource our clinical trial activities and usually perform only a small portion of the start-up activities in-house. We rely on independent third-party contract research organizations (CROs) to perform most of our clinical studies, including document preparation, site identification, screening and preparation, pre-study visits, training, program management and bioanalytical analysis. Many important aspects of the services performed for us by the CROs are out of our direct control (Gilead Sciences, 2012).

In a featured article in the British Medical Journal, a reporter investigates the impact contract research organizations have had on low-income countries, specifically:

CROs reduce costs partly by their ability to recruit volunteers quickly and partly by recruiting participants from impoverished regions of the world. The savings can be impressive. According to former chief executive of GlaxoSmithKline, Jean-Paul Garnier, a trial conducted in Romania costs only \$3 000 per participant compared with \$30 000 in the United States. He told *Fortune* magazine in July 2005 that a third of his company's trials were already being conducted in "low-cost countries"—a portion he hoped to ratchet up to a half within two years. "Globalization," he said, "is the ultimate arbitrage for companies like GlaxoSmithKline" (Lenzer, 2008).

In this way, companies are able to reduce their expenses, reduce the scrutiny of their clinical trials, and distance themselves from obligations to research participants and communities. The gains to research companies participating in these arrangements are high, with the biggest disadvantages likely felt by the participants and communities in which research takes place.

The last – and perhaps most important and pervasive issue – concerns the transparency of research and clinical trials. This is partly to do with concerns around protecting intellectual property and a company's investment in new knowledge. Although many interview respondents in Chapter 3 cited access to the research findings and the generation of knowledge as being some of the most important outcomes of research for participants, communities, and countries, a lack of transparency within the industry makes access to personal or anonymized study results unlikely.

The European Parliament passed legislation earlier this year that would require researchers to publish the results of all clinical trials, regardless of whether the results are positive or not (Secret Clinical Trial Data to Go Public [Editorial], 2014). The US Food and Drug Administration also requires companies to post the results of clinical trials in an online government registry, but fails to enforce this requirement in any meaningful way (Secret Clinical Trial Data to Go Public [Editorial], 2014). Internationally, Canada lags behind in transparency of clinical trial data (Belluz, 2013). While Health Canada publishes *information* on all clinical trials that they authorize, they fail to publish the *results* of the trials, arguably the most important piece of information (Belluz, 2013).

A lack of transparency not only limits access to valuable information on the safety of therapies tested in clinical trials but can also silence academics and researchers. One case worth noting – and one that was specifically mentioned by one of the Chapter 3 interview respondents – is the Dr. Nancy Olivieri case. Olivieri was conducting clinical trials on a drug she was testing for Apotex, a Canadian generic drug manufacturer (Baylis, 2004). Early results of the trials indicated that the drug might not only be ineffective but could also potentially be toxic. When Olivieri took steps to inform research participants about the potential dangers of the medication, Apotex responded that Olivieri's confidentially agreement prevented her from discussing her concerns with patients, and that doing so would result in legal action (Baylis, 2004). Silencing researchers who advocate for participants and failing to inform participants of potential dangers raises serious concerns around the extent of a company's intellectual property rights.

Although the preceding concerns are pertinent to all research, they seem to be particularly damaging when viewed in the context of commercial research companies, in which a financial return on investment is the primary concern. While there is ample debate around which – if any – parties should be providing post-trial access, it is unlikely that commercial research companies will change their practices without a carrot and a stick. There are few incentives to voluntarily offer post-trial benefits, and many disincentives, including a loss of revenue and the possibility of setting an expensive precedent.

As this issue is gaining more interest amongst academics, researchers, and governments, it is important to continue to track the evolving state of legislation and regulation with respect to post-trial access. As much of the upcoming HIV research will be conducted in HIV-endemic areas such as South Africa, it is important to investigate the views of REB members in these regions of the world as well. Further to this, interviewing prospective research participants to investigate their attitudes towards post-trial access would be very informative. While it would be informative to confirm the interview findings with similar studies conducted in other high-income countries, it would also be particularly useful to compare and contrast the interviews between high-income country REB members with interviews in low-income settings.

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Appendix A.

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Appendix B.

Tables: Chapter 2

Table B.1. Selection Guidelines for Literature Review

Subject	Literature Type	Search Terms
Post-trial access	Academic	"post trial access" "reasonable availability" "fair benefit*" "post trial obligation*" "post trial responsibility*" "post trial provision"

Table B.2. Academic Literature: Action Categories

Action Category	Count
Post-trial access involving research participants	15
Post-trial access involving communities	4
Indirect benefits and fair benefits involving research participants	1
Indirect benefits and fair benefits involving communities	6
Procedural actions	13

Table B.3. Academic Literature: Rationale Categories

Rationale Category	Count
Fiduciary relationship	3
Reciprocity	2
Beneficence	4
Justice	2
Fairness	10
Exploitation	9

Table B.4. Legislation: Action Categories

Action Category	Count
Post-trial access involving research participants	2
Post-trial access involving communities	1
Indirect benefits and fair benefits involving research participants	1
Indirect benefits and fair benefits involving communities	2
Procedural actions	3

Table B.5. Guidelines: Action Categories

Action Category	Count
Post-trial access involving research participants	9
Post-trial access involving communities	6
Indirect benefits and fair benefits involving research participants	1
Indirect benefits and fair benefits involving communities	4
Procedural actions	8

Appendix C.

Tables: Chapter 3

Table C.1. Are there requirements around benefits for research participants?

Response	Count
No	12
No direct benefit, but a societal benefit	7
Proportional benefit	3
Unsure	1

Table C.2. What do you think is morally required, in terms of benefits for participants?

Response	Count
Knowledge	13
Not worse off, compensated for expenses or time	11
Continued access to interventions	6
Whatever benefits were specified in the consent form	5
No benefits	1

Table C.3. Why are these benefits for participants morally required?

Response	Count
Transparency	5
Offering anything would be coercive	3
Cost prevents offering benefits	2
Not the role of the researcher	1
Fairness and reciprocity	14

Table C.4. Are there requirements around benefits for community members?

Response	Count
Nothing	9
Generalizable knowledge	8
Study results	2
Unsure	1

Table C.5. What do you think is morally required, in terms of benefits for community members?

Response	Count
Access to information	18
Access to the intervention	3
No benefits	2

Table C.6. Does adolescent participation raise any special issues around benefits?

Response	Count
Same benefits as adult participants	10
Relevance of benefits	6
Shift in measuring proportionality	2
Fewer benefits to avoid coercion	2