

**ADDRESSING POTENTIAL EXPLOITATION IN CLINICAL
RESEARCH ON HUMAN SUBJECTS**

by

Andrew Dean Foley Ross

A thesis submitted to the Department of Philosophy
In conformity with the requirements for
the degree of Doctor of Philosophy

Queen's University
Kingston, Ontario, Canada
(June, 2015)

Copyright ©Andrew D. F. Ross, 2015

Abstract

Numerous claims have been made to the effect that clinical research on human subjects can be exploitative — and hence morally problematic — even if there is informed consent and in the absence of any harm. If such claims are true, it follows that research ethics bodies ought to include avoidance of exploitation amongst their guiding principles. In order to evaluate these claims and provide guidance to implement a principle of avoidance of exploitation, three main questions must be addressed: what exactly do we mean by “exploitation”; how does exploitation affect the morality of clinical trials on human subjects; and what can be done to tackle exploitation in clinical trials. Chapter 2 provides an expository account of the historical context of the claims that sparked the current debate. Chapter 3 addresses the first main question by outlining three main types of exploitation accounts — namely micro fairness exploitation, macro fairness exploitation, and mere use exploitation — with examples of each from the literature. This typology is used in subsequent chapters to conduct a type-by-type analysis in order to determine whether or not particular controversial practices could constitute exploitation. Chapter 4 examines the nature of the connections (if any) between the three types of exploitation and a) concerns about standards of care and placebo controls, as well as b) concerns about participants’ post-trial access to successfully tested interventions. Both of these concerns arose in the context of international research conducted in Low and Middle Income Countries, but neither is necessarily unique to that context. Chapter 5 examines if and when benefits to entire communities might be necessary to avoid exploitation of either the communities themselves or individual trial participants. Chapter 6 advances a proposal aimed at reducing exploitation in commercial clinical trials by recognizing commercial clinical trial participation as a form of labour, which ought to be financially compensated, and suggesting the adoption of a locally indexed “living wage” model as a minimum standard of compensation.

Acknowledgements

I have many people to thank for their help, insight, inspiration and support.

My partner, Dr. Georgie Columbus, for her constant support and belief in me.

My supervisor, Prof. Udo Schüklenk, for his honest feedback and helpful guidance.

Prof. Lynn Gillam, for generously providing me with a workspace in Melbourne.

Dr. Ben Ferguson, Dr. Robert Hughes, and Dr. Trisha Phillips for helpful comments on an earlier incarnation of this project.

And last, but certainly not least, my family: Gordon Ross, Mandy Foley, Taylor Ross, Luke Ross, and Aaron Ross, for all of their encouragement and support.

Table of Contents

Abstract	ii
Acknowledgements	iii
List of Tables	vii
Chapter 1 Introduction	1
Chapter 2 Why Worry About Exploitation?	7
2.1 History	8
2.1.1 Background Conditions	9
2.1.2 Outsourcing	11
2.1.3 Offshoring	11
2.1.4 Controversial LMIC Short Course Zidovudine Trials	13
2.2 Approaches to the Problem of Exploitation in Offshored Research	17
2.2.1 Reasonable Availability	17
2.2.2 Fair Benefits	22
2.2.3 The Scope Problem	28
2.3 So What <i>Is</i> Exploitation?	31
Chapter 3 Exploitation Theory	35
3.1 General Features of Exploitation	37
3.1.1 Exploitation Need Not Involve Coercion	37
3.1.2 Exploitation Need Not Involve Harm	38
3.1.3 Exploitation Necessarily Involves Advantage	39
3.1.4 Exploitation and Vulnerability	40
3.2 Types of Exploitation	41
3.2.1 Micro Fairness Exploitation	42
3.2.2 Macro Fairness Exploitation	47
3.2.3 Mere Use Exploitation	56
3.2.4 Siegel's Mere Use Account	59
3.2.5 Sample's Mere Use Account	63
3.3 Exploitations	67
Chapter 4 Exploitation by Design	70
4.1 Placebo Controls and Exploitation in Offshored Clinical Trials	71
4.1.1 History Revisited	73

4.1.2 “Local Standard of Care”	75
4.1.3 Placebo Controls and Micro Fairness Exploitation	80
4.1.4 Placebo Controls and Macro Fairness Exploitation	82
4.1.5 Placebo Controls and Mere Use Exploitation	84
4.2 Exploitation and Participants’ Post-Trial Access to Successful Interventions	89
4.2.1 General Considerations	91
4.2.2 PTP and Micro Fairness Exploitation	94
4.2.3 PTP and Macro Fairness Exploitation	96
4.2.4 PTP and Mere Use Exploitation	98
Chapter 5 Exploitation and Communities	101
5.1 Defining Communities	103
5.1.1 Types of Communities	104
5.1.2 Benefits to Host Communities: a Concern Unique to LMICs?	106
5.1.3 Two Conceptions of “Community”	107
5.2 Community Benefits and Micro Fairness Exploitation	108
5.2.1 Host Community Benefits and Micro Fairness Exploitation of Individual Participants	108
5.2.2 Host Community Benefits and Micro Fairness Exploitation of Host Communities ..	110
Physical or Financial Community Contribution	112
Indirect Risk to a Community	114
Direct Risk to a Community	115
Community Ownership	116
5.3 Community Benefits and Macro Fairness Exploitation	118
5.4 Community Benefits and Mere Use Exploitation	123
5.4.1 Community Benefits & Mere Use Exploitation of Individual Participants	124
5.4.2 Community Benefits and Mere Use Exploitation of Host Communities	128
5.5 Community Benefits and Avoiding Exploitation	130
Chapter 6 Participation, Compensation and Exploitation	132
6.1 Clinical Trial Participation As Labour	132
6.1.1 What Counts as Labour?	133
6.1.2 A <i>Prima Facie</i> Case For Clinical Trial Participation as Labour	134
6.1.3 Objections to Participation as Labour	135
Health Benefit Objection	135
Motivation Objection	136

Passivity Objection	138
No Free Labour Objection	140
Unique Nature of Medicine/Medical Research Objection	141
Double Toiler Objection	141
No Product Objection	142
Naïve Advantage Objection	142
6.2 Exploitation and Compensation for Participation	142
6.2.1 Micro Fairness Exploitation and Compensation	146
6.2.2 Macro Fairness Exploitation and Compensation	147
6.2.3 Mere Use Exploitation and Compensation	149
6.3 Competing Concerns	153
6.3.1 Undue Inducement as a Reason to Limit Compensation	153
6.3.2 “Bad Incentive” Reasons to Limit Compensation	156
6.3.3 Prudential Reasons to Limit Compensation	159
6.4 Towards a Model for Compensation of Commercial Trial Participation	161
Chapter 7 Conclusion	164
Bibliography	173
Appendix A Abbreviations Used	180

List of Tables

Table 1. Possible Readings of "Local Standard of Care"	79
--	----

Chapter 1

Introduction

Numerous claims have been made to the effect that clinical research on human subjects can be exploitative — and hence morally problematic — even if there is informed consent and in the absence of any harm. For instance, Ezekiel Emanuel, David Wendler and Christine Grady argue avoidance of exploitation is one of the central ethical values justifying requirements for determining whether research trials are ethical:

“By placing some people at risk of harm for the good of others, clinical research has the potential for exploitation of human subjects. Ethical requirements for clinical research aim to minimize the possibility of exploitation by ensuring that research subjects are not merely used but are treated with respect while they contribute to the social good.”¹

Furthermore, they argue elsewhere that the avoidance of exploitation is an even more central concern with regards to research in developing countries, since such research “creates a greater risk of exploitation: individuals or communities in developing countries assume the risks of research, but most of the benefits may accrue to people in developed countries.”² If such claims are true, it follows that bodies charged with the independent ethical review of clinical research ought to include avoidance of exploitation amongst their considerations, particularly for international research to be conducted in Low- and Middle-Income Countries (LMICs). In order to evaluate these claims and provide guidance to implement a principle of avoidance of exploitation, three main questions must be addressed. Firstly, what exactly do we mean by

¹ Emanuel, Wendler & Grady (2000), p. 2701.

² Emanuel et al. (2004), p. 930.

“exploitation”? Secondly, how does exploitation affect the morality of clinical trials on human subjects? Finally, what can be done to tackle exploitation in clinical trials?

In the second chapter of the present work, I will provide an expository account of the history and context of the exploitation claims that sparked the current debate about exploitation in research. These claims all allege that, in one form or another, a given clinical trial was (or would be) exploitative by (wrongfully) taking advantage of participants and/or host communities. Such claims can largely be divided into three groups:

- (A) Claims based on unsatisfactory treatment of participants, such as by lack of continued access to successful interventions post-trial, or by use of placebo controls when proven treatments exist.
- (B) Claims based on unsatisfactory treatment of host communities, such as by non-assurance of local availability of successful interventions post-trial.
- (C) Claims based on the discrepancy between, on the one hand, the prospective benefits to researchers and sponsors, and on the other hand, prospective benefits to participants and host communities.

I will discuss these claims in the context of a particularly controversial set of trials sponsored by entities from High-Income Countries (HICs) and conducted in LMICs in the mid-1990s. I will describe the two main approaches to addressing these claims in the literature, arguing that both the Reasonable Availability and Fair Benefits approaches are ultimately problematic. Amongst other problems, they both focus exclusively on exploitation in HIC-sponsored trials conducted in LMICs (offshored trials), and neither provides a completely satisfactory account of what exactly constitutes exploitation.

I begin to address the question of what constitutes “exploitation” in the third chapter of this dissertation, by exploring some influential theoretical accounts of exploitation. This chapter begins by describing several features of exploitation that are generally agreed upon, including the independence of exploitation from coercion and harm, and the necessity of advantage to exploitation. Following Jeremy Snyder’s typology of exploitation,³ I will argue that there are at least three different types of exploitation, corresponding with three different accounts of the concept in the literature, and provide an explanation of each. These three types are micro fairness exploitation, exemplified by Alan Wertheimer’s⁴ influential account; macro fairness exploitation, drawing on work by Iris Marion Young,⁵ and exemplified by Agomoni Ganguli Mitra and Nikola Biller-Andorno,⁶ as well as Thomas Pogge;⁷ and mere-use exploitation, exemplified by Andrew Siegel’s⁸ interpretation of Kant and Ruth Sample’s⁹ original account. This three-pronged account of exploitation will serve to inform my analyses in subsequent chapters.

Returning to the issues raised (but not resolved) in the second chapter, Chapter 4 uses the three-pronged account of exploitation developed in Chapter 3 to make sense of the group (A) claims outlined in chapter 2. Chapter 4 begins with an examination of whether the use of placebo controls in LMIC settings constitutes exploitation when proven treatments exist and are available in HICs. By necessity, this involves some discussion of the concept of a “local standard of care”, which was used to justify placebo use in the controversial cases discussed in Chapter 2. This discussion is followed by an analysis of whether or not such trials constitute instances of micro

³ Snyder (2010a); Snyder (2010b); Snyder (2012).

⁴ Wertheimer (2010).

⁵ Young (2006).

⁶ Mitra & Biller-Andorno (2013); Mitra (2013).

⁷ Pogge (2008).

⁸ Siegel (2008).

⁹ Sample (2003).

fairness exploitation, of macro fairness exploitation, or of mere use exploitation. The second half of Chapter 4 deals with claims that international trials conducted in LMICs are exploitative when they fail to ensure participants' post-trial access to (successful) tested interventions. Following a review of general considerations, drawing on the work of Zhiyong Zong,¹⁰ regarding when post-trial access to tested interventions constitutes a benefit to participants, I examine whether provision of this particular benefit is necessary to avoid each type of exploitation. An important point arising from discussion of the issues addressed in this chapter is that despite the focus on offshored research in the literature, neither of these issues is entirely unique to offshored trials.

The fifth chapter continues to address the question of how exploitation affects the morality of clinical trials on human subjects by examining some of the group (B) claims outlined in Chapter 1, concerning exploitation of and benefits to the host community. The chapter begins with an overview of the different types of communities, following the typology laid out by Charles Weijer and Ezekiel Emanuel.¹¹ The first half of the chapter looks at arguments, put forward by Robert Hughes¹² and Agomoni Ganguli Mitra,¹³ purporting to link a failure to sufficiently benefit host communities with the exploitation of individual participants. The second half of the chapter looks at a number of arguments that claim host communities themselves can be exploited by clinical trials. Analysis of these claims is complicated by the fact that the subject of the claims (the exploited party) is a community rather than an individual; this need not pose a major difficulty for either micro or macro fairness accounts of exploitation, but is potentially problematic on a mere use account of exploitation. This is because obligations to avoid mere use exploitation have a particular grounding not in the distribution of benefits and burdens, but rather

¹⁰ Zong (2008).

¹¹ Weijer & Emanuel (2000).

¹² Hughes (2012).

¹³ Mitra (2013).

a respect for the inherent value of persons. Four different types of cases are examined within fairness exploitation frameworks, as these are all based on the fairness or unfairness of the distribution of benefits and burdens from the research.

In the sixth chapter, I begin to address the question of what can be done to tackle exploitation in clinical trials with a proposal aimed at reducing exploitation (of at least the two fairness kinds) in clinical trials. The chapter begins by arguing that clinical trial participation is a form of labour, even when participants are ill rather than healthy volunteers. A number of potential objections to this argument are considered and rejected. An important distinction is also drawn between commercial research and non-commercial research, with implications for compensation requirements. The second section of the chapter moves on to examine how each of the three types of exploitation might be mitigated or exacerbated by offering compensation for participation in commercial research trials. In the third section of this chapter, I address a number of competing ethical concerns that have been (or could be) claimed as arguing in favour of limiting offers of compensation for participation in clinical research. Foremost among these is the concern that offers of compensation (financial or otherwise) constitute “undue inducement” of potential participants. There are also a number of related concerns that compensating participants could provide undesirable incentives, and prudential reasons to limit compensation. I will argue that these competing concerns are not serious enough, singly or in concert, to override the argument in favour of compensation as a means to avoid exploitation of participants. I conclude the chapter by outlining some desiderata for a potential model of compensation for clinical trial participants.

Finally, in my conclusion I will recap the main findings of each chapter, highlighting the connections between them and the way the overarching argument addresses the main questions,

as well as some of the areas where further study is needed. In particular, a non-controversial account of fairness is needed, and more work needs to be done in addressing some of the root causes of exploitation such as the 10/90 gap, the global drug patenting system, and the continuing problem of lack of access to health care in LMICs. One interesting proposal to improve the relationship between HIC researchers and LMIC communities is the collaborative model of research,¹⁴ whereby the host community is involved in the decision-making process from the design stage onwards. Another proposal that, if implemented, would be helpful in this regard is Aidan Hollis and Thomas Pogge's Health Impact Fund.¹⁵

¹⁴ Buchanan et al. (2008); Godard, Hunt & Moube (2014).

¹⁵ Hollis & Pogge (2008).

Chapter 2

Why Worry About Exploitation?

Since at least the late 1990s, the problem of exploitation in clinical research on human subjects has frequently been mentioned and discussed in the bioethics literature.¹ However, the concept of exploitation has often not been clearly defined in these discussions, and when it has been defined, there have been disagreements about these definitions. In this chapter, I will begin by reviewing the historical context for these debates, including both background events and trends, as well as some prominent controversial cases. These historical contingencies help to explain why discussions of exploitation in clinical research on human subjects have tended to focus on research conducted in low or middle-income countries (LMICs) by researchers and/or sponsors from high-income countries (HICs). I will argue that two separate controversial issues are at stake in the debate, both of which can be (and have been) cast in terms of exploitation: relevant standard(s) of care, and post-trial availability of tested interventions. I will then examine two proposed approaches to resolving exploitation concerns relating to HIC research in LMICs: the “reasonable availability” standard, espoused by the Council for International Organizations of Medical Sciences (CIOMS);² and the “fair benefits” framework, advanced by the Participants in the 2001 Conference on Ethical Aspects of Research in Developing Countries (Participants).³ I will argue that both of these approaches fail to resolve exploitation concerns relating to HIC

¹ Angell (1997); Lurie & Wolfe (1997); Annas & Grodin (1998); Bayer (1998); Emanuel, Wendler & Grady (2000); Emanuel et al. (2004); et cetera.

² CIOMS (2002).

³ Participants (2002); Participants (2004). Note the initial capitalization in “Participants”, which differentiates this group of authors from “participants”, the people who participate as subjects in clinical research.

research conducted in LMICs, while at the same time actually raising exploitation concerns relating to clinical research more generally. This failure is at least partly attributable to both approaches' reliance on vague or partial accounts of the concept of exploitation; the final section of this chapter consists of a survey of claimed features of exploitation from the literature.

2.1 History

This section provides a briefing on the background conditions and some of the controversial cases that were arguably the genesis of the current discussions about exploitation in clinical trials. The primary focus is on the time period from the mid-1990s onwards, with an emphasis on illuminating conceptual issues rather than historical details.⁴ After reviewing some of the relevant background conditions and trends that have fostered the relevance of exploitation concerns in clinical trials, one controversial case will be outlined: the lightning-rod case of the trials conducted in LMICs on short-course zidovudine for prevention of vertical Human Immunodeficiency Virus (HIV) transmission, which used placebo-controlled designs despite the fact that there was a proven effective therapy. Two central issues arise from discussions of these trials: standard(s) of care and post-trial availability of tested interventions. Since it has been claimed that both of these issues are really about avoiding exploitation of clinical trial participants, an attempt will be made to elucidate what such claims imply about the concept of exploitation.

⁴ For those more interested in the historical aspects, Adriana Petryna's work will be of interest, as will the work of Melinda Cooper and Cathy Waldby: see Petryna (2009); Cooper & Waldby (2014).

2.1.1 Background Conditions

In spite of massive advances in medical science, drug research and development, medical technology, and surgical techniques, there has been and continues to be a large incidence of preventable illness in the world. Thomas Pogge notes that roughly one third of all human deaths are premature and due to treatable medical conditions, and that “nearly all the avoidable mortality and morbidity occurs in the poor countries [...] particularly among their poorer inhabitants.”⁵ This is due in large part to the stark disparity between affluent and poor nations: while citizens of HICs typically have effective access to life-saving medications and are able to afford those medications, many people in LMICs do not have access to affordable medication. To a lesser extent, this is mirrored by disparities in access to and affordability of medical care between rich and poor individuals within both HICs and LMICs. Although infectious diseases such as pneumonia can be effectively treated (if not cured) with existing drugs, they continue to contribute significantly to the global disease burden in LMICs.⁶

Several factors exacerbate this situation. Firstly, conditions of extreme poverty — characterized by persistent malnutrition, lack of access to safe drinking water, lack of sanitation, and lack of adequate shelter — increase individuals’ susceptibility and exposure to infectious disease. Hundreds of millions of people currently endure this kind of poverty, living on less than \$1 per day.⁷ Secondly, poverty and illness tend to be mutually reinforcing: even as poverty increases an individual’s likelihood of becoming ill, illness diminishes their productivity and causes them additional expenses, worsening their poverty. This cycle of poverty and illness also operates at the societal level. As David Resnik notes, “infectious diseases also have an economic

⁵ Pogge (2005), p. 182.

⁶ Ibid.

⁷ Pogge (2007), p. 97.

and social impact. . . . [They] restrict productivity, erode economic growth, discourage foreign investment, disrupt families, undermine education, and expend valuable resources on healthcare.”⁸ Thirdly, there is a strong commercial bias in drug research and development. This bias favours development of drugs to treat conditions (including baldness, impotence, and obesity) that affect affluent consumers who are willing and able to pay high prices for such treatments. The commercial bias has led to the existence of the so-called “10/90 gap,” whereby only 10 per cent of all funding for drug research and development is allocated to addressing the conditions that account for 90 percent of the global disease burden.⁹ Fourthly, existing patented drugs are often unaffordable to most in developing nations and basic healthcare infrastructure is badly lacking in many of these nations.¹⁰ Finally, the Trade-Related Aspects of Intellectual Property Rights agreement (TRIPs) and “TRIPs-plus” provisions in subsequent trade agreements mean that developing countries must respect drug patents and allow monopoly drug pricing for a minimum of 20 years. Although there are provisions for compulsory licensing and parallel generic importation (allowing for manufacture by generic producers and marginal-priced sales in the event of a public health crisis), these are not widely used due to “excessively burdensome conditions.”¹¹ In short, there is a real problem of lack of access to medicines in the developing world. Against this background, two trends have emerged that have both raised concerns about potential exploitation of participants in clinical research: a trend towards outsourcing of clinical research from sponsor firms to third-party firms, and a trend toward “offshoring” of clinical research from the HICs, which are the main markets for new drugs, to LMICs whose health systems often cannot afford new drugs during the patent period.

⁸ Resnik (2006), p. 88.

⁹ *Ibid.*, p. 89.

¹⁰ *Ibid.*, p. 88.

¹¹ Labonté, Blouin & Chopra (2007), p. 19.

2.1.2 Outsourcing

Since at least the late 1990s to early 2000s, commercial clinical trials are increasingly being outsourced from pharmaceutical companies to Clinical Research Organizations (CROs).¹² Pharmaceutical companies outsource to CROs in order to cut costs and reduce turnaround times. Turnaround times are especially significant as the life of the patent on a drug is 20 years starting from when the patent is filed, not from when the drug receives regulatory approval to be marketed. For this reason, “every day’s delay in bringing a drug to market can cost as much as \$1.3 million, according to industry estimates.”¹³ Due to intense competition between CROs for business from pharmaceutical companies, each CRO has strong market incentives to minimize their costs, which could potentially have a negative impact on their treatment of participants. “CROs’ dependence on Big Pharma carries risks. Contracts can range from three months to three years or longer, and they can end anytime, especially if a drug is not testing well.”¹⁴ By 2002, pharmaceutical firms were outsourcing more than 60% of their clinical trials to CROs, with the total value of such contracts being in the neighbourhood of \$10 billion (US).¹⁵

2.1.3 Offshoring

Against the background of global inequality and increased outsourcing of clinical trials from pharmaceutical companies to CROs, there has also been a trend toward “offshoring”¹⁶ of

¹² See Abrams (2005); Alva (2008); Gwynne (2002).

¹³ Rowland (2004), p. 555.

¹⁴ Abrams (2005), p. 12.

¹⁵ Gwynne (2002), p. 71.

¹⁶ Ballantyne (2010) uses the term “outsourced drug trials” to refer to research conducted in developing countries by for-profit pharmaceutical companies from developed countries, on drugs aimed primarily at developed-world markets. However, I will use that term to refer to research conducted by a third party (typically a CRO) on behalf of the research sponsor. This is in contrast

drug trials to LMICs.¹⁷ This is an especially attractive option for CROs, due to the economic forces driving them to slash costs and minimize turnaround times. LICs in particular tend to have many sick people with little or no access to medical care (as noted above), facilitating speedy recruitment of participants. LMICs may have less strict regulation regimes and fewer patient protections than HICs, helping to minimize bureaucratic delays and improve turnaround time. There are also significant cost savings due to lower wages, lower real estate costs, and favourable exchange rates.¹⁸ In the early 2000s, this offshoring was largely focused on MICs in Eastern Europe, as exemplified by the following excerpt from a 2003 business report:

“In comparison [to Western European CROs], Eastern European clinical CROs are becoming an increasingly attractive proposition for drug developers in both the U.S. and Western Europe. Among the obvious, [sic] advantages of the region are low costs of patient reimbursement and the presence of highly skilled medical staff. This has been reinforced by centralized healthcare systems. Sizable, homogenous populations having similar racial characteristics to the United States, have, in addition, facilitated patient recruitment drives. This has been aided by traditionally high compliance with study protocols. Patients in this region tend to be relatively under medicated, thus reducing the risk of patients using competing medications and compromising the integrity of the final data. The high-quality data obtained has helped accelerate the process of securing regulatory approval. The first wave of east European countries that profited from the trend toward outsourcing clinical work includes Poland, Hungary, Russia, and the Czech Republic. Now, lured by the prospect of even greater savings, CROs are looking to establish facilities in Russia, Bulgaria, Romania, and

to “offshored” trials, in which HIC-sponsored drugs are tested in LMICs, despite being aimed primarily at HIC markets.

¹⁷ Ballantyne (2010), p. 27. See also Petryna (2007); Petryna (2009).

¹⁸ The full extent of these savings is not known, but Ballantyne (2010), citing various sources, estimates that LIC-hosted trials cost about 60% less than if the same trials were conducted in HICs.

Serbia as well. Russia, in particular, represents an untapped market with vast potential.”¹⁹

As this report makes clear, the “host countries” for offshored research are being selected for practical and economic reasons as much as for scientific ones. Offshoring raises exploitation concerns because successful products of offshored research may not be made available (either in principle or in practice) to the research participants or the broader host countries afterwards. Effectively, this means that many of the risks inherent to clinical trial participation are offshored to LMICs, while the rewards could potentially stay in HICs. Notably, this concern only grew as by the end of the decade, the offshoring trend had shifted towards even lower income countries, with India in particular becoming a major centre for offshored research.²⁰ The potential for improper treatment of participants is also magnified in offshored research, due to the lack of established regulatory frameworks for ethics and oversight. As recently as 2008, ethics committees in India were described as “still evolving and the concept of what being ‘independent’ implies [was] still being developed.”²¹

2.1.4 Controversial LMIC Short Course Zidovudine Trials

There were several controversial trials conducted or proposed by HIC sponsors and/or researchers in LMICs during this period, including the 1990 Havrix (hepatitis A vaccine) trial conducted in Thailand²², the proposed 2000 placebo-controlled trial of Surfaxin in Bolivia,²³ and

¹⁹ Biotech Business Week (2003), p. 108.

²⁰ See Edwards (2008); Sunder Rajan (2007); Cooper & Waldby (2014).

²¹ Edwards (2008), p. 25.

²² Hawkins & Emanuel (2008b), p. 55. This study was co-sponsored by the U.S. Army, SmithKline Beecham Biologicals, and the Thai Ministry of Public Health.

²³ *Ibid.*, p. 59. This (proposed) study was to be sponsored by a U.S.-based company, Discovery Labs.

Pfizer's 1996 Trovan (antibiotic) trial conducted during a bacterial meningitis outbreak in Nigeria.²⁴ However, I want to focus on a case that generated extensive discussion about exploitation. These are the multi-centre placebo-controlled short-course zidovudine trials, some of the most hotly debated studies of the era. The reason I want to focus on these trials is that they featured placebo controls despite the existence of treatments that were already proven effective at the time. The studies were also labeled by some as exploitative, despite the supposedly beneficent motivations behind their use of placebo controls. In this subsection, I will summarize the details of the case, highlighting two particular issues raised, and how each has been claimed to constitute exploitation.

It has been known since 1994 that a particular long regimen of the antiretroviral drug zidovudine, developed by the AIDS Clinical Trials Group (ACTG) and known as the ACTG 076 regimen, was effective in reducing the rate of maternal-foetal HIV transmission.²⁵ However, ACTG 076 was prohibitively expensive (costing much more than local annual per capita health expenditures) and logistically unrealistic for many women in developing countries (requiring the screening of all pregnant women for HIV infection, followed by extended prenatal and antenatal care for infected women.)²⁶ As a result, a series of trials was conducted to evaluate the efficacy of shorter courses of zidovudine. The short-course zidovudine trials aimed to find if a short course would be better than nothing for preventing maternal-foetal HIV transmission, because the long course (ACTG-076, which was the established best standard treatment in HICs at that time) was considered unattainable for the LMIC populations which were most affected by the disease.²⁷

²⁴ Petryna (2007), p. 31.

²⁵ Connor et al. (1994).

²⁶ Lurie & Wolfe (1997), p. 853.

²⁷ Ibid.

Many of these trials were later criticized on the basis that they were placebo-controlled rather than active controlled trials, despite the fact that there was an established effective treatment. It was argued that the use of placebo controls, and the fact that no plans were in place to ensure host country populations would have access to the tested intervention if it were successful, made these trials exploitative.²⁸ George Annas and Michael Grodin argued the latter point, claiming

“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.”²⁹

Implicit in this argument is the claim that recruiting clinical trial participants in LMICs, without first ensuring that any successful tested intervention will be available to others of similar socio-economic standing in those countries, constitutes exploitation. This view of exploitation is consistent with the “reasonable availability” standard for international research espoused by CIOMS,³⁰ among others, and discussed in the following section.

With regards to the use of placebo controls in offshored research when proven treatment is available in HICs, this point was raised by several commentators,³¹ who noted that such use of placebo would never have been approved for trials conducted in HICs. As Lurie and Wolfe put it,

“Residents of impoverished, postcolonial countries, the majority of whom are people of color, must be protected from potential *exploitation* in research. Otherwise, the abominable state of

²⁸ It is worth noting that in some instances, effective treatments were eventually implemented in the LMICs where they were tested, despite the lack of a plan to do so. See, e.g., Hawkins & Emanuel (2008), p. 56.

²⁹ Annas & Grodin (1998), p. 561. Emphasis added.

³⁰ CIOMS (2002).

³¹ See, e.g., Angell (1997); Lurie & Wolfe (1997).

health care in these countries can be used to justify studies that could never pass ethical muster in the sponsoring country.”³²

The justifications given for placebo use in these trials were two-fold: on the one hand, it was argued that this was scientifically necessary to address a local health priority,³³ on the other hand, it was argued that the participants given placebo were not thereby made worse off than if they had not participated, since the local standard of care was no treatment.³⁴ Critics of the use of placebo in such instances maintained that such trials were exploitative even if participants were no worse off for taking part. Marcia Angell argued that such placebo use amounted to ethical relativism, which could “result in widespread *exploitation* of vulnerable Third World populations for research programs that could not be carried out in the sponsoring country.”³⁵ Ronald Bayer, meanwhile, combined the worries about placebo use and lack of post-trial availability. He argued that even if the short course trials succeeded, the new treatments might still be unaffordable for the host countries, so that the cost-savings of the new treatments would primarily benefit HICs. As a result, he claims, “the placebo-controlled trials are *exploitative* of poor people, who are being manipulated into serving the interests of those who live in wealthy nations.”³⁶

A certain notion of exploitation is also implicit in the concerns about the use of placebo controls in offshored research when proven treatment is available in HICs. On this view, taking advantage of the situation of people in LMICs (such as their lack of access to current best proven

³² Lurie & Wolfe (1997), p. 855. Emphasis added.

³³ Wertheimer (2010), p. 193.

³⁴ Much ink was spilled concerning the relevant standard of care to consider when designing a trial – whether the local standard or the best available standard should apply. (See, e.g., Schüklenk (2004); Wendler, Emanuel & Lie (2004).) For present purposes, we can bracket that particular question as it will not help to illuminate our inquiry, but I do take it up in some detail in chapter 4.

³⁵ Angell (1997), p. 848. Emphasis added.

³⁶ Bayer (1998), p. 569. Emphasis added.

treatments) in order to conduct experiments that would not be permitted in HICs, amounts to exploitation.

2.2 Approaches to the Problem of Exploitation in Offshored Research

There have been two main approaches to the problems raised by the controversial cases mentioned in the previous section. The first of these approaches, the “reasonable availability” approach, is expressed in the ethical guidelines for international clinical research put forward by CIOMS.³⁷ Critics of this approach advanced an alternative, which they called the “fair benefits” framework for avoiding exploitation in international clinical research.³⁸ In this section, I will begin by outlining the reasonable availability approach, then highlighting some of its shortcomings. I will then proceed to describe the fair benefits approach, including both its strengths and its fundamental flaws. Finally, I will highlight a further shortcoming shared by both approaches, namely their exclusive focus on research conducted in LMICs by HIC sponsors and/or researchers.

2.2.1 Reasonable Availability

In responding to the controversial cases described in the previous section, particularly the placebo controlled LMIC trials of short course zidovudine for prevention of vertical transmission of HIV, one possible tactic is to stipulate that research ought not to be conducted in an LMIC if the people of that LMIC will not have access to the products of said research. This is the tack

³⁷ CIOMS (2002).

³⁸ Participants (2002); Participants (2004).

taken by the reasonable availability approach. The core of this approach is to ensure that international research conducted in LMICs benefits people in those LMICs, thereby avoiding (or at least minimizing) charges of exploitation. The “reasonable availability” approach primarily concerns the post-trial benefits available to participants and host communities, specifically, that the eventual products of trials (such as successful tested interventions or scientific knowledge) must be made reasonably available to both participants and host communities, in order to avoid exploiting them.³⁹ On such accounts, an offshored trial is exploitative if the products of the trial (should it succeed) will not be available to either the trial subjects or the host community. There are a number of accounts which emphasize the importance of local availability of the trial intervention post-trial as an ethical consideration,⁴⁰ but for present purposes it will be instructive to consider one such account in particular, that which is put forward in the CIOMS *International Ethical Guidelines for Biomedical Research Involving Human Subjects*.⁴¹ This account, which has been a preferred target of critics of reasonable availability, is clearly laid out in Guideline 10 (Research in populations and communities with limited resources):

“Before undertaking research in a population or community with limited resources the sponsor and the investigator must make every effort to ensure that:

the research is responsive to the health needs and the priorities of the population or community in which it is to be carried out; and

any intervention or product developed, or knowledge generated, will be made reasonably available for the benefit of that population or community.”⁴²

³⁹ Hawkins & Emanuel (2008a), p. 9.

⁴⁰ See, e.g., Bayer (1998); Annas & Grodin (1998).

⁴¹ CIOMS (2002).

⁴² Ibid.

The first clause, which I shall refer to as the responsiveness clause, is important to ensuring local benefit from international research because it precludes the conduct of research that could not be of benefit to the host community even if it were made locally available. For instance, this clause would proscribe the testing of a novel antimalarial agent in Mongolia, an LMIC where malaria is not a local health priority. In other words, it only allows international research in LMICs when there is a potential benefit to the host community.⁴³ The second clause, which I shall refer to as the availability clause, then aims to ensure that there is some sort of arrangement or plan in place to actualize the potential benefits to the host community.

The CIOMS document also provides some commentary on its guidelines. Echoing the concerns raised by Annas and Grodin in relation to the short-course zidovudine trials, the CIOMS commentary on Guideline 10 notes that host countries may be unable to afford even treatments costing less than the current best standard treatment. It goes on to argue that

“If the knowledge gained from the research in such a country is used primarily for the benefit of populations that can afford the tested product, the research may rightly be characterized as *exploitative* and, therefore, unethical.”⁴⁴

Hence the reasonable availability approach can be characterized as aimed at avoiding exploitation, although its proponents do not present a detailed account of the nature of exploitation, beyond implying that it has something to do with benefit distribution and specifying that it is a wrong-making feature. The main strength of this approach, arguably, is its identification of exploitation as a relevant moral concern for clinical research on human subjects.

⁴³ Note that there is an ambiguity in the terms “population” and “community”, such that it is not entirely clear how the boundaries of these groups are to be drawn; this ambiguity is discussed in detail in chapter 4, but for the purposes of this chapter it is not necessary to disambiguate these terms.

⁴⁴ Ibid. Emphasis added.

This brings us to the shortcomings of the reasonable availability approach. There are four main issues⁴⁵ with the reasonable availability approach, which taken together suggest that it does not offer a promising solution to exploitation concerns in human subjects clinical research.

Firstly, it must be noted that while it does address the exploitation concern about post-trial availability identified in the previous section, the reasonable availability approach (as laid out by CIOMS) is largely silent on the parallel concern about standard(s) of care in clinical trials.

Secondly, as proponents of the alternative “fair benefits” approach point out, the reasonable availability approach focuses on the type, rather than the amount, of benefit to host communities. As a result, it does not allow for researchers to offer benefits other than post-trial availability of the products of research, even when these would be preferred by participants and/or the host community.⁴⁶ For the same reason, the reasonable availability approach may fail to provide sufficient benefits to host communities in phase I or II trials, as well as unsuccessful phase III trials, since these do not establish the efficacy of tested interventions.⁴⁷

Thirdly, the reasonable availability approach can potentially worsen the situations of the very LMIC prospective participants it is intended to protect, as it arguably did in the Surfaxin case. Surfaxin, a synthetic surfactant, was intended for use in treating respiratory distress syndrome (RDS) in newborn infants. Four other surfactants had previously been proven effective

⁴⁵ There are also a number of lesser issues, such as the following problem with the responsiveness clause: it turns out to be superfluous in many cases, and too weak in others. It is superfluous in many cases because practical and scientific considerations will often effectively rule out conducting a trial in a location where it would not be responsive to local health needs: no-one would propose a phase III antimalarial trial to be conducted in Mongolia anyway, since the trial could only demonstrate effectiveness in an area with a significant incidence of malaria. The responsiveness clause is also too weak in other cases, in that it could be interpreted to require only that the research respond to a health need and priority of the population from which participants are recruited: with a sufficiently narrow reading of “population”, such as “the people in the host country afflicted with the target condition,” this is reduced to a tautology.

⁴⁶ Participants (2002), p. 2133.

⁴⁷ Ibid.

in treating RDS and approved for such use by the United States of America's Food and Drug Administration (FDA) between 1990 and 1999.⁴⁸ Discovery Labs, the American company that developed Surfaxin, was planning a phase III study of the drug in 2000, and consulted with the FDA regarding acceptable study designs. The company did not think they would succeed at showing superiority to existing surfactants, and the FDA did not think that a non-inferiority study would provide a sufficient basis for approval.⁴⁹ Eventually, a randomized double-blind placebo-controlled trial was proposed, to be conducted in Bolivia, where surfactant treatment was not generally available due lack of equipment, lack of medical expertise, and the prohibitive cost (over USD \$1000 per child).⁵⁰ Importantly, Surfaxin was primarily intended for HIC markets, so the trial was being conducted in Bolivia only because the local standard of care was lower there than in the US. According to the design for the proposed trial, "parents of infants showing symptoms of RDS would be asked to give consent... The infants would then be intubated and either given air suffused with Surfaxin or air without any drug."⁵¹ Although this meant that half the infants in the study would not receive any surfactant, the ventilator support they would receive was still superior to the local standard of care they could expect to receive outside of the study. Due to controversy surrounding the use of a control that was less than the standard of care in HICs, Discovery Labs ultimately scrapped the proposed trial in Bolivia, conducting an active-controlled trial in the US instead. As a result, none of the RDS-afflicted Bolivian infants who might have been in the proposed trial would have received ventilator support (with or without surfactant), making them significantly worse off than they would have been if the planned trial had gone ahead.

⁴⁸ Hawkins & Emanuel (2008), p. 60.

⁴⁹ Ibid.

⁵⁰ Ibid.

⁵¹ Ibid., p. 61.

Finally, the reasonable availability approach proposes a standard that is overly vague and hence difficult to evaluate: there is no obvious way to determine what constitutes “reasonable” availability, other than by appealing to pre-theoretic inclinations, which are likely to diverge. Not only is it unclear what constitutes “reasonable” availability, it is also unclear why meeting this standard would be either necessary or sufficient to avoid exploitation, as the concept of exploitation is left undefined. Taking together the vagueness of the reasonable availability approach with the preceding problems, it becomes clear that this approach does not constitute a promising avenue for addressing exploitation concerns in offshored clinical trials.

2.2.2 Fair Benefits

Largely in response to the perceived failings of the reasonable availability approach to exploitation avoidance in international clinical research, a group of HIC and LMIC researchers came up with an alternative approach at a meeting in 2001: the “fair benefits” framework.⁵² According to advocates of the fair benefits approach, “the fundamental problem with the reasonable availability standard is that it guarantees a benefit—the proven intervention—but not a *fair level* of benefits, and therefore it does not necessarily prevent exploitation.”⁵³ In particular, an insistence on reasonable availability disallows research that offers other benefits (but not post-trial availability of the tested intervention), even when the participants and/or the host community might prefer the other benefits.⁵⁴ Their proposed alternative approach aims to remedy this problem by ensuring that research participants get a fair level of benefits, which may or may not include post-trial access to the tested intervention, depending on the particulars of the case and

⁵² Participants (2002).

⁵³ Participants (2004), p. 20.

⁵⁴ Participants (2002), p. 2133.

the (collective) preferences of the participants. As they put it, “exploitation is about ‘how much,’ not ‘what,’ each party receives. The key issue is fairness in the level of benefits.”⁵⁵

Exploitation avoidance in international clinical research is the central concern of the fair benefits approach, and accordingly the proponents of this approach provide an explicit definition of the concept of exploitation, which they take from Alan Wertheimer. On this view,

“A exploits B when B receives an unfair level of benefits as a result of B’s interactions with A. The fairness of the benefits B receives depends on the burdens that B bears as a result of the interaction, and the benefits that A and others receive as a result of B’s participation.”⁵⁶

Following Wertheimer, proponents of the fair benefits approach claim that exploitation is a feature of micro level transactions, and that macro level concerns such as background injustices are therefore not relevant to determining whether a particular interaction is exploitative or not.

Proponents of the fair benefits approach agree with the reasonable availability approach’s conditions that research must address a health problem of the local population, that scientific reasons must justify conducting the study in a particular host country, and that the research must either pose few risks to participants or the benefits to the participants must clearly outweigh the risks.⁵⁷ In addition to these, the fair benefits approach posits “three additional fundamental principles to protect developing communities from exploitation”: fair benefits, collaborative partnership, and transparency.⁵⁸

“Fair benefits” refers to the need to ensure that participants receive sufficient benefit from their participation in order to avoid being exploited. In general, the level of benefits to

⁵⁵ Participants (2004), p. 20.

⁵⁶ Participants (2002), p. 2133, citing Wertheimer (1999).

⁵⁷ Ibid.

⁵⁸ Ibid.

participants should increase as the burdens and potential risks of participation increase; benefits to participants should also increase as the benefits to researchers, sponsors and others increase.⁵⁹ It is up to the participants (collectively) to determine which benefits they would prefer, and whether the level of benefits offered by a particular study is fair. Reasonable availability of a tested intervention might still be an important benefit in some cases, but other post-research benefits can also be considered. The fair benefits approach also recognizes that, in addition to participants, the host community may contribute to the research project (by bearing certain burdens or costs, for instance providing health care personnel and infrastructure). As a result, “to avoid exploitation, consideration of the benefits for the larger community may also be required.”⁶⁰

“Collaborative partnership”, in the context of the fair benefits approach to avoiding exploitation, “means that researchers must engage the population in developing, evaluating, and benefiting from the research.”⁶¹ While this may sound like a deep sort of engagement and collaboration, all the proponents of this approach actually talk about in this connection is the need for the population of participants to freely decide to participate in the research, and to decide amongst themselves whether the benefits offered for their participation are sufficiently fair.⁶² In other words, collaboration is really just a sort of collective bargaining process. This process is necessitated by the lack of a consensus standard of fairness, particularly with respect to international distributive justice.

“Transparency” is included as a fundamental principle in this framework in order to ensure that participants are fully informed not only about what benefits are being offered to them

⁵⁹ Participants (2004), p. 22.

⁶⁰ Ibid.

⁶¹ Participants (2002), p. 2134.

⁶² Participants (2004), p. 23.

in a particular instance, but also what types and levels of benefits have been offered and accepted in previous studies of a similar nature. The idea is to allow for comparisons with similar transactions, so that participants can better judge whether or not the current offer is a fair one.

Finally, although the proponents of the fair benefits approach readily acknowledge the entrenched disagreements about substantive accounts of macro fairness (i.e. distributive justice), they propose the adoption of an idealized market standard of micro fairness:

“Fairness in individual interactions, which is the concern of exploitation, is based on ideal market transactions. Thus a fair distribution of benefits at the micro-level is based on the level of benefits that would occur in a market transaction devoid of fraud, deception, or force, in which the parties have full information.”⁶³

Combining this with the three principles gives the following result: to avoid exploiting LMIC participants in international clinical research, the participants must be offered (and agree to) a level of benefits equivalent to what they might get in an idealized market transaction. To the extent that a host community also bears costs and burdens related to the conduct of research, the community must similarly be offered (and agree to) a level of benefits equivalent to what it could expect to get under ideal market conditions.

The fair benefits approach has some clear advantages over the reasonable availability approach, but it also has a number of significant shortcomings. First and foremost, the fair benefits approach recognizes (and attempts to fulfill) the need for an account of what constitutes exploitation. Importantly, it also recognizes that post-trial availability is neither the only, nor necessarily the most important, benefit that can result from research participation. It also recognizes the need to distinguish between the exploitation of individual participants and the

⁶³ Participants (2004), p. 20, citing Wertheimer (1999).

exploitation of host communities. Unfortunately, these strengths are outweighed by the severity of the approach's faults. There are a number of flaws⁶⁴ in the fair benefits approach, but I will focus here on the issue of fairness: this approach defines exploitation, but defines it in terms of fairness, a concept whose nature is even more hotly disputed than the one it was meant to clarify.

With regards to the issue of fairness, the fair benefits approach contains significant ambiguity. One of the major supposed advantages of the fair benefits approach is that it is a procedural account, meaning that it does not rely on (or even discuss) controversial questions about distributive justice. However, this alleged strength turns out to be a critical flaw, as it is impossible to meaningfully determine what constitutes a fair share of benefits without some conception of justice. By using the ideal market as a benchmark, the fair benefits approach actually tacitly appeals to a minimalist but highly implausible conception of justice, namely that whatever distribution people actually agree to accept is a just distribution. Not even a hard-line libertarian such as Robert Nozick could accept this notion of justice – it is not sufficient to have a theory to explain justice in transactions, because the justice of a transaction depends on the justice of background conditions.⁶⁵ This conception, taken in combination with the fact that the other conditions laid out by advocates of “fair benefits” generally do not impose significant limitations on research, means that the fair benefits approach boils down to a question of what developing countries are willing to accept. Given that there are many developing countries and that outsourced drug trials offer access to medical care often otherwise unavailable to the populace of these countries, Alex London and Kevin Zollman argue, the “fair benefits approach” quickly

⁶⁴ For one, there is the issue of scope: contrary to the assertions of the proponents of the fair benefits approach, major concerns about exploitation are not limited to LMIC contexts. As this issue is a problem shared by both the reasonable availability and fair benefits approaches, it will be taken up separately in the following subsection.

⁶⁵ See Nozick (1974).

becomes a race to the bottom: whichever community will accept the smallest share of benefits will “win” the privilege of hosting the research in question.⁶⁶ To demonstrate this implication of the fair benefits approach, they attempt to model research benefit negotiations along the lines of an auction, with different prospective host communities “bidding” on the privilege of hosting a study.⁶⁷ The reasoning behind this approach is that “auction-like structures do an excellent job of realizing the features of ideal markets... that are central to the fair benefits approach,”⁶⁸ such as all parties having full information, and the absence of force, fraud and deception. Under auction-like conditions, they conclude, benefits to participants are unlikely to reflect either the burdens and risks that participants bear or the level of benefits to others. The reason for this is that “auctions—and markets in general—are designed to harness the power of *competition*, not collaboration.”⁶⁹ London and Zollman’s critique of the fair benefits approach is so devastating that even Reidar Lie, one of the co-authors of the approach, admits that the critique “makes it clear that there is something fundamentally wrong with the fair benefits approach.”⁷⁰

⁶⁶ London & Zollman (2010), p. 41.

⁶⁷ In fact it is more similar to a tender process, where the lowest bid wins the contract, but they are conceptually analogous so this is not problematic for their analysis.

⁶⁸ Ibid., p. 40

⁶⁹ Ibid., p. 43. (Emphasis in original).

⁷⁰ Lie (2010), p. 3. Interestingly, Lie seems to draw the conclusion that ethical review should not concern itself at all with exploitation of participants, but rather with ensuring “reasonable use of scarce resources in terms of [a research proposal’s] expected impact on the disease burden, inside the country or outside.” However, this is a complete *non sequitur* from London and Zollman’s arguments.

2.2.3 The Scope Problem

One problem, which pertains equally to both the reasonable availability and fair benefits approaches, is the identification of exploitation as a concern specific to research conducted in LMICs. As the proponents of the latter approach put it,

“The potential for clinical research to exploit populations is not a major concern in developed countries since there are processes, albeit haphazard and imperfect, for ensuring that interventions proven effective are introduced into the health-care system and benefit the general population.”⁷¹

Similarly, although the CIOMS guidelines are somewhat ambiguous in terms of referring to reasonable availability as a requirement for research in “a population or community with limited resources,”⁷² the commentary on the guidelines makes clear that the discussion is about the potential for exploitation in international research conducted in LMICs. However, there is often potential for exploitation in research conducted in HIC settings as well. For instance, in the USA at least, there are a significant number of professional “guinea pigs”, people whose primary source of income is the financial inducement offered for participation in early-phase clinical trials as a “healthy volunteer.”⁷³ Clinical trials in HICs may also raise exploitation concerns when they recruit participants who are uninsured,⁷⁴ economically disadvantaged,⁷⁵ or lack reliable access to the regular healthcare system for other reasons such as immigration status or residence in a remote community.

The potential for exploitation of healthy subjects or “guinea pigs” rests on the fact that by definition, there is no prospect of medical benefit for these participants. If their participation was

⁷¹ Participants (2002), p. 2133.

⁷² CIOMS (2002).

⁷³ Elliot (2008), p. 36.

⁷⁴ See Pace, Miller & Danis (2003).

⁷⁵ See Denny & Grady (2007).

motivated by altruism, it could be argued that they need not benefit from their participation at all; however, this notion of altruistic healthy subjects turns out to be largely fanciful. As Trudo Lemmens and Carl Elliot note, “the relation between the CRO and [healthy] subjects is based on commercial interests, and this is clear from the outset. The core of the relationship is the payment of money in exchange for services.”⁷⁶ Since the money offered to healthy subjects is the only benefit to them, the amount of money being offered becomes centrally relevant to ensuring that they are not exploited (at least according to the same principles that drive the fair benefits approach to avoiding exploitation in international research.) Because of regulations intended to prevent “undue inducement”, the amounts offered to these participants are kept artificially low, which also serves to ensure that the inducement is enticing primarily to poorer people. Elliot clearly describes how these factors lead to a situation ripe with potential for exploitation:

“Guinea pigs are paid to test drugs, but everyone pretends that guinea-pigging is not really a job. I.R.B.s allow sponsors to pay guinea pigs, but, consistent with F.D.A. guidelines, insist on their keeping the amount low. Sponsors refer to the money as ‘compensation’ rather than as ‘wages,’ but guinea pigs must pay taxes, and they are given no retirement benefits, disability insurance, workmen’s compensation, or overtime pay. And, because so many guinea pigs are uninsured, they are testing the safety of drugs that they will probably not be able to afford once the drugs have been approved. ‘I’m not going to get the benefit of the health care that is developed by this research,’ [professional guinea pig Bob] Helms says, ‘because I am not in the economic class to get health insurance.’”⁷⁷

Hence, the example of professional “guinea pigs” serves to highlight one way in which exploitation of clinical trial participants is a relevant concern for research conducted in those HICs that have multi-tiered health care systems.

⁷⁶ Lemmens & Elliot (1999), p. 15.

⁷⁷ Elliot (2008), p. 36.

Similarly, concerns about distribution of the benefits of research have been raised with regards to clinical trial participation by economically disadvantaged or medically uninsured⁷⁸ people within HICs. The economically disadvantaged, it could be argued, may be particularly susceptible to exploitation by trials offering unfair levels of benefits: “because of limited resources and fewer options for meeting health and financial needs, [the economically disadvantaged] may be more likely to enrol in research with exploitative benefit levels.”⁷⁹ A study offering minimal benefits to participants might also be more likely to enrol medically uninsured participants. Extending the logic of the reasonable availability approach to avoiding the exploitation of uninsured HIC citizens, “it might be argued that the uninsured should be excluded if they will not have access to research products, when proven effective, after the trial.”⁸⁰

Many of the same concerns about the distribution of burdens and benefits from research that highlight the potential for exploitation of participants in LMICs are also applicable in HIC research, notably when it involves healthy participants, medically uninsured individuals, or people who are economically disadvantaged. These concerns are magnified by the significant overlap in membership between these three groups. While the benefits of a successful trial in an HIC might reach the general population reasonably well, this is not sufficient to rule out the possibility of exploitation of the individual participants in the study. As the proponents of the fair

⁷⁸ Naturally, this concern is most prominent in the USA, since all other HICs provide universal health care for their citizens. However, not all HICs provide universal insurance coverage of prescription drug costs—Canada, for instance, does not—which means that people of limited economic means who are without drug insurance may not be able to afford new drugs, even if they have participated in the research which led to a drug’s approval. Hence while it is more pronounced there, the concern is not limited to the USA.

⁷⁹ Denny & Grady (2007), p. 384.

⁸⁰ Pace, Miller & Danis (2003), p. S122.

benefits approach put it, with regards to avoiding exploitation in clinical research, “the important question is how much *the participants* will benefit.”⁸¹

2.3 So What *Is* Exploitation?

What conclusions regarding the problem of exploitation in clinical trials on human subjects can be drawn from the history of this period? There seems to be a degree of consensus in the literature that avoiding exploitation is relevant and important to determinations about the ethical standing of particular studies, but there is extensive disagreement about what that actually entails. At least four different types of claims about exploitation have been put forward in this literature, connecting exploitation to standards of care, post-trial availability of tested interventions, benefits to participants, and benefits to host communities.

The first type of exploitation claim concerns permissible study design, such as the use of local (typically economic) conditions to justify using a lower standard of care (typically placebo) for participants in the control arm than what is currently known to be the best treatment. This type of exploitation claim is exemplified by Lurie and Wolfe’s assertion that LMIC residents “must be protected from potential *exploitation* in research. Otherwise, the abominable state of health care in these countries can be used to justify studies that could never pass ethical muster in the sponsoring country.”⁸² Implicit in study-design exploitation claims is a notion of exploitation as taking advantage of another’s unjust or desperate situation.

⁸¹ Participants (2004), p. 22 (emphasis added).

⁸² Lurie & Wolfe (1997), p. 855 (emphasis added). Similar exploitation claims are also made by, e.g., Angell (1997) and Bayer (1998).

The second type of exploitation claim, the availability exploitation claim, involves a failure to ensure provision of successfully tested interventions from the participants or populations on whom these were tested. For example, Annas and Grodin make this type of claim when they argue “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....”⁸³ The notion of exploitation implicit in availability exploitation claims is one where exploitation involves a failure to ensure that the health benefits of medical research accrue to those who assume the health risks.

The third type of exploitation claim concerns the level of benefits to participants, and the fairness or unfairness of that level, based on the overall distribution of burdens and benefits from a study. This type of claim is most often put forward by proponents of the fair benefits approach, and is frequently associated with Alan Wertheimer’s account of exploitation. A typical level-of-benefits exploitation claim can be found in the Participants’ first article describing the fair benefits approach, which notes that LMIC participants

“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*.”⁸⁴

⁸³ Annas & Grodin (1998), p. 561. Emphasis added. This type of claim is also made by Bayer (1998); CIOMS (2002); and even by Participants (2002), as an explanation for why exploitation “is not a major concern in developed countries.”

⁸⁴ Participants (2002), p. 2133. Emphasis added.

The notion of exploitation associated with level-of-benefits exploitation claims is laid out explicitly by the proponents of the fair benefits approach: “A exploits B when B receives an unfair level of benefits as a result of B’s interactions with A.”⁸⁵

Finally, there have also been exploitation claims made about benefits to host communities. Community-benefit exploitation claims allege that research is exploitative when host communities do not receive appropriate benefits, although there is some ambiguity with regards to who is exploited (participants or the community) and there are also differing views about what constitutes “appropriate” benefits (post-trial availability of the tested intervention or merely a fair level of benefits.) For example, the proponents of the fair benefits approach argue that since host communities often contribute to the conduct of research in various ways, such as by providing infrastructure, “to avoid *exploitation*, consideration of the benefits for the larger community may also be required.”⁸⁶ The notion of exploitation implicit in community-benefit claims can be any one of the three previous notions, depending on the theoretical slant of the person making the claim. In this example, exploitation is understood to mean that the distribution of benefits between the community and the researchers/sponsor(s) is unfair; but in other instances of community-benefit exploitation claims, exploitation might refer to taking advantage of others’ desperate or unjust situations,⁸⁷ or again to the failure to provide health benefits to the population asked to bear the health risks of research.⁸⁸

The first order of business, if any progress is to be made in this discussion, will be to provide a theoretical account of the nature of exploitation. That is the task of the following chapter. Once an acceptable account of exploitation is established, it will be possible to

⁸⁵ Participants (2002), p. 2133, citing Wertheimer (1999) *Exploitation*.

⁸⁶ Participants (2004), p. 22.

⁸⁷ See, e.g., Lurie & Wolfe (1997).

⁸⁸ See, e.g., Annas & Grodin (1998).

meaningfully evaluate the different types of exploitation claims that have been made in the literature. Chapter 3 takes up the question of whether or not it constitutes exploitation when local standards of care are used to justify inclusion of a placebo control arm despite the availability (in HICs) of a proven intervention; this chapter also addresses the question of whether assurances of reasonable post-trial availability of tested interventions for trial participants are necessary to avoid exploitation. In the fourth chapter, I will examine the arguments surrounding the connection between exploitation avoidance and benefits to host communities. Finally, chapter five will address the issue of non-health benefits to trial participants, and how these can help prevent exploitation of participants.

Chapter 3

Exploitation Theory

Though its use in the literature on clinical trials is not uncommon¹, the concept of exploitation is much more difficult to pin down than it first appears. As a preliminary, I should point out that I am concerned here with a non-Marxist concept of exploitation; Marxist conceptions of exploitation also exist, but are of little use outside of a Marxist historical-material analysis. The goal of the discourse in the literature I will be engaging with is to provide a liberalism-compatible account of exploitation (i.e. one which does not define wage-labour as inherently exploitative); the Marx scholar will be unsurprised at the difficulty of this undertaking. Obviously there is the distinction between the use of “to exploit” as simply a synonym for “to use”, and the sense of “to exploit” which denotes one’s wrongful use of another; however, this latter sense turns out to be fairly elusive. Examples are easily furnished — the master exploits the slave; the lord exploits the serf; the pusher exploits the user — but it is harder to say exactly what distinguishes these acts as instances of exploitation rather than coercion, or unjust distribution of benefits, or harm, or some combination of other moral wrongs. Despite several areas of general agreement, there is also some divergence amongst non-Marxist theories of exploitation. The primary points of consensus are that exploitation is a feature of interactions (rather than agents or relationships between agents); that exploitation is separable from coercion and from harm; and that exploitation involves one party taking advantage of another. The more contentious questions concern whether exploitation is about fairness between parties or improper use of another party;

¹ For a selection of instances, see Wertheimer (2010), p. 195.

which account of “fairness” or “use” is applicable; and whether background conditions are relevant to determining if an interaction is exploitative.

Three main types of non-Marxist accounts of exploitation predominate in the literature. The most influential (or at least, the most widely-cited) is Alan Wertheimer’s account, which views exploitation as a matter of unfair distribution of the social surplus of an interaction between the parties to the interaction, taken independently of background conditions. There are other accounts, such as Mitra and Biller-Andorno’s, which hold that while exploitation is a matter of unfair distribution of the social surplus of an interaction, background conditions factor importantly into determining what would constitute a fair distribution. Finally, there are accounts such as Ruth Sample’s, which hold that exploitation involves one party using another party as a mere means, rather than being primarily a matter of benefit distribution. Each of these types of accounts of exploitation captures some important aspects of our intuitive notion of exploitation, and each of them claims to provide a complete picture of exploitation, but none of them truly delivers on this claim. Instead, as Jeremy Snyder persuasively argues, each of these accounts picks out a particular *kind* of exploitation. Snyder argues that all three types of accounts are mutually compatible, and that multiple forms of exploitation can also coexist in a single case.

In the present chapter, I will begin by describing some general features of exploitation in all its forms. I will then proceed, following Snyder’s analysis, to describe each of the three types of exploitation, with reference to some prominent accounts of each type, and noting the limitations and problems associated with each type of account. This three-pronged analysis of exploitation will then provide the basis for subsequent chapters to examine how exploitation affects the morality of clinical research on human subjects, as well as what can be done to address exploitation in the context of clinical research on human subjects.

3.1 General Features of Exploitation

Before getting into the specifics of the various types of exploitation, it is worth noting some general features of exploitation that are shared by all three types. These include the fact that exploitation is separable from coercion, that it is separable from harm, and that it involves taking advantage of another. In addition, it will be helpful to make some brief observations about the notion of vulnerability and its connection to the notion of exploitation.

3.1.1 Exploitation Need Not Involve Coercion

Let us begin the discussion of exploitation by noting an important feature: issues of exploitation are independent from issues of consent. This feature may be obscured by the fact that one of the most egregious examples of exploitation is slavery, which is both exploitative and coercive, and also harms the exploited party. However, it is possible to exploit someone with or without their consent, and it is possible to intervene without obtaining consent from the object of one's intervention and yet not exploit them; in other words, exploitation does not necessarily involve coercion.² This can be seen from examination of the case of students paying for the privilege of an unpaid internship.

Many post-secondary students undertake internships during their studies in order to boost their résumés and, hopefully, their career prospects after graduation. It is not uncommon for internships to be unpaid positions, and in some instances, students are actually paying significant

² This is a point of general agreement in the literature; see e.g. Goodin (1988); Wertheimer (2010); Steiner (1984).

amounts of money to placement agencies in exchange for unpaid internship positions.³ There is strong *prima facie* reason to think that these students are being exploited: they are not only providing free labour to profitable businesses; they are also paying another profitable business for the “privilege” of working for free. For the sake of argument, let us assume that in at least some cases, such an arrangement can be exploitative of students. However, there is nothing to suggest that these students are being coerced in any way: there are still many internship positions without placement fees, and internships are not generally mandatory. The students are also not being misled about the fact that they will not be paid for their work; they give their voluntary and informed consent to the transaction. Thus we can see that a transaction can be (*prima facie*) exploitative, and yet not involve coercion.⁴

3.1.2 Exploitation Need Not Involve Harm

Exploitation also does not necessarily involve any harm⁵ to the exploitee, though it is certainly possible for exploitees to be harmed by an exploitative interaction, as in the case of slavery. However, exploitation can occur without harming the exploitee, and an exploitative transaction can even be mutually beneficial. Returning to the previous example of a student paying to get an unpaid internship placement, imagine a case where the student in question (or more likely, her parents) can afford the expense of the placement fee and the lack of offsetting income in the short term. Let us further stipulate that the working conditions are acceptable, and

³ Johnson (2010). See also: Shih (2009); Olen (2013); Patty (2014).

⁴ One potential objection to this example would be the claim that the students who pay for unpaid internship placements do so only because they have no reasonable alternatives. I do not think this objection is plausible, since these placements are optional, and there are alternatives to paying for an unpaid placement.

⁵ Here I am setting aside the question of whether exploitation itself is (or could be) a harm, as different accounts of exploitation could diverge on this issue.

that the work experience, networking opportunities and the added line on her résumé actually do improve her early career prospects, such that her future earnings will be greater than they would have been without the internship, even after factoring in the associated costs of the placement fee and the lost short-term earnings. In this case, it is very difficult to see how the student has been harmed: she is actually better off than she would have been without the internship. Nonetheless, there is still *prima facie* reason to think that the arrangement is exploitative, particularly since other students received similar career benefits from paid internships. As Wertheimer notes, the philosophically interesting cases of exploitation are the ones where the interaction is consensual and mutually beneficial.⁶

3.1.3 Exploitation Necessarily Involves Advantage

Colloquially, to exploit something or someone is to take advantage of that thing or person; the moralized sense of the term is often associated with taking unfair advantage of a person. Accordingly, a key element of exploitation is that an exploitative interaction must promise an advantage for someone other than the exploitee. As Ruth Sample puts it, “exploitation is an action taken not for its own sake, but for the sake of further advantage.”⁷ This advantage typically goes to the exploiter, but need not do so — the slave owner who donates all his profits to charity has still exploited his slaves, even though it is the charity that benefits. Wertheimer plausibly claims that in determining whether an interaction is exploitative, benefits to all parties should be viewed from an *ex ante* perspective.⁸ Thus an interaction can be exploitative if it offers the putative exploiter prospective benefits (either for himself or a third party), even if these never

⁶ Wertheimer (2010), p. 202.

⁷ Sample (2003), p. 14.

⁸ *Ibid.*, p. 203.

eventuate. Conversely if we reject the *ex ante* perspective, then interactions become failed attempts at exploitation if the exploiter's benefits never materialize. Either way, there must be some advantage to an interaction in order for it to count as taking advantage of someone.

3.1.4 Exploitation and Vulnerability

One thing that comes up in every account of exploitation is vulnerability. Wertheimer explicitly rejects it as a criterion of exploitation on the grounds that it is possible to have a fair transaction even if one party is vulnerable. He may have a point here, but in his discussion of an example to demonstrate that B can actually gain more than A and yet still be exploited, he writes that "...on closer inspection, the exploiter's power over the exploitee typically stems precisely from the fact that the exploiter does *not* stand to gain too much and can walk away from the transaction more easily than the exploitee."⁹ This points to the fact that vulnerability of the exploitee (or, conversely, bargaining power of the exploiter) is at least suggestive of the potential for exploitation. For Agomoni Ganguli Mitra and Nikola Biller-Andorno (among others), vulnerability is central to exploitation, as we shall see below. However, I will be bracketing the debate about the necessity of vulnerability in cases of exploitation, as it is somewhat moot within the context of clinical research on human subjects, given that the human subjects of research are inherently vulnerable to the researchers.

⁹ Wertheimer (2010), p. 208.

3.2 Types of Exploitation

Having established some of the general features of exploitation, I will now proceed to describe, in turn, each of the three varieties of exploitation identified in Jeremy Snyder's typology: micro fairness exploitation, macro fairness exploitation, and mere use exploitation. These three types of exploitation correspond to the three main camps in the literature, so there is value in describing each of them regardless of the merit of Snyder's claim that they are mutually compatible. If Snyder is right, then a complete account of exploitation must include descriptions of all three types of exploitation. If Snyder is wrong, there are still three main schools of thought on non-Marxist exploitation represented in the literature; absent any consensus on which account of exploitation is the "right" one, it makes sense to cover all the bases. Although I will focus on one exemplar account of each type, I will also cover some general traits, which are common to all accounts of that type. I will also note some advantages, limitations and problems associated with accounts of each type; collectively, I will argue, these serve to bolster Snyder's claim that none of the accounts actually provides a unified theory of exploitation, and that there are therefore multiple forms of exploitation. I will begin by discussing micro fairness exploitation, using Wertheimer's influential outcomes-focused account as an example. Next, I will discuss macro fairness exploitation, using Iris Marion Young's account of structural injustice as a springboard to discuss several other authors' approaches to macro fairness exploitation. Finally, I will discuss mere use exploitation, using the examples of the strictly Kantian account outlined by Andrew Siegel and the more original account provided by Ruth Sample.

3.2.1 Micro Fairness Exploitation

Colloquially, to exploit someone is to take advantage of them, and so we might think that to exploit someone wrongfully is to take wrongful advantage of them. One way to parse this notion of “wrongful advantage” is to think of it in terms of fairness, so that to exploit someone is to take unfair advantage of them. Of course, it remains to be determined what constitutes unfairness. Unfairness can be thought of in terms of unfair outcomes or unfair processes; it can also be thought of within the confines of a particular interaction or as situated in a larger context of background conditions, institutions, and enterprise-specific norms.

The large shadow cast by John Rawls’ theory of justice as fairness will lead many to think of fairness in terms of the distribution of benefits. Hence it is unsurprising that one of the more prevalent approaches to exploitation in the literature is to examine it in transactional terms, with emphasis on the level of benefits to each party (i.e., focused on outcomes rather than process). This approach is given the micro fairness label by Snyder because it explicitly restricts the range of contextual factors to be considered in determining the fairness of outcomes; “external factors such as global economic structures, past injustices against individuals, and the socioeconomic position of various actors will not factor into the determination.”¹⁰ The most prominent champion of this approach is Alan Wertheimer,¹¹ who is by far the most widely cited author on exploitation in the bioethics literature, not least because his account of exploitation is central to the arguments put forth by the proponents of the Fair Benefits Framework.¹² He notes that there are many accounts of exploitation in the literature, but “most—although not all—are

¹⁰ Snyder (2012), p. 253.

¹¹ In particular, see Wertheimer (1999); Wertheimer (2010). For other micro fairness accounts of exploitation, see e.g. Valdman (2008); Zwolinski (2007).

¹² See Participants (2002); Participants (2004).

compatible with the claim that *A exploits B when A takes unfair advantage of B.*¹³ Although this model exploitation claim has a two-person format (as do many of his examples), Wertheimer insists that “A” and “B” could just as easily stand for groups, institutions or organizations as for individuals. ‘Taking unfair advantage’ can then be parsed in one of two ways: as referring to the outcome of the interaction, or as referring to the process by which the outcome is reached. Wertheimer rejects the latter option, instead arguing that a moral defect in the outcome is necessary and sufficient to constitute exploitation.¹⁴ Given this interpretation, there are two components of the outcome: the effect on A and the effect on B. In order for an interaction to count as exploitative on this account, A must extract some benefit from B (whether the benefit is for A or for a third party); however, “benefit” could be very loosely interpreted. A transaction can be exploitive if B is harmed or unaffected by it while A benefits, but Wertheimer argues that it can also be exploitative even in some cases where B benefits – namely, where the division of benefits between A and B is unfair. Importantly, Wertheimer argues, we should view the benefit (or lack thereof) to both parties from an *ex ante* perspective, meaning that expected benefits are what matter, rather than actual benefits. In the context of clinical trials, this will prove to be an essential point as it allows for his theory to deal with unsuccessful trials, and conveniently mirrors the vantage point available to IRBs when they review proposed studies.

The crux of Wertheimer’s account, then, must lie in his account of fairness. He himself admits that “we need an account of a fair transaction” in order to make sense of exploitation claims, but also admits, “I know of no non-problematic accounts of fair transactions, including one I have defended elsewhere.”¹⁵ The account he has defended in the past appeals to a normative

¹³ Wertheimer (2010), p. 198.

¹⁴ *Ibid.*, p. 202.

¹⁵ *Ibid.*, p. 206.

standard for benefit distribution based on a hypothetical (ideal) market. On this account, A exploits B when A's expected gain from a transaction is greater than what A could expect from the transaction if it were to take place under ideal market conditions. To illustrate, consider the following example (similar in style to Wertheimer's examples, but of my own invention):

Long Weekend Plumbing. It's the middle of a long weekend, and B has a burst pipe in his house. The usual fee for this type of call-out is \$50, plus parts and labour. A, a plumber, happens to know that all the other plumbers in town are either fully booked or on vacation this weekend, so she offers to come fix B's pipes for \$200 plus parts and labour; B accepts.

In this example, according to the original version of Wertheimer's account, A exploits B because she receives an excessive level of benefit relative to what she would have received under ideal market conditions. (On Wertheimer's revised account, he can only say that A exploits B because she receives an excessive level of benefit relative to what would be fair, but cannot specify what would constitute a fair level of benefits.) This is true even though B gives fully informed and rational consent, B benefits rather than being harmed, and arguably B actually benefits more than A does (by having his plumbing fixed before it causes extensive property damage, B's gain relative to the case where there is no transaction is much greater than A's gain relative to the case where there is no transaction.)

Wertheimer's account also draws a distinction between the "ethics of interaction" and the "ethics of intervention".¹⁶ The ethics of interaction are the norms governing a particular transaction (for example), such as the norm that exploitation is wrong. The ethics of intervention refers to the justification he feels must be given in order to intervene in a mutually beneficial interaction between two parties. Effectively, this distinction allows Wertheimer to argue that

¹⁶ Ibid., p. 197.

exploitation is wrong, but that we ought not to intervene in cases of mutually beneficial and consensual exploitation. He does so in arguing for what he calls the Permitted Exploitation Principle (PEP): “PEP claims that it is wrong to prevent Pareto superior or win-win transactions on the grounds that the terms of such transactions are unfair.”¹⁷ According to Wertheimer, this principle applies when six conditions obtain: there is no moral obligation for A to transact with B; A proposes to transact with B on unfair terms; though the transaction is unfair, both A and B stand to benefit (*ex ante*); the transaction will not harm other persons; B gives voluntary, informed, rational consent to the transaction – and we can reliably determine that this is the case; and if an unfair transaction is not allowed, A will not transact with B on fair terms.

Wertheimer’s account has earned its popularity, at least in part, due to its clarity, concision and ontological frugality. Once an account of fairness is agreed upon, it becomes an almost trivial matter to determine whether or not party A has exploited party B in a given instance, by reference to the expected or proposed distribution of benefits and comparison to the ideal (fair) distribution of benefits. Wertheimer’s account has no need to examine power structures, background conditions, or the internal dispositions of either party. On this view, an interaction is either fair (and hence not exploitative) or not (and hence exploitative), and this can be determined *ex ante* by looking at the expected benefits and burdens for each party. The implications of Wertheimer’s account in particular are somewhat ambiguous, as he argues that we should presume against interfering with mutually beneficial interactions even if they are exploitative. However, should we find grounds to interfere in a particular case (or in general), the remedy to micro fairness exploitation is simply to alter the distribution of benefits and burdens

¹⁷ Ibid., p. 219.

until it is fair, such as by increasing the benefits to the potentially-exploited party. This is what was envisioned by proponents of the Fair Benefits framework.

There are, by design, limitations to a micro fairness account of exploitation. Micro fairness exploitation excludes factors such as background conditions, enterprise-specific norms, and power structures from the analysis. This makes micro fairness exploitation easier to describe and identify, but it also makes it an incomplete description of exploitation. The most glaring problem with Wertheimer's account is that it does depend entirely on an account of fairness in transactions, yet even he admits that no satisfactory account has yet been given. His previously preferred account of fairness is seriously flawed, as it offers no justification for choosing any particular set of hypothetical market conditions as representative of normative fairness. Indeed, any proposed market standard of fairness essentially collapses into saying that fairness is just whatever people will voluntarily accept; but this runs counter to Wertheimer's own repeated assertions that it is possible for an agent to give fully voluntary and rational consent to an unfair transaction. This is not to say that Wertheimer's account is without merit, but rather that any attempts to apply his account to particular cases will have to be somewhat imprecise. Arguably, the minimal fairness threshold of the hypothetical market standard provides some guidance in that any transaction that falls short of fairness on this standard would very likely be unfair according to whatever standard of fairness should eventually be agreed upon. Beyond that, however, one could only generalize that the greater the benefits of a transaction to B (the potentially exploited party), the less likely it will be that A is exploiting B in that transaction.

3.2.2 Macro Fairness Exploitation

While micro fairness accounts of exploitation specifically exclude consideration of background conditions, consideration of such conditions is central to macro fairness accounts of exploitation. This approach is embraced in various forms by a number of writers, such as Agomoni Ganguli Mitra and Nikola Biller-Andorno, Thomas Pogge, and Iris Marion Young. Macro fairness accounts of exploitation recognize that “structural injustice can disadvantage some parties within a transaction.”¹⁸ In other words, background conditions can affect the (macro) fairness of a transaction, and thereby whether or not it is (macro) exploitative. The practical implications of macro fairness accounts of exploitation vary, ranging from a political responsibility to help pursue reforms of structural injustices to an ethical responsibility to restrict the kinds of terms of interaction one offers to victims of structural injustices. In this section, I will begin by describing what is generally meant by “background conditions” and “structural injustice” in the context of macro fairness accounts of exploitation. Next, I will describe Young’s influential and compelling argument that structural injustice has implications for fairness, as well as her account of what form those implications take. I will then summarize some of Mitra’s work that builds on Young’s analysis, as well as an argument from Pogge, to illustrate some of the different notions regarding the implications of structural injustice for the fairness of particular transactions. Finally, I will discuss some of the advantages, limitations, and problems associated with macro fairness accounts of exploitation.

According to Young, social structures are the convergence of

“institutional rules and interactive routines, mobilization of resources, as well as physical structures... [that] constitute the

¹⁸ Snyder (2010b), p. 191.

historical givens in relation to which individuals act, and which are relatively stable over time.”¹⁹

These social structures are the background conditions for any interaction (and indeed any action at all), and as such they provide options to actors. Borrowing a metaphor from Jeffrey Reiman, Young describes social structures as “‘channels’ that both enable action and constrain it.”²⁰ In the present age of globalization, these social structures are global rather than national in scope (though the effects of these structures can vary widely between nations). As Charles Beitz argues, “there exists an international *society* even in the absence of a comprehensive political constitution to regulate it.”²¹ Young claims that social connection is ontologically and morally prior to political institutions, and that the “moral status of political institutions arises from the obligations of justice generated by social connection: such institutions are instruments through which these obligations can be discharged.”²² It follows from this that obligations of justice obtain between sponsors/researchers and subjects in cases of offshored clinical research: the fact of their interaction constitutes a social connection between them, which generates the obligations of justice. The structural injustices suffered by the citizens of a host community become the (partial) responsibility of the research sponsor by the fact of the sponsor’s social connection with the host community. Onora O’Neill gives a different argument that can be used to support the same conclusion; according to her, one’s moral obligations extend to everyone whom one assumes in conducting one’s activity. Because the sponsor’s actions assume the participants and the host

¹⁹ Young (2006), p. 112.

²⁰ *Ibid.*, p. 112.

²¹ *Ibid.*, p. 105.

²² *Ibid.*, p. 105.

community, according to O’Neill, the sponsor has made “practical moral commitments to them” by virtue of the sponsor’s actions.²³

Structural injustice occurs when there are different and unequal “channels” for different groups of people. As Young puts it, “structural injustice exists when social processes put large categories of persons under a systematic threat of domination or deprivation of the means to develop and exercise their capacities, at the same time as these processes enable others to dominate or have a wide range of opportunities for developing and exercising their capacities.”²⁴ What marks an injustice as structural is that it is not (necessarily) the result of wrongful actions on the part of individuals, or outright discrimination by institutions. Structural injustice is the net product of the actions taken by various institutions and individuals to advance their own interests and pursue their own goals, as directed and constrained by the prevailing rules and norms. Thus, structural injustices need not be intentional on the part of any particular individual or institution (although they *can* be intentional, as in the 20th century case of racial segregation and Jim Crow laws in the American South). Examples of structural injustice include “trade laws that disadvantage citizens of LMICs and histories of colonialism.”²⁵ It is also worth noting that structures are not unjust simply by dint of constraining actors, as all structures inherently constrain and enable actions. What matters is the way structures constrain and enable, and how this affects the opportunities of individuals; unjust structures do this in a way that limits the opportunities of certain groups and expands the opportunities of others.

Global structural injustice, then, is clearly undesirable. But whose responsibility is it to deal with global structural injustice? In connection with this question, Snyder brings up an

²³ Ibid., p. 106.

²⁴ Ibid., p. 114.

²⁵ Snyder (2010b), p. 191.

argument made by Wertheimer, to the effect that individuals cannot be required to singlehandedly rectify the effects of structural injustice in each of their interactions. Wertheimer uses this argument to bolster his claim that exploitation is best thought of as an exclusively micro level concern. The aim of a macro fairness account of exploitation, according to Snyder, is to

“Give voice to the intuition that it can be morally problematic to take advantage of systemic injustices without requiring that each individual be responsible for repairing the effects [of] these injustices when interacting with disadvantaged populations.”²⁶

One way to do this is to advance an alternative model of responsibility, such as the one put forward by Young, which provides a middle ground between ignoring structural injustice and making individuals singly accountable for it.

According to Young, responsibility for structural injustice is collectively shared (to varying degrees) by all who are socially connected to each other. Everyone who participates in the system is responsible for the social structures, says Young, “in the sense that they are part of the process that causes them.”²⁷ Yet in most instances, no individual can really be said to be responsible in the sense of being to blame for a structural injustice. This blame-worthiness sense of responsibility is associated with the traditional model of responsibility, which Young refers to as the liability model. The liability model of responsibility focuses on harms resulting from an individual or institution’s deviation from societal rules and norms. In order to address structural injustices (which are the result of individuals and institutions following, rather than deviating from, social rules and norms), Young proposes the social connection model of responsibility. This model is concerned with the background conditions that the liability model assumes as normal. According to the social connection model, “all agents who contribute by their actions to the

²⁶ Snyder (2010a), p. 41.

²⁷ Young (2006), p. 114.

structural processes that produce injustice have responsibilities to work to remedy these injustices.”²⁸ For Young, those responsibilities are primarily collective and political, such that agents are obliged to work towards collective actions that will reform social structures in ways that make them more just. Because structural injustice is ongoing and responsibility for it is collective, Young’s model proposes to focus on promoting processes of reformative collective action. However, she does claim that responsibility for structural injustice also admits of degrees, with those who have more power to influence the processes resulting in unjust outcomes having a greater degree of responsibility to push for reform.²⁹

While Young focuses on promoting social change through collective action, Agomoni Ganguli Mitra and Nikola Biller-Andorno adopt Young’s account of structural injustice to help explain the moral wrong of (macro fairness) exploitation. In so doing, they develop a thorough and convincing account of macro fairness exploitation in a bioethical context, specifically addressing exploitation in international clinical research. According to Mitra, “the concern regarding exploitation stems primarily from the fact that people take advantage of gross injustices to others.”³⁰ In an article co-written by Mitra and Biller-Andorno, they argue that exploitation is best understood as taking advantage of vulnerabilities, with the understanding that vulnerabilities should be viewed within a broader context of structural injustices.³¹ While they discuss vulnerability at length, endorsing the account of vulnerability put forward by Samia Hurst,³² for present purposes I will focus on their application of Young’s account of structural injustice to a macro fairness understanding of exploitation. As alluded to in an earlier footnote, there is much

²⁸ Ibid., p. 102.

²⁹ Ibid., p. 125.

³⁰ Mitra (2013), p. 113.

³¹ Mitra & Biller-Andorno (2013), p. 92.

³² Hurst (2008).

dispute surrounding the relationship between vulnerability and exploitation. One problem with tying the two concepts together (particularly on Hurst's account of vulnerability) is the potential for circularity. On Hurst's view, vulnerability is an increased susceptibility to some specified wrong, such as exploitation; but if exploitation is defined as taking advantage of vulnerabilities, then the account becomes circular. (Exploitation is taking advantage of someone's increased susceptibility to being exploited.) It may well be possible to alter one or both definitions in a way that averts this circularity, but for present purposes this is not necessary; the definition of exploitation in terms of vulnerability is somewhat superfluous to Mitra and Biller-Andorno's argument. As they say themselves, "it is the presence of structural injustices that makes the vulnerabilities embedded within them, and arising from them, morally significant in our ethical assessment."³³ Little is lost, therefore, if we redefine exploitation as taking advantage of another's desperate situation and inferior bargaining position, when these result from structural injustices.

This focus on background conditions in determining the fairness of the terms of a transaction is necessary, according to Mitra and Biller-Andorno, because injustice in the background conditions significantly influences the kinds of terms each party has reason to accept. They argue that since micro fairness accounts of exploitation ignore asymmetries in the bargaining powers of the parties to a transaction, these accounts seem inadequate in cases where these asymmetries are both pronounced and a product of structural injustice. A comprehensive account of fairness-based exploitation ought to "take into account the macro-considerations, that is, the structural injustices that push individuals to make certain choices, even when they are fully aware of, and consent to, others taking advantage of their unjust situation."³⁴ Returning to the "channel" metaphor, structural injustices can enable some agents to exploit others, while

³³ Mitra & Biller-Andorno (2013), p. 98.

³⁴ Ibid., p. 98.

constraining those others from turning down exploitative offers. In another article, Mitra also argues that structural injustices will affect the degree to which a transaction is exploitative, as

“unfair circumstances, instances of dire poverty or medical need play a crucial role in defining what counts as beneficial to B and therefore will immensely influence how readily B agrees to the exchange, especially since A can walk away and transact on more agreeable terms elsewhere.”³⁵

In terms of practical implications, there are at least two significant differences between micro fairness accounts of exploitation and Mitra and Biller-Andorno’s macro fairness account. Firstly, our moral judgments of the exploiter may actually be softened somewhat, as the macro fairness perspective suggests that everyone has some degree of responsibility for the structural injustices that enable the exploitative transaction. Secondly, they note that the strength of both negative and positive obligations towards the victims of structural injustice “will depend on the role, power, and privilege of the various agents involved.”³⁶ In the case of an offshored and outsourced clinical drug trial, for instance, it may be that the relative power and privilege of the executives of the CRO and the sponsoring pharmaceutical company mean that they have stronger moral obligations to the participants than the individual researchers who actually interact directly with the participants.

A different spin on macro fairness exploitation can be found in a paper by Thomas Pogge — or at least, in Jeremy Snyder’s interpretation of his arguments. Pogge’s account has strong parallels with the account developed by Mitra and Biller-Andorno, but unlike their account, Pogge’s does not rest on the foundation of Young’s work. His account is also written specifically in response to questions about exploitation of clinical trial participants in offshored commercial

³⁵ Mitra (2013), p. 113.

³⁶ Mitra & Biller-Andorno (2013), p. 100.

research, making it ideal for the purposes of the present discussion. In “Testing Our Drugs on the Poor Abroad,” Pogge argues that it is morally problematic to take advantage of someone’s unfortunate predicament, particularly when that predicament arises in part from social injustice, and even more so when the agent taking advantage is at least partly responsible for creating or perpetuating that social injustice. (Snyder’s interpretation of Pogge is essentially to recast this taking advantage in terms of exploitation; in the original paper, Pogge notes that the moral complaint he is concerned with “could be discussed in terms of exploitation,”³⁷ although he avoids using that particular term.) Pogge focuses on cases where agents take advantage of someone’s bad situation, which focus is informed by the use of the example case of Discovery Labs’ proposed placebo-controlled trial of their synthetic surfactant treatment for infant respiratory distress syndrome, Surfaxin. As discussed in chapter 1, Discovery Labs, a for-profit American pharmaceutical company, proposed that the placebo-controlled study be conducted in Bolivia because there was already proven treatment (i.e. animal-derived surfactant therapy) available in the US, which meant that the trial could not be conducted there with a placebo control. The company wanted to use a placebo-control, rather than active-control, design because they were not confident that they could demonstrate non-inferiority to the existing gold-standard treatment.³⁸ Since there were already proven treatments for respiratory distress syndrome available in HICs at the time of the proposal, the sponsor was proposing to take advantage of the Bolivian parents’ lack of access to such treatments in order to use a placebo control rather than an active control design. With regards to the origin of a person’s predicament, Pogge claims that it may be less wrong to take advantage of such a predicament if the person in question is partly or wholly at fault for the predicament, as they might be if it was a result of, e.g., their own

³⁷ Pogge (2008), p. 106.

³⁸ Hawkins & Emanuel (2008b), p. 60.

recklessness. Conversely, “such conduct may be rendered *more* wrong by the fact that the predicament is partly due to wrongful conduct on the part of people other than the victim.”³⁹ Even if one is not responsible for the social injustice that causes another’s bad situation, by transacting with them for profit on terms that are only rendered acceptable by their bad situation, one is thereby taking advantage of the social injustice, and becomes complicit in it. To avoid taking advantage of social injustice, says Pogge, one must treat the victims of the injustice “as [one] would have to treat them if this injustice did not exist.”⁴⁰ In other words, when proposing to transact with victims of injustice, there is an obligation not to offer them terms that are only acceptable because of the victims’ bad situation arising from the injustice. Failure to heed this obligation constitutes macro fairness exploitation.

In summary, then, macro fairness exploitation is characterized by a focus on the fairness of background conditions, whether conceived as structural injustice (as in the accounts of Young, and of Mitra and Biller-Andorno) or as social injustice (as in Pogge’s account). Such accounts describe how these background conditions create morally arbitrary asymmetries in agents’ bargaining powers, and how more powerful agents can exploit less powerful agents by using their asymmetrical bargaining power to secure an unfair distribution of the social surplus of the interaction. The practical implications of macro fairness accounts of exploitation vary. On the more expansive end of the spectrum, as Snyder writes, “a macro fairness account of exploitation will include background, structural inequalities and injustices when determining whether the distribution of resources resulting from an interaction is fair.”⁴¹ Pogge’s argument falls on this side of the spectrum, with its conclusion that powerful agents must offer victims of injustice

³⁹ Pogge (2008), p. 112. Notice that Pogge does not draw on Young’s notion of structural injustice, instead limiting his notion of injustice to situations resulting from wrongful actions.

⁴⁰ Ibid., p. 113.

⁴¹ Snyder (2012), p. 254.

terms of interaction that would be acceptable to them if there were no injustice. Interestingly, this is a different and stronger claim than what is made by Young's social connection model of responsibility; for Young, the emphasis is less on the terms of a particular transaction and more on the political responsibility of powerful agents to help change social structures in a way that makes them more just. In the realm of offshored clinical trials, for instance, this might involve industry sponsors pushing for (or at least cooperating with) efforts to modify TRIPS in ways that allow for expanded use of mandatory licensing or other means to reduce drug prices and increase (affordable) access to medicines for people in LMICs.

3.2.3 Mere Use Exploitation

The other main camp of exploitation accounts — and the third category of exploitation in Snyder's typology — conceives of exploitation in terms of wrongful use of another rational agent, rather than unfairness of outcomes. The name Snyder gives to this type of exploitation suggests its roots in Kantian ethics, although mere use accounts of exploitation vary in the strictness of their fidelity to Immanuel Kant's philosophy. In this section, I will begin by describing some general features of mere use accounts of exploitation. I will proceed to outline the strictly Kantian account of exploitation provided by Andrew Siegel, then do the same for Ruth Sample's account, which is also inspired by Kant's thought but is less strictly derived from it. All strictly Kantian accounts of exploitation should be essentially similar, but Siegel's account is particularly pertinent as it is specifically aimed at exploitation in the context of clinical research in LMICs. Sample's account, while not particularly widely cited, is perhaps the most thoroughly developed alternative to Wertheimer's account of exploitation in the literature.

Predictably, Kantian accounts of a moral wrong tend to explicate that wrong by demonstrating how it falls afoul of the Categorical Imperative. On a mere use account, exploitation is not about fairness at all. Instead, exploitation is a matter of using others as mere means, rather than also as ends-in-themselves, thereby violating the formula of humanity version of the Categorical Imperative.⁴² Questions about the fairness of a transaction's expected distribution of goods are put aside in favour of questions about transagents' treatment of each other. Mere use accounts of exploitation associate "its wrongness with a failure to treat others with respect or with a loss of dignity for the exploitee."⁴³ According to Snyder, the issue is not that the level of benefits to exploitees is unfair, but that it constitutes a failure on the part of the exploiter to respect the exploitee as a rational agent. Mere use exploitation can occur in conjunction with micro and/or macro unfairness, or independently of any unfairness. Much like macro unfairness accounts of exploitation, mere use accounts of exploitation are compatible with exploitation being widespread or even systemic.

Central to any mere use account of exploitation is the notion that treating others as ends-in-themselves, rather than as mere means, can involve positive duties of beneficence as well as negative duties such as non-deception or non-coercion. In the context of offshored clinical research, "the concern is that relatively well-off researchers and sponsors fail to discharge a specified duty of beneficence to their research subjects."⁴⁴ The source of the positive duty of beneficence is the fragility of rational agency as embodied in human persons; humans have certain physical and psychological needs, and their continued ability to reason and act autonomously depends on the fulfilment of these needs. Since the fulfilment of these needs is

⁴² "Act in such a way that you treat humanity, whether in your own person or in the person of another, always at the same time as an end and never simply as a means." Kant (1993), p. 36.

⁴³ Snyder (2010b), p. 196.

⁴⁴ Snyder (2012), p. 254.

contingent on external forces, it would be inconsistent for a rational agent to will the universalization of a maxim of non-beneficence, and hence there must be a duty of beneficence. Equivalently, at least according to Kant, adopting a maxim of non-beneficence would lead to acting in ways that fail to treat others as ends in themselves.

Rather than defining exploitation in terms of unfairness, mere use accounts of exploitation connect the duty not to exploit others to the general imperfect duty of beneficence. The nature and extent of the duty of beneficence is open to some interpretation, as will become evident below; differences in interpretation of this duty are the main source of the differences between Siegel's and Sample's accounts. The major difference between the two accounts is that Sample argues that the duty of beneficence is specified to particular others in certain cases, while it remains unspecified on Siegel's account. For this reason, Sample's account is more compatible with the pre-theoretic intuition that exploitation of a particular individual cannot be avoided or offset by beneficence to other individuals.

Another significant difference between Sample's account and Siegel's account is their handling of what the latter calls indifference and the former refers to as neglect. For Siegel, indifference is a more serious moral wrong than exploitation: everyone with means who has not helped to eradicate global poverty is implicated in indifference, and exploiters are guilty of both indifference and the lesser charge of exploitation. Sample, on the other hand, says that we often think exploitation is worse than neglect, even when the consequences of neglect are worse. Her account reflects this intuition by affirming that neglect can be the product of ignorance or inattention and need not involve any malice or forethought, while exploitation involves confronting another's desperate situation and deciding to turn it to one's own advantage.

3.2.4 Siegel's Mere Use Account

Andrew Siegel offers a Kantian account of exploitation which is in line with a very strict adherence to Kant's philosophy and a narrow interpretation of the requirements thereof.

Following some preliminary explanation of Kantian moral theory, Siegel provides a formal definition of exploitation, according to his interpretation of Kant:

“A exploits B when A secures a benefit from B by acting toward B on a maxim that (1) subverts the conditions of B's rational agency, (2) fails to acknowledge needs that are essential to B qua rational agent, or (3) demeans or degrades B despite the fact that preservation of B's agency is not at issue.”⁴⁵

Condition (1) mainly pertains to issues such as coercion and deception, which are of less interest in the present discussion. With regards to condition (3), Siegel simply notes that such an act “treats a person *as if* she is of lower rank than other persons... [a degrading act] displays a lack of respect for the equal moral worth of the other.”⁴⁶ Condition (2) is the primary focus for Siegel, as he claims that most exploitation in the context of international clinical research involves violation of the duty of beneficence.

There are two major questions surrounding the requirements of the duty of beneficence. Which range of needs are agents obliged to help satisfy, and how much latitude do agents have in determining when to help those in such need? While there is room for disagreement in interpreting Kant on these points, Siegel suggests that even on a narrow reading, relations between the world's well off and the global poor are morally problematic; it is basically

⁴⁵ Siegel (2008), p. 181.

⁴⁶ *Ibid.*, p. 185.

impossible to argue that the well off (collectively, at least) are discharging their duties of beneficence.⁴⁷

With regards to the range of needs of others that beneficence requires us to help satisfy, a narrow interpretation of Kant would include “those needs that are crucial to maintaining our status as rational agents.”⁴⁸ Under this narrow reading, the unmet basic needs of the global poor — such as reliable access to food, clean drinking water, shelter, and basic medical care — are among the needs that beneficence obliges agents to address. Siegel notes that there may be a plausible case to be made for a broader interpretation of relevant needs to consider with regards to the duty of beneficence, but that even the narrow interpretation will be sufficient to ground a discussion of exploitation in offshored clinical trials. For the purposes of the present discussion, I will refer to whichever needs the duty of beneficence requires agents to help address as essential needs.

With respect to the second question (the degree of moral latitude available to agents), beneficence is an imperfect duty on Kant’s account. This means that agents do have significant latitude to determine how they fulfill their duty of beneficence. As an imperfect duty, beneficence does not imply that agents are obliged to help meet the essential needs of any particular individual; rather, agents have leeway to choose how best to fulfill their duty of beneficence, and this duty is to be balanced against all the other imperfect duties which agents ought to fulfill. Given that there are a number of imperfect duties, and that the global poor number in the many millions, agents are morally permitted to decide to help some at the expense of not helping others. In other words, there is no right to assistance as a corollary to the duty of beneficence. Ordinarily,

⁴⁷ Ibid., p. 188.

⁴⁸ Ibid., p. 188.

then, A taking advantage of B's unfortunate circumstances does not imply that A has gained by violating an obligation to aid B.

The situation is different, according to Siegel, when A is complicit in B's unfortunate circumstances; in such instances, "A wrongs B in gaining from the transaction because the gain trades on a larger moral failing to which A contributes."⁴⁹ This claim should sound familiar, because it is essentially the conclusion of Pogge's argument for a macro fairness account of exploitation. However, it is less than clear that Siegel has provided sufficient grounding for this claim in Kant's theory. Interestingly, on Siegel's account, an agent who discharges her obligations of beneficence elsewhere may *not* commit a wrong by taking advantage of another's bad situation. For example, imagine a case where A is the head of a Canadian charity and B is a recently laid-off Canadian construction worker. A offers B a job building free housing for very poor families in LICs, but will only pay B the prevailing wage for unskilled labour in those countries, and will deduct the cost of B's travel, food, and accommodations from B's wages, meaning that B will be paid almost nothing. If enough people in LICs are helped to satisfy the demands of beneficence on A, then it seems we cannot say that A exploits B on this account. Regardless of such counter-intuitive results in particular cases, Siegel's account is still able to capture some of our intuitions about exploitation. Given the facts about global poverty and global inequality, Siegel argues, "our individual and collective failures to provide aid essential to the eradication of global poverty constitute a violation of the duty of beneficence."⁵⁰

According to Siegel, there are actually two wrongs involved when one party exploits another by violating the duty of beneficence: exploitation and indifference. The exploiter treats the exploitee as a mere means because the exploiter's actions demonstrate indifference toward the

⁴⁹ Ibid., p. 193.

⁵⁰ Ibid., p. 191.

exploitee's essential needs as a rational agent; this is so even when the exploiter fails to secure any advantage from the transaction. This wrong of indifference is committed not just by the exploiter but by all who are in a position to help the exploitee but fail to do so without valid excuse (such as that they were fulfilling their obligations of beneficence elsewhere). In a case of successful exploitation that violates the duty of beneficence, the exploiter's gain constitutes a second wrong in addition to the wrong of indifference: the wrong lies in the exploiter's "gaining from her own failure to fulfill her obligations."⁵¹ Returning to the case of the housing charity boss and the construction worker, there seems to be no room on Siegel's account for claims that A exploits B. A is not demonstrating indifference to anyone's essential needs; she is (permissibly) choosing to address the essential needs of homeless families in LICs rather than the needs of B. A's gain is therefore not the product of her own failure to fulfill her obligations, so A does not exploit B in this sense either. There is one response available to Siegel, which is that A exploits B in such a case by demeaning or degrading B (thus fulfilling condition (3) in Siegel's definition). However, recall that this would mean A was treating B as if he is of lower rank than other persons. Since A is offering to pay B the same as she would offer to pay another worker in the same LIC, it is not clear how she is treating him as if he is of lower rank than other persons. Siegel's interpretation of exploitation does not seem to be able to account for the pre-theoretic intuition that avoiding exploitation necessarily involves ensuring that a transaction sufficiently benefits the other party to that transaction. This is because the duty of beneficence is imperfect and unspecified: it is not owed to any particular individual.

⁵¹ Ibid., p. 192.

3.2.5 Sample's Mere Use Account

Sample's account of exploitation attempts to avoid the pitfalls of an unspecified duty of benevolence. Her account is based on exploitation as degradation, which she describes as a kind of failure of respect for persons that in turn thwarts human flourishing. Exploitation "involves interacting with another being for the sake of advantage in a way that degrades or fails to respect the inherent value in that being."⁵² Sample aims to provide an account of exploitation (and the duty not to exploit others) that can explain why some beneficial interactions are not beneficial enough, while maintaining beneficence as an imperfect duty. Her strategy is to argue that while beneficence is an imperfect duty, in certain instances it becomes a specified duty, meaning that it is owed to particular others — namely, those with whom one is proposing to interact.

Sample's account is grounded in a particular notion of respect for persons, which requires moral agents to constrain their behaviour towards them.⁵³ As a result, she acknowledges, her notion of exploitation will only have resonance for people who recognize an obligation to respect others. Respect, on Sample's account, "is a way of comporting oneself toward others that acknowledges the claims that others make on us."⁵⁴ Respect involves refraining from certain kinds of behaviour, but it does not involve love, identifying another's good with our own, or a certain kind of sentimental disposition. The object of this respect is the inherent value of human beings, and Sample describes several broad categories of ways that an agent can fail to respect the inherent value of human beings, such as by "neglecting what is necessary for their well-

⁵² Sample (2003), p. 57.

⁵³ Sample notes that her account brackets the question of whether non-human animals are persons in the sense of having the kind of inherent value that commands moral respect. For the sake of brevity and simplicity, I also bracket that question throughout the present work.

⁵⁴ *Ibid.*, p. 65.

being/flourishing,” by “taking advantage of an injustice done to [them],”⁵⁵ or by “commodifying... an aspect of that person’s being that ought not be commodified.”⁵⁶

Exploitation, according to Sample, is a “kind of disrespect toward a person in pursuit of our own advantage – the disrespect of merely using another person.”⁵⁷ Mere use, in this context, means refusing to take another person’s genuine interests seriously, which could involve any of the three ways Sample describes to fail to respect the inherent value of human beings. The common thread between the various types of disrespect is this notion of genuine interest or genuine need. The genuine needs of an individual will vary depending on the era, location, and circumstances of the entire community in question, but in general the notion correlates roughly with the notion of essential needs on Siegel’s account. According to Sample, “when we exploit others, we make use of their genuine need for the sake of advantage in ways that fail to respect them.”⁵⁸

In contrast to Siegel, Sample does attempt to directly connect the wrong of exploitation to the particular other being exploited, rather than simply to the general duty of beneficence. In order to make this connection, she draws on Joseph Raz’s account of the duty of respect, which involves (limited) positive engagement when we meet with particular beings of value: “it is a duty to acknowledge, to refrain from harming, and to some degree to preserve what valuable

⁵⁵ This connection between exploitation and background injustice may seem to indicate that Sample’s account is actually a macro fairness account, rather than a mere use account. However, taking advantage of an injustice done to another is simply evidence of a failure of respect for persons on this account. Since the moral wrong is located in the failure of respect for persons, the account is properly thought of as a mere use account of exploitation.

⁵⁶ *Ibid.*, p. 57. I will discuss concerns about commodification in a later chapter, as concern about commodification is used as an objection to monetary compensation for research participation.

⁵⁷ *Ibid.*, p. 70.

⁵⁸ *Ibid.*, p. 75.

things we do encounter.”⁵⁹ With regards to persons, this means when we interact with an individual, we must refrain from harming them, but we may also have to assist them if they have unmet genuine needs. As Sample puts it:

“While we have an obligation to avoid worsening the situation of others in certain ways, we also have an obligation to improve the situation of others in certain ways when we interact with them. For ignoring the needs of others can be just as disrespectful as harming them and can also be exploitative when we profit from the interaction. In both cases we fail to acknowledge the value of our interactors.”⁶⁰

Acknowledging the value of one’s interactors — treating them as ends in themselves — necessarily involves taking seriously their genuine needs, as these are required for living a human life. When one interacts with an individual whose genuine needs are unmet, and one could help to address those needs through the interaction, but one chooses to maximize one’s own profit instead, then one exploits that individual by merely using them.

On Sample’s account, beneficence remains an imperfect duty, and so agents are not automatically obligated to provide for the genuine needs of others. Nonetheless, others’ genuine needs do impose constraints on an agent’s interactions with them, and certain acts of beneficence may be obligatory. “While imperfect duties allow us some discretion in determining whether to act beneficently in a given case,” says Sample, “those situations in which we are confronted by vulnerable others in transactions for advantage could not be [considered], by any reasonable person, *optional* opportunities for beneficent action.”⁶¹ In such cases, the scope of one’s duty of beneficence is specified by the duty of respect, as failure to act beneficently in such an instance

⁵⁹ Ibid., p. 68.

⁶⁰ Ibid., p. 67.

⁶¹ Ibid., p. 71.

would constitute a failure of respect for the inherent value of the particular other with whom one is interacting.

However, beneficence is not always obligatory, and Sample makes the upshot of this quite explicit: “If the only mutually beneficial transaction possible is one in which [their genuine] needs cannot be satisfied, then such interaction is not exploitative.”⁶² It may not be immediately clear that this follows on her account, because even if all possible mutually-beneficial transactions between parties A and B would fail to satisfy B’s genuine needs, there are still several alternatives for A (presuming A is in a better situation than B). Firstly, A could transact with B in a way that only benefits B (i.e. charitably); secondly, A could refrain from transacting with B entirely. Presumably, both of these alternatives are better than the mutually beneficial transaction that does not satisfy B’s genuine needs. The first is supererogatory and the second is, at worst, neglectful (which Sample has already said is not as bad as exploitation, even when it leads to worse outcomes). Given that these alternatives exist (or even in the case where only one of the alternatives exist), why should the mutually beneficial transaction that fails to meet B’s genuine needs not be considered exploitative? The answer, on Sample’s account, is that beneficence is an imperfect duty and exploitation is *only* about failure to respect inherent value – its wrongness is completely separable from outcomes. There is no duty for A to interact with B when there is no benefit to A. If A can interact with B in a way that is mutually beneficial while satisfying B’s genuine needs, then A should interact in this way with B (or refrain from interacting with B, as long as A is discharging the duty of beneficence elsewhere). But if all the possible mutually-beneficial interactions between A and B fail to meet B’s genuine needs, then A

⁶² Ibid., p. 75.

is not “neglecting what is necessary” for B’s well-being by engaging in such an interaction (since none of the relevant alternatives would meet B’s needs.)

3.3 Exploitations

Snyder argues that the three forms of exploitation in his typology are each necessary to a full understanding of exploitation, and that all three accounts are mutually compatible. It would be more accurate to say that a version of each type of account can be given which would be compatible with accounts of the other types, as Snyder himself notes that most accounts in the literature “claim to provide a single, unified account of the moral wrong of exploitation.”⁶³ Regardless of the validity of Snyder’s claim that these three types of accounts of exploitation are all mutually compatible because they describe different forms of exploitation, these three types of accounts correspond to the three main theoretical camps in the non-Marxist exploitation literature. Taken together, these three types of accounts detail three ways that exploitation can occur. However, my approach in the following chapters will be to treat each of the three types of exploitation accounts separately. If the reader agrees with Snyder’s claims, then these can be read as describing the way various factors affect each of the three forms of exploitation; but if the reader rejects Snyder’s claims, then subsequent chapters can be read as simply detailing the implications of each type of account of exploitation, without presumption as to which type of account best captures the phenomenon.

Micro fairness exploitation highlights the unfair distribution of benefits that can arise from one party’s unusual advantage over another in a given interaction. Avoidance of micro

⁶³ Snyder (2012), p. 255.

fairness exploitation in clinical research on human subjects will typically involve ensuring a sufficient level of benefits to trial participants. The concept of macro fairness exploitation shows how background conditions can routinely privilege certain parties and disadvantage other parties, leading to interactions that can exacerbate already-unjust distributions of goods. Avoidance of macro fairness exploitation in the context of clinical research on human subjects could involve such diverse measures as restricting offshoring where treatments are unlikely to become locally available through the routine health care system or working to address the structural factors that cause and sustain the conditions of poverty and lack of access to medical care in LMICs. The concept of mere use exploitation describes how the genuine needs of those with whom one interacts can serve to specify the otherwise unspecified general imperfect duty of beneficence. Avoidance of mere use exploitation in the context of clinical research on human subjects will involve ensuring that trial participants are treated in a manner consistent with respect for the inherent moral value of persons, which may involve addressing participants' unmet essential needs. The common thread between these three types of exploitation, according to Snyder, is that they each identify "distinct kinds of vulnerabilities that generate exploitable bargaining asymmetries."⁶⁴ On Snyder's view, any or all of the three types of exploitation can co-occur in a single case, so it will be necessary to examine any given case through each of the three lenses. Given the lack of consensus in the literature, this three-pronged approach would be recommended by prudence, Snyder's view notwithstanding.

In the following chapters, these accounts of exploitation will be used to address several questions about exploitation in clinical research on human subjects. These questions can be divided into two broad categories: concerns about permissible study designs, and concerns about

⁶⁴ Snyder (2012), p. 256.

the distribution of goods arising from a study. The first category includes questions about standards of care and post-trial access, while the second includes questions about community benefits and compensation for participants. In chapter 4, I will use the three types of accounts of exploitation to address questions about the permissibility of using local standards of care to justify employing placebo controls when proven treatments already exist. I will then use the same accounts to consider whether it is exploitative to recruit participants who will not likely have post-trial access to the tested intervention. In chapter 5, I will shift the focus from study design to distribution of benefits, examining the connection between exploitation(s) and community benefit. Finally, in chapter 6, I will discuss the issue of distribution of financial benefits from commercial clinical trials.

Chapter 4

Exploitation By Design

The literature debate about exploitation in clinical trials on human subjects focuses primarily on offshored trials, and within that context it is generally centered around two issues: the use of placebo controls in an LMIC setting despite the availability of proven treatment in HICs, and the appropriate type and level of benefits to LMIC participants and host communities. Both issues have attracted charges of potential exploitation. In the present chapter, I will begin by addressing the issue of using placebo-controlled trials despite availability of proven treatment in HICs, which has been justified in the past by appeal to a local standard of care. In section 4.1, I will revisit some of the history discussed in Chapter 2 as it relates to the issue. Next, I will analyse exactly what is meant by “standard of care” in these debates, along with the implications of the various interpretations of this term. The remainder of the section will be devoted to a breakdown of how this practice might be evaluated with regards to each of the three types of exploitation discussed in Chapter 3.

The second issue, appropriate types and levels of benefits for participants and host communities, is more complex. I will therefore break it down into three smaller parts. In the second section of this chapter, I will address the first of these, which is the issue of post-trial provision of beneficial interventions to trial participants. Benefits to host communities during and post-trial, and compensation for research participants, will be discussed in Chapters 5 and 6, respectively. With regards to post-trial provision of beneficial interventions to trial participants, I will begin by going over some general considerations about when this would or would not

constitute a benefit. I will then proceed to discuss whether this particular type of benefit is necessary to avoid each of the three types of exploitation.

4.1 Placebo Controls and Exploitation in Offshored Clinical Trials

There has been some debate in the literature¹ about standards of care in trials conducted in LMICs, which has included charges of exploitation. However, making sense of such charges requires some background information about clinical trial design. When investigators wish to test the efficacy of a novel intervention (i.e., one that would be the first of its kind, not simply a new alternative to existing intervention(s)), they cannot simply try it on some participants and observe the results². Such a trial would not be sufficient to demonstrate efficacy, due to problems such as confirmation bias, the placebo effect, and the fact that “many diseases have trajectories that are hard to predict,”³ meaning that improvements in a particular patient’s condition may not necessarily be the result of treatment. Clinical trials are scientific experiments, and so they require controls in order to be sure that the result observed is the effect of the experimental variable. In a clinical trial of a drug, this means that participants will be split into (at least) two groups, called arms. Participant in the active arm(s) will receive the drug(s) being investigated, while participants in the control arm will receive the current standard treatment. If there is no proven treatment currently available, then the participants in the control arm will be given a placebo. In order to minimize statistical “noise” and the potential for introduced bias, participants are

¹ For example, see Lurie & Wolfe (1997).

² Here, and throughout the current chapter, I will primarily be focused on clinical trials of drugs, rather than vaccines, equipment, or diagnostic or surgical techniques. Unless otherwise specified, “clinical trial” is hereinafter used to refer to “clinical drug trial”.

³ Avorn (2005), p. 46.

randomized (assigned to an arm at random), and where possible the trial is conducted double-blind (meaning that for the duration of the experiment, neither the participant nor the investigator knows to which arm the participant has been assigned.)

“Giving all subjects [in the control arm of a randomized controlled study] some kind of inert pill or injection can control for the placebo response as a cause of any salutary outcomes that might occur, since all subjects would be equally likely to think they were being treated. This also helps in evaluating side effects because of a parallel phenomenon called the nocebo response... in which a patient experiences new symptoms that are blamed on the treatment, even though it may be a completely inactive substance.”⁴

While all of this is perfectly valid from a scientific perspective, clinical trials must be designed in a way that ensures ethical treatment of participants as well as scientific validity. The use of placebo control is justified by the principle of clinical equipoise. Clinical equipoise is “a state of genuine uncertainty regarding the comparative merits of treatments A and B for population P.”⁵ Essentially, if it is unknown at the outset whether the trial intervention is superior, inferior, or equivalent to the standard intervention, then the demands of beneficence can be met by providing a participant with either intervention. Where there is already a proven effective treatment, then clinical equipoise does not allow for placebo use. In such a case, it is known that the proven treatment is better than placebo (typically because the treatment has been proven in a trial against placebo). The principle of beneficence requires that the known treatment be given to a participant in the control arm. But it is still unknown whether the experimental treatment is

⁴ Ibid., p. 53.

⁵ Freedman (1987), p. 141.

superior, inferior, or equivalent to the proven treatment, so there is (initially) equipoise between the experimental treatment and the proven treatment.⁶

4.1.1 History Revisited

As discussed in chapter 1, a new treatment regimen to prevent maternal-foetal transmission of HIV was proven effective in 1994: the AIDS Clinical Trial Group (ACTG) 076 regimen, which involved a long course of treatment with zidovudine (AZT).⁷ While effective, reducing the vertical transmission rate from 25% to 8% (in a non-breastfeeding population) the ACTG 076 regime was expensive and intensive.⁸ The regime “comprises a three part prophylactic protocol that involves giving oral AZT to HIV-infected pregnant women several weeks before birth, intravenous AZT during labour and delivery, and AZT syrup daily to the infants for six weeks after birth.”⁹ Given that pregnant women in LMICs often present for antenatal care late in pregnancy, at labour, or not at all, ACTG 076 was impractical in such settings. This impracticality could be compounded by a lack of necessary infrastructure and the absence of HIV screening to identify which pregnant women were infected.¹⁰ Furthermore, the regime cost around \$800 (USD) per woman at the time, far more than the contemporary per capita health care budget of many LMICs.¹¹ For these reasons, the ACTG 076 regime was deemed unaffordable and impractical for LMICs, including the countries most affected by HIV.

⁶ Equipoise continues to constrain investigators throughout the process – if at some point during the trial, it becomes clear that one arm is superior to the other, then the investigator is supposed to break the blind and halt the trial so that all the participants can be put onto the superior treatment.

⁷ Connor et al. (1994).

⁸ De Zulueta (2001), p. 291.

⁹ Ibid.

¹⁰ Ibid.

¹¹ Schüklenk & Ashcroft (2000), p. 166.

Therefore, a number of trials were commissioned in an effort to find a less expensive and intensive regimen that would still be effective.

Some of these trials were conducted in LMICs specifically so that they could use a placebo control design. The justification given was that the standard of care in those countries was no treatment at all, and hence a placebo could be used to represent standard treatment. This caused a serious controversy, epitomized by the stinging rebuke of such trials as exploitative, “Unethical Trials of Interventions to Reduce Perinatal Transmission of the Human Immunodeficiency Virus in Developing Countries,” penned by Peter Lurie and Sidney Wolfe.¹²

Supporters of the use of placebo-controlled trials in this case (despite the demonstrated efficacy of the ACTG 076 regime) advanced a number of arguments. The most important of these were two arguments related to the local standard of care. The first argument claims that since ACTG 076 could not be implemented in LMICs, the relevant research question was whether or not an alternative (potentially LMIC-implementable) treatment would be better than nothing. The only way to answer that question would be to conduct a placebo-controlled trial of the alternative treatment.¹³ The second argument claims that LMIC participants who were given placebo were not harmed, despite the fact that ACTG 076 was already known to be effective, since the LMIC participants would not have received ACTG 076 (or any effective treatment) outside of the trial. In addition to these central arguments, a number of supporting claims were also put forward, such as that placebo-controlled trials would be quicker to produce results; or that future benefits to others in the host country would outweigh the lack of benefits for women assigned to placebo.¹⁴

¹² Lurie & Wolfe (1997).

¹³ De Zulueta (2001). See also Wertheimer (2010); Varmus & Satcher (1997).

¹⁴ De Zulueta (2001), p. 294; also Schüklenk & Ashcroft (2000), p. 166.

Critics of the post- ACTG 076 placebo-controlled trials argued that the methodological concerns with using equivalency studies were not insurmountable. They also argued against the pro-placebo camp's assumptions about the local context in LMICs, the relevance of the local standard of care, and even the usefulness of the very concept of a local standard of care.¹⁵

Much ink has been spilled on the subject already, so rather than rehashing all of the old arguments, I will look at two questions arising from the debate, which have implications for the problem of exploitation in clinical trials. Firstly, I will examine the concept of a “local standard of care” — under several possible interpretations — in order to see if an intelligible and non-arbitrary account can be given of the concept. Secondly, I will attempt to assess whether the use of the concept of a local standard of care in trial design could entail exploitation.

4.1.2 “Local Standard of Care”

While advocates of the controversial post-076 placebo-controlled vertical transmission trials argue that the use of placebo was justified by the local standard of care, some critics of these trials have gone as far as to question the very notion of a local standard of care. Schüklenk and Ashcroft, for instance, cast aspersions on the notion of a readily identifiable local standard of care, noting “the local standard of care in, for instance Ivory Coast, is a standard of care determined crucially by the prices set by Western pharmaceutical multinationals.”¹⁶ While a drug is still on patent, the patent owner effectively has an enforced global monopoly on the production of that drug, and so can set prices arbitrarily¹⁷ high.¹⁸ When it comes to determining what

¹⁵ De Zulueta (2001), p. 294.

¹⁶ Schüklenk & Ashcroft (2000), p. 167.

¹⁷ While on-patent drug prices are not truly arbitrarily high in a mathematical sense, they are largely disconnected from the marginal cost of production due to the lack of competition.

constitutes a “local standard of care” (LSC), there are several different possible interpretations, depending on how the terms “local” and “standard of care” are parsed. I shall begin by examining each of these terms in turn, then proceed to look at the resultant potential readings of “local standard of care” in order to clarify whether there is a meaningful and non-arbitrary account to be given.

Let us begin with the slipperier term, “local”. This term is completely relative, and could be meaningfully used to denote any level of locality from a single neighbourhood to a regional group of nation-states.¹⁹ For the sake of simplicity, I will divide the possible readings of “local” into four groups. In order of increasing magnitude, these are: local as smaller than municipal (e.g. a neighbourhood); local as municipal or larger, but smaller than national (e.g. a province or state); local as national; and local as larger than national (e.g. a global region such as Sub-Saharan Africa, or a supranational organization such as the European Union). Naturally, not all of these interpretations are going to be equally plausible in this context. Within the context of a local standard of care, it is clearly too narrow an interpretation of “local” to define the standard of care relative to a neighbourhood, or any other division within a single metropolitan area or rural district, as evidenced by the fact that healthcare facilities frequently serve larger areas. Proceeding up the scale, we arrive at a group that includes many of the frequent referents of the term “local”, including municipalities, counties, districts, metropolitan areas, states, territories and provinces. Although a metropolitan area (or, equivalently, a rural district) is the appropriate level of locality for use in defining a locally-indexed living wage, since cost of living is largely

¹⁸ This is a market inefficiency, in that it prevents some mutually-beneficial transactions from occurring (i.e. the sale of on-patent drugs in LMICs at reduced, but still profitable, prices). Aidan Hollis and Thomas Pogge attempt to address this issue with their proposal to create a Health Impact Fund for drug development. See: Hollis & Pogge (2008).

¹⁹ The relativity of the term “local” is perhaps best evidenced by its use in astronomy – the “local group” refers to a group of galaxies including the Milky Way.

determined at this level of locality, the localities in this range are still too narrow for defining a local standard of care. While the cost of living can vary significantly between metropolitan areas within the same polity, the medical, scientific, and pharmaceutical regulatory frameworks generally do not. Intuitively, the catchment area for the clinic or hospital which is the site of a particular trial could, in one sense, seem to be the relevant local area in determining the local standard of care. Within said area, the standard of care would seem to be literally identical in the sense that the people in that area will be treated by the same health care professionals, with the same infrastructure. However, catchment areas frequently overlap, and different institutions within the same polity typically operate under the same regulatory frameworks, authorities, and (in theory at least) aim to uphold the same standards.

This brings us to the likeliest candidate for what is meant by the “local” in “local standard of care”: the country or nation-state. This is the level of locality at which patents are issued, new drugs are approved for use, and (typically) the highest courts have jurisdiction. While the sovereign power of the nation-state may be in decline in the age of globalization, the decline is not absolute. If there is a non-arbitrary reading of “local” in “local standard of care”, this is most likely it.

Finally, the term “local” could be interpreted to refer to something larger than an individual country, such as a supranational entity or a global region. The European Union technically fits into this range on the spectrum, but actually behaves much like a country in many ways, particularly in terms of issuing patents through the European Patent Office and regulating pharmaceuticals through the European Medicines Agency. So, for simplicity’s sake, let us expand slightly the former category to include both individual countries and multinational but country-like bodies like the EU. This leaves multi-country regions (MCRs) as additional candidates to be

the referent of “local” in “local standard of care.” However, it is difficult to see a case in favour of this interpretation. While countries generally have defined boundaries within which there are shared institutions, this is not the case for most MCRs (with the obvious exception of the EU). In particular, regions can have shifting and overlapping boundaries, and often exist simply as terms of convenience rather than concrete or even social entities, and lack the defining characteristics that are the basis for national sovereignty. In relation to the notion of a local standard of care, there is no real point in defining “local” as including several countries but excluding all others. If the concept is to stand, then treatment available by travelling to another country must be excluded from the local standard, or else it quickly collapses into the global standard.

Next, let us move on to the potential interpretations of “standard of care”. There are at least two relevant interpretations of the term in the context of the present discussion: standard as normal, or standard as best available. On the former reading, the local standard of care refers to the routine treatment for a given condition that a typical member of the pool of prospective participants would normally receive outside of the trial in question. On this view, determining the local standard of care is more a question of economics than scientific knowledge. If people in the pool of prospective participants would typically get no treatment for the condition in question, then the local standard of care is amenable to a placebo-controlled study design. This is regardless of whether or not a proven effective treatment exists. In effect, the standard of care is governed by the local *affordability* of a treatment, rather than its *availability*.

The remaining interpretation of “standard” in “local standard of care” takes it to mean the best treatment a participant could get.²⁰ In other words, the standard of care is the local gold

²⁰ A third possible interpretation of “standard of care” – reading “standard” as “recognized best practice” – has slightly different implications. On this interpretation, the local standard of care is whatever is recognized by local medical professionals or their governing body as the best

standard, the best treatment that can be had there by a person with means. On this reading, the standard of care is determined by availability in a technical sense, rather than availability in a practical sense (which often amounts to affordability.) So in the famously-critiqued maternal-foetal HIV transmission prevention trials, a placebo control could only have been used in countries where the ACTG 076 regimen was literally unavailable, as opposed to merely not accessible. In other words, the only way that the local standard of care will vary from the global standard of care on this reading is when a proven treatment is illegal in the host country, or illegal to export to the host country (i.e. due to sanctions or an embargo). While logically possible, such circumstances will most likely be exceedingly uncommon.

With the different readings established, it may be helpful to have a visual overview of the possible resultant interpretations of “local standard of care”.

	“Standard” as Typically Available	“Standard” as Best Available
“Local” < Municipality	A	B
Municipality ≤ “Local” < Country	C	D
“Local” = Country	E	F
“Local” > Country	G	H

Table 1. Possible Readings of "Local Standard of Care"

Interpretations A, B, C, D, G, and H can all be ruled out as arbitrary on the basis of the arbitrariness of the corresponding readings of “local”, as discussed above. Interpretation E is the

treatment. On this reading, local standards of care will generally not vary much for very long, since medical research is now disseminated online, but cases of disagreement between countries could theoretically crop up.

one most likely intended by the supporters of the controversial trials, but as we have just seen, it suffers from arbitrariness in its reading of “standard”. This leaves only interpretation F as a potentially non-arbitrary way to define a local standard of care, but note that in all but a few exceptional cases, the local standard of care in interpretation F turns out to be the same as the global standard of care. Even interpretation F has some arbitrariness to it, in that it can only vary from the global standard of care at all if we preclude medical tourism from factoring in to our determinations. So, in summary, the prospects for providing a meaningful and non-arbitrary account of local standards of care are exceedingly dim. Nonetheless, since interpretation E of “local standard of care” is the one most likely intended by most of the participants in the debate over the post-ACTG 076 vertical HIV transmission trials, let us now bracket the question of its arbitrariness for a moment, and inquire whether the use of this concept in the design of a trial could lead to exploitation.

4.1.3 Placebo Controls and Micro Fairness Exploitation

In order to get a sense of whether there might be micro fairness exploitation concerns with the practice of offshoring trials specifically to enable the use of placebo controls, I will be using the (admittedly flawed) older version of Wertheimer’s account of micro fairness exploitation, which appeals to a hypothetical ideal market as a standard against which to measure the fairness of the distribution of the social surplus of an interaction. While Wertheimer himself acknowledges that this is a problematic standard of fairness, it is problematic mainly in the context of a standalone micro fairness account of exploitation; the cases of exploitation “missed” by application of this standard will be “caught” by one of the other prongs of our Snyderian exploitation trident. Furthermore, in the present context it makes little difference which standard

of micro fairness is used: by definition, standards of care in other countries can have no bearing on the *micro* fairness of a given research interaction. For present purposes then, this vintage Wertheimer account of micro fairness exploitation will suffice to provide a general indication of the exploitation status of trials offshored to enable use of placebo controls (hereinafter referred to as OPC trials, for brevity).

On the classic Wertheimerian account of micro exploitation, A exploits B when A takes unfair advantage of B — meaning that B risks too much and/or benefits too little from the interaction, by comparison with the baseline distribution of benefits that would be expected in a hypothetical ideal market. With regards to OPC trials, it is not clear that the use of a placebo control is sufficient to qualify such trials as micro fairness exploitative. Prospective LMIC participants in such trials do not stand to lose by their participation, since *ex hypothesi* they would not have access to the proven treatment inside or outside of the trial. Given that the local standard of care is no treatment, *ex ante*, all prospective participants have roughly a 50% chance of receiving the investigational intervention, which may translate into a personal health benefit. Obviously the chance of a participant in the active arm benefitting from the investigational intervention cannot be known *ex ante*, so let x ($0 \leq x \leq 1$) represent the chance that the treatment will be effective for that participant; then $(0.5)(x)/1$ is the chance that the prospective participant will benefit medically from participation.²¹ If a prospective participant judges the risks and burdens associated with participating in the trial to be worth a $0.5x$ chance of personal medical benefit, this judgment is unlikely to be reversed in an ideal market. An ideal market, in this

²¹ For the sake of simplicity, I am ignoring here the fact that a certain proportion of participants in the placebo arm will benefit from the placebo effect (which is of course why placebo controls are used in the first place.) More accurately, a prospective participant's chance of medical benefit from participation is $(0.5)(x)+(0.5)(p)$, where p is the chance of benefitting from the placebo effect.

context, would entail that both parties have full information, and that the transaction occurs in the absence of fraud, deception, and coercion.²²

The case of the proposed Bolivian trial of Surfaxin is much-discussed in the literature, even though it did not involve a true placebo; infants in the control arm were not going to be given any surfactant, but they were still to be intubated and put on a ventilator, which was known to be superior to no treatment.²³ The parents of infants to be recruited would have been faced with a choice between non-participation (and no treatment for their infant), or participation (and treatment of their infant with a ventilator, and a chance of the experimental surfactant being used in conjunction with the ventilator.) There is no reason to think that hypothetical competitor researchers would have offered better terms, as the only reason for conducting the trial in Bolivia was in order to include a placebo control. Nor is there reason to think that parents were lacking any information that would have led them to refuse participation. It follows that the use of a control that was less than the best-proven treatment would not, in and of itself, constitute an exploitative offer, in micro fairness terms. Similarly, the use of placebo controls in LMIC trials of short-course AZT to prevent maternal-foetal HIV transmission is insufficient grounds to claim that such trials were micro fairness exploitative.²⁴

4.1.4 Placebo Controls and Macro Fairness Exploitation

While it may not amount to micro fairness exploitation when a trial design calls for use of a placebo control when proven treatment exists but is not locally available, there are other types

²² Participants (2004), p. 20.

²³ Hawkins & Emanuel (2008b), p. 61.

²⁴ This is not to say that such trials were therefore ethically sound; simply that the use of a placebo control when proven treatment exists (but is not locally available) is not necessarily indicative of micro fairness exploitation.

of exploitation. In particular, macro fairness exploitation's focus on structural injustice seems like a promising venue for exploitation claims in this context. Unlike micro fairness accounts of exploitation, a macro fairness understanding of exploitation requires that unfair circumstances be taken into account. This can lead to different judgments on whether a particular transaction is exploitative or not. As previously discussed, OPC trials are not inherently micro fairness exploitative, given that prospective participants' decision to enrol would not generally vary between the real world and a hypothetical ideal market. Conversely, a macro fairness understanding of exploitation recognizes the impact of participants' circumstances on their willingness to transact.

Recall that one version of macro fairness exploitation involves one party taking advantage of another party's desperate situation and inferior bargaining position, when these result from structural injustices. Recall, too, that structural injustice is the systematic disadvantaging of certain groups and advantaging of other groups by social processes and institutions. It is difficult to imagine a case in which a proven treatment exists and is available to some groups of people but is not available to another particular group of people, where this does not amount to structural injustice. On this understanding of macro fairness exploitation, the use of local standards of care to justify inclusion of a placebo control in a study design is dubious. The fact that local standards of care vary systematically in relation to economic factors, expanding the options available to HIC citizens and constraining the options available to LMIC citizens, constitutes a structural injustice. Designing a trial to be offshored so that it can use a placebo control rather than an active control is taking advantage of this structural injustice; this practice is therefore macro fairness exploitative, on such an account.

However, it does not necessarily follow that it is always macro fairness exploitative to use a placebo control when a proven treatment exists but is not locally available. Note that macro fairness exploitation still requires one party to be taking advantage; while this condition is clearly met in the case of the proposed Bolivian trial of Surfaxin, it might not be met in other cases. For instance, in the LMIC trials of short-course AZT for prevention of vertical HIV transmission, it could be argued that the research itself was trying to address a structural injustice, namely the fact that effective treatment to prevent vertical HIV transmission was available in HICs but not in LMICs. It is not clear that this argument can ultimately be sustained, given that contemporaneous trials in HICs were done using the proven effective ACTG 076 regimen as an active control; nonetheless, it does point to the possibility that there might be cases where local circumstances somehow excluded the possibility of using an active control design, even though effective treatment existed. If local circumstances did legitimately rule out use of an active control design, and the trial in question was aimed at addressing a structural injustice, a third condition would still need to be met in order to avoid macro fairness exploitation: it would need to be shown that an active-controlled trial in another location could not be used to address the structural injustice in question.

4.1.5 Placebo Controls and Mere Use Exploitation

Next, let us examine the question of whether OPC trials constitute mere use exploitation. The accounts of mere use exploitation provided by Siegel and Sample, as discussed in the preceding chapter, largely agree in their answers to this question, though they differ somewhat in their reasoning. After reviewing the two accounts, I will proceed to discuss three different

scenarios, and the responses suggested by each account as well as the reasoning behind those responses.

Siegel's article addresses the question of mere use exploitation in OPC trials directly, though he stops short of providing an outright answer in the case he discusses. Recall that on Siegel's account, the relevant moral duty is the imperfect duty of beneficence; exploiters violate this duty primarily by showing indifference to the unmet essential needs of other rational agents, and secondarily by taking advantage of other rational agents' neediness to further their own ends. According to Siegel, withholding effective treatments that are not otherwise available to participants is wrong if and only if "it denies them a kind of aid that investigators have an obligation to provide as members of the global moral community."²⁵

Sample's account takes a somewhat different approach. According to her, exploitation is the failure to respect the inherent moral value of another person in pursuit of one's own advantage; this disrespect can take the form of neglecting another person's genuine needs, of taking advantage of an injustice done to them, or of commodifying some aspect of them that ought not be commodified.²⁶ Agents also have a positive obligation to aid specific other persons when we interact with them, meaning that the imperfect duty of beneficence becomes, in effect, a perfect duty in particular instances when an agent is interacting with persons whose genuine needs are not being met. However, Sample provides the caveat that if an agent cannot possibly meet the genuine needs of another person by any mutually beneficial transaction, then a mutually beneficial transaction that does not satisfy the other person's genuine needs is not exploitative.²⁷

²⁵ Siegel (2008), p. 201.

²⁶ Sample (2003), p. 57.

²⁷ *Ibid.*, p. 75.

With these two accounts in mind, let us turn to the controversial 1990s OPC trials of short-course AZT for prevention of vertical HIV transmission. Straight away, a problem arises for both accounts: the treatments being tested by the trials in question were intended to benefit foetuses, but it is not clear that a foetus could be plausibly described as a person, let alone a rational agent. This can be a contentious issue, but it is simple enough to bracket by considering the possible interpretations in turn. If the treatment is interpreted as intended to benefit the foetus (rather than the mother, or the potential future person/rational agent that the foetus might become), and the foetus is neither a person nor a rational agent, then there are no grounds to make any claim about mere use exploitation on either account, because only persons/rational agents can be the objects of mere use exploitation.

Alternatively, the treatment could possibly be interpreted as offering a benefit to the mother (the benefit of preventing her foetus/future child from vertical HIV transmission); or it could be interpreted as offering a benefit to the future person/rational agent who might develop from the foetus; or any other interpretation that allows for the identification of a person/rational agent who could be the victim of mere use exploitation. On such interpretations, the post-ACTG 076 trials would likely be considered guilty of mere use exploitation, on either account. For Siegel, the issue would be that investigators showed indifference to the essential needs of rational agents (mothers or future children, depending on the interpretation) in the control group. If members of the global moral community have an obligation to provide medical aid (in the form of AZT) to HIV-positive individuals in LMICs, as they arguably do, then it follows that the investigators in these trials failed (along with the collective failure of other HIC agents) to fulfill this obligation. Furthermore, the investigators are guilty of exploitation since they profited from their own failure of beneficence by conducting a placebo-controlled trial. Similarly, for Sample,

the investigators' neglect in the control arm of the genuine needs of persons (mothers or future children, depending on the interpretation) is a form of disrespect. This disrespect is compounded by the investigators' interaction with the participants, and amounts to exploitation because it was done in order to further the investigators' own (admittedly well-intentioned) ends. Therefore the 1990s post-ACTG 076 regimen OPC trials could be meaningfully described as mere use exploitative, but only so long as one can provide a plausible interpretation whereby persons or rational agents could be identified as the victims of such exploitation.

Next, let us consider the case of Discovery Labs' proposed trial of Surfaxin in Bolivia. Firstly, the same issues about personhood/rational agency apply, since the subjects were to be infants. In order to make any claims about mere use exploitation, it must be possible to provide a plausible interpretation whereby persons/rational agents can be identified as the victims of such exploitation. If this is not possible, then the trials could not be mere use exploitative. For argument's sake, let us investigate the implications for mere use exploitation if such an interpretation is possible.

While the Surfaxin case might seem, intuitively, to be a clearer instance of exploitation since the sponsor's motivation was financial gain rather than combating the spread of a deadly disease (as in the short-course AZT trials), it turns out to be somewhat murkier in terms of mere use exploitation. The reason for this is that all the subjects would have received more effective treatment in the trial than they actually received outside of it. Recall that the study design called for investigational arm subjects to be given artificial ventilation and Surfaxin (synthetic surfactant), and for control arm subjects to be given artificial ventilation and 'sham air' (i.e. air alone, with no surfactant). The local standard of care for treatment of infants with respiratory distress syndrome in Bolivia at the time did not include artificial ventilation, as the local health

system did not have the necessary equipment. Importantly, artificial ventilation alone was known to be superior to no treatment.²⁸ Therefore, a case could be made that the sponsor and investigators were meeting their obligations of beneficence. On Siegel's account, the fact that an effective intervention would have been offered to all subjects seems to show that the sponsor and investigators were *not* indifferent to the essential needs of the subjects, even if they did not intend to do everything they could to meet those needs by providing the most effective intervention known. If this line of reasoning is correct, then the proposed Surfaxin trial would not have been mere use exploitative, despite the fact that the sponsor and investigators would have profited from the participants' unfortunate or even unjust circumstances. On Sample's account, there is more room for disagreement about whether or not the proposed trial would have amounted to mere use exploitation of the subjects. On the one hand, Discovery Labs was proposing to take advantage of the subjects' bad situation, which was arguably at least partly the result of injustice. On the other hand, it could be argued that the proposed trial was the only mutually beneficial transaction possible — that an active-controlled trial using a competitor's drug in Bolivia would not have been beneficial for Discovery Labs — and that the proposed trial would therefore not have been mere use exploitative. Overall, then, it is not clear that the proposed Surfaxin trial would have been mere use exploitative due to its “placebo” controlled design, and indeed there is a fairly strong case to be made that the trial would not have constituted mere use exploitation.

Finally, let us consider how mere use accounts of exploitation might be applied to OPC trials more generally. One thing is clear on both Siegel's and Sample's accounts: the seriousness and severity of the intervention's target condition will make a difference to judgments about mere use exploitation. If treatment for the condition does not constitute an essential/genuine need, then

²⁸ Hawkins & Emanuel (2008b), p. 61.

the use of an OPC trial design is not mere use exploitative. If it is an essential/genuine need, then use of an OPC trial design is likely to be mere use exploitative, unless the control arm subjects' needs cannot be met by a mutually beneficial transaction.

4.2 Exploitation and Participants' Post-Trial Access to Successful Interventions

Consider for a moment the following scenario. You are living in a LMIC and suffering from a chronic condition. You are then invited to participate in a phase III clinical trial of a new drug to treat your condition. This multi-site, international trial is sponsored by a large multinational pharmaceutical company, though locally it is being conducted by a CRO on behalf of the pharmaceutical company. From your perspective as a prospective drug trial participant, it seems natural to assume that if the drug to be tested in the trial turns out to be effective and safe, then you will continue to have access to the drug following the conclusion of the trial. If you lived in an HIC with a universal health care system (or, alternatively, if you lived in a two-tier health care system and you had health insurance), your assumption would generally be warranted – you would likely be able to continue treating your condition with the new drug post-trial (although your country's healthcare system or health insurance might have to cover the cost of the treatment.) However, you live in an LMIC in this scenario, and so even if the trial is a success, the drug being studied might not become generally available in your country following the trial. Indeed, even as a trial participant, you may not have access of any kind to the drug post-trial. It is not difficult to see how you might think these terms are exploitative.

The sentiments of some actual LMIC prospective trial participants, as reported by Shaffer et al., are telling. “Because I will get into this trial, I get better, and then afterwards I am going to

die. You have promised me life and then you take it back; that's not fair."²⁹ One Kenyan woman asked, "if a patient is still sick, how will you stop the drugs?"³⁰

The researchers interviewed in the same study had a different view, namely that "therapy could be discontinued at some point following the trial if participants were fully informed before the trial that treatment would be of limited duration and would be stopped once the trial was over."³¹ Given that the treatment in question in this case was antiretroviral therapy for HIV/AIDS, the stakes are heightened and the divergence of views is particularly striking.³²

In the present section, I will be looking at the issue of post-trial provision of experimental interventions to trial participants (PTP), and whether PTP is necessary in order to avoid exploiting the participants³³. As in the previous section, I will be relying on the Snyderian typology of exploitation laid out in chapter 3. I will begin by outlining some general considerations that apply to discussions about PTP with regards to all three types of exploitation, namely when PTP should count as a benefit to participants, and some objections to the notion of any PTP obligations on the part of sponsors or investigators. Next I will discuss each type of exploitation and the degree to which PTP is or is not necessary to avoid that type of exploitation of participants.

²⁹ Shaffer et al. (2006), p. 57. This quote is from a clinician researcher, reporting to Shaffer et al. on behalf of trial participants.

³⁰ Ibid.

³¹ Ibid., p. 58.

³² There is debate in the literature relating to post-trial treatment obligations for participants who become infected with HIV in the course of an HIV prevention trial: see, e.g., Stobie & Slack (2010); Weijer & Leblanc (2006). This is a separate question from the question of post-trial provision of the tested intervention, so I will be bracketing this issue as it is beyond the scope of the present project.

³³ In the literature, there is also much discussion as to whether successful drugs must be made available to the host community, and what constitutes "availability" and "community". The reasonable availability standard put forward in CIOMS (2002), and criticisms of that standard by advocates of the Fair Benefits Approach, both fall into this category. I will be addressing these questions in the following chapter on exploitation of groups by clinical trials.

4.2.1 General Considerations

There is one major consideration which looms over the following discussion, namely the question of when continued post-trial access to an intervention is beneficial at all. There is no reason to provide participants with non-beneficial interventions, and hence no reason to think that providing such interventions constitutes a moral obligation. Some types of cases are clear-cut in terms of whether PTP would constitute a benefit to participants: PTP would not be beneficial in cases of unsuccessful trials, but would be beneficial in cases of successful phase III trials of treatments for chronic conditions. Zhiyong Zong attempts to define a set of criteria for determining whether and when PTP should be mandatory, and in the process draws attention to a number of other situations in which continued post-trial access to the trial intervention might not be a benefit to participants.³⁴ In the present subsection, I will discuss several of the types of cases mentioned by Zong, where it is less clear whether PTP would be beneficial to participants or not. These include early-phase clinical trials, successful trials of interventions for acute diseases, and trials where participants are not (medically) in the target group.³⁵

To begin with, let us examine the case of early-phase trials. Zong rules out PTP for early-phase trials on the grounds that the experimental intervention's efficacy is not considered to be proven by such trials.³⁶ Zong may be too quick to rule out PTP for participants in early-phase trials. Phase I trials are typically conducted on healthy volunteers, but phase II trials often include participants who have the condition that the intervention is designed to treat. In phase II trials at least, one could argue against Zong that it might benefit participants if the investigational

³⁴ Zong (2008), p. 189.

³⁵ Zong (ibid) also discusses trials of novel antimicrobial agents, arguing that such products can legitimately be kept in reserve in order to delay the advent of microbial resistance, despite the fact that participants might benefit from PTP.

³⁶ Ibid.

treatment could be made provisionally available to those participants who showed improvement during the phase II trial, while the phase III trial is being conducted. A seeming alternative arrangement might be to offer to include phase II participants in the phase III trial, but this may not be feasible or desirable, even when the phase III trial is being conducted at the same site(s). Presumably, phase II participants who responded well to experimental treatment would be much more likely to choose to continue on in the phase III trial, potentially biasing the results of the phase III study. Furthermore, if PTP is beneficial for participants in a successful phase III trial, then it is likely just as beneficial to provide post-trial access to all early-phase participants with the target condition, upon successful completion of the phase III trial. This would not generally be a major imposition on trial sponsors, due to the small numbers of participants in phase I and phase II studies. Of course, it does not follow that anyone has an obligation to provide PTP just from the fact that participants would benefit, but the category of participants who could benefit from PTP is broader than just those who were in the phase III trial.

There is no benefit to participants from PTP in cases of successful trials of treatments for acute conditions, according to Zong, because there is no ongoing need for treatment.³⁷ While this is generally true, it is still possible that participants in such trials could benefit from being able to access the treatment again in the future, if the condition can recur. (Once one's tapeworm is gone, one no longer needs treatment for the condition, but one might need treatment again if one gets another tapeworm.) Similarly, participants in vaccine trials might benefit from PTP if the vaccine's efficacy diminishes over time, requiring a booster shot. It may be unreasonable to expect PTP obligations to cover such eventualities, but in principle it would be beneficial to participants in certain cases.

³⁷ Ibid.

In some trials, participants are not in the target group of the research: obviously this is the case with phase I trials on healthy participants; but Zong also mentions the example of trials of new drugs for treatment of severe fatal malaria, which “recruited patients with moderately severe disease.”³⁸ In connection with this example, Zong claims that PTP is not necessary in all situations. However, in this instance, it could potentially benefit the participants with moderately severe malaria to continue to receive the trial drug, particularly if they responded well to the treatment and if they would not normally have access to effective treatment for their condition outside of the trial.

Setting aside for a moment questions of benefit to participants, there are also some general objections to the notion of any PTP-related obligation on the part of a trial’s sponsor(s) or investigator(s). As mentioned above, some researchers hold the view that they can be absolved of any PTP-related obligations by the informed consent of participants.³⁹ In response to this view, Zong argues that informed consent in international trials conducted in LMICs is compromised by the participants’ “inadequate understanding” and many investigators’ “inability” to effectively explain their trials, and hence no excuse to flout PTP obligations.⁴⁰ However, this is not a convincing argument: not only is it implausible to claim that LMIC participants are categorically unable to understand the implications of their consent to participate in research, it is also clear that if LMIC participants’ informed consent really were compromised, then people in LMICs should not be allowed to participate in research under *any* terms. Regardless, the question of the validity of participants’ consent is orthogonal to questions about exploitation, since exploitation can be consensual *or* non-consensual.

³⁸ Ibid.

³⁹ Shaffer et al. (2006), p. 58.

⁴⁰ Zong (2008), p. 190.

Another general argument against any PTP-related obligations on the part of research sponsors or investigators draws on the distinction between the role of an investigator and the role of a physician, or equivalently on the distinction between the norms of scientific research and the norms of medical care. According to this argument, PTP is healthcare, not research, and therefore cannot be required of investigators or sponsors. However, this argument too is orthogonal to the question of whether PTP is necessary to avoid exploitation, since exploitation is a matter of taking advantage of micro or macro unfairness, or of merely using participants to one's advantage. It may well be possible to exploit someone without violating any particular set of role-specific norms, or the norms of a particular enterprise. Therefore, questions about role-specific obligations and enterprise-specific norms can be set to one side for the purposes of the present discussion.

4.2.2 PTP and Micro Fairness Exploitation

In the literature, advocates of the Fair Benefits framework have applied a micro fairness understanding of exploitation to the question of PTP to trial participants, arguing that PTP to trial participants is neither necessary nor sufficient to avoid exploitation. According to the Participants in the 2001 Conference on Ethical Aspects of Research in Developing Countries (Participants),⁴¹ post-trial availability of the tested intervention is just one potential benefit to participants among many. On this view, avoiding exploitation is a matter of ensuring a sufficient (fair) level of benefits, rather than ensuring any particular type of benefit; hence post-trial provision of a

⁴¹ Participants (2002); Participants (2004).

successful intervention is not necessary to avoid exploitation of the participants.⁴² Furthermore, PTP is not always sufficient to avoid exploitation of the participants: as discussed in the previous section, PTP is not always beneficial, and even when it is beneficial, it might not be sufficient to constitute a fair level of benefits on its own.

Of course, the problem will then be to specify what constitutes a fair level of benefits to participants. The most influential version of the fair benefits approach is the formulation put forward by the Participants in 2004, which argues that, following Alan Wertheimer's account of (micro fairness) exploitation, an ideal market standard can be used to determine a fair distribution of benefits for a transaction. The baseline of fairness is not given by a substantive account of justice, thus sidestepping the entrenched disagreements of distributive justice accounts. On Wertheimer's account, to determine whether a proposed trial design would exploit participants or not, it is necessary to consider whether the participants would agree to the offered terms of research participation in an ideal market situation. The fair benefits framework proposes to simulate ideal market conditions by requiring a consultation process whereby the host community agrees to the terms offered by the research sponsor, and by requiring transparency, in the form of an open, international repository of benefits agreements. In this way, communities will be able to see what benefits have been agreed to by other LMIC communities in the past.⁴³ Effectively, this means that post-trial provision of effective interventions to trial participants will generally not be

⁴² As discussed in Chapter 2, Alex London and Kevin Zollman convincingly argued against the fair benefits framework as a means to ensure greater benefits to participants and host communities in offshored research; see London & Zollman (2010). Nonetheless this account can still be used to determine what might be required to avoid micro fairness exploitation, even though London and Zollman have demonstrated that avoiding micro fairness exploitation will not be sufficient to ensure that participants and host communities are not exploited by offshored research. As discussed in Chapter 3, on Snyder's account, this should come as no surprise given that there are three distinct types of exploitation, of which micro fairness exploitation is one.

⁴³ Participants (2004), p. 23.

necessary to avoid micro fairness exploitation, so long as it is not typically offered by research sponsors and the host community agrees to these terms.

Avoidance of micro fairness exploitation may still require PTP for participants in some instances, depending on the specifics of the particular case and how these relate to the micro fairness of the distribution of benefits from the research interaction. The profit status of the research sponsor, and the nature of the condition that the intervention is intended to treat, will both factor into such determinations of fairness. The level of benefits from research to a for-profit sponsor will generally be greater than the level of benefits to a non-profit sponsor, hence requiring a higher level of benefits to participants in order to preserve fairness. However, this requirement relates to the overall level of benefits to participants, and does not specify the necessity of any particular type of benefit to participants, such as PTP. Not coincidentally, research on treatments for common diseases (particularly those with relatively high incidence rates in HICs) will generally yield greater benefits than research on neglected diseases, hence requiring more benefits for participants in order to achieve a fair distribution.

4.2.3 PTP and Macro Fairness Exploitation

In contrast to micro fairness accounts of exploitation, macro fairness accounts of exploitation recognize that “structural injustice can disadvantage some parties within a transaction.”⁴⁴ In other words, background conditions can affect the fairness of a transaction, and hence whether or not it is exploitative. In the case of off-shored clinical drug trials in LMICs, these relevant background conditions include the widespread lack of access to health care, the TRIPS treaty (and subsequent related agreements) which guarantee worldwide patent protection

⁴⁴ Snyder (2010 b), p. 191.

for new medicines without consideration of whether or not such medicines are even submitted for regulatory approval in all countries (much less actually made available in all countries), the history of colonialism, et cetera.⁴⁵ Macro fairness accounts of exploitation either contend that there is a duty not to profit from background injustices,⁴⁶ or go further and argue that individuals and organizations (including research sponsors) have responsibilities to address structural injustices.⁴⁷ Rather than requiring research sponsors to provide or ensure the provision of continued post-trial treatment to participants, avoidance of macro fairness exploitation will primarily involve responsibilities to help address the unjust background conditions that result in participants' inability to access such treatment on their own.

Macro fairness accounts of exploitation have been applied to the debates surrounding off-shored clinical trials in LMICs, notably by Angela Ballantyne and Agomoni Ganguli Mitra.⁴⁸ Ballantyne proposes a global research tax on off-shored clinical trials, to benefit participants and host communities through improving local health-related capacity, to be implemented along a maximin principle (so that the worst off, i.e. participants and host communities, benefit the most). Mitra, on the other hand, proposes a reciprocity constraint on off-shored clinical trials, such that trials will need to be designed in a way that ensures the medical benefits of the research are distributed to the host community through the health care system (and thereby to the participants).

Ballantyne does not specifically address the question of participants' post-trial access to tested interventions, but to the extent that this figures into avoiding exploitation on her account, the cost of ensuring post-trial provision would presumably be covered by the global research tax.

⁴⁵ See Chapter 2 for a more thorough description of the relevant background conditions.

⁴⁶ See, e.g., Mitra (2013), p. 116.

⁴⁷ A particularly good example of such an argument is given by Iris Marion Young (2006). This argument is also called upon by Mitra & Biller-Andorno (2013).

⁴⁸ Ballantyne (2010); Mitra (2013).

On Mitra's account, ensuring participants have post-trial access to proven interventions is necessary to prevent exploitation of participants, due to what she terms the reciprocity constraint. Instead of sponsors providing treatment directly to the participants after the trial ends, participants should get access to the treatment through the local health system; trials should generally not be conducted in locations where this cannot be done. The reciprocity constraint "does not require research to directly benefit participants, but rather requires research to match and contribute to an infrastructure from which patients can, and do in fact, benefit."⁴⁹

4.2.4 PTP and Mere Use Exploitation

Mere use accounts of exploitation provide perhaps the clearest case for claiming that a failure to ensure participants have post-trial access to proven interventions amounts to exploitation. In particular, Sample's account of mere use exploitation allows us to say with some specificity whether sponsors or investigators have obligations to ensure participants' post-trial access to (successfully) tested interventions. Siegel directly addresses the question of post-trial benefits, but does not give an unequivocal answer to that question, nor is it entirely clear what answer might follow from his account.

On Siegel's account of mere use exploitation, there are two wrongs involved: the more serious and fundamental wrong of indifference to the essential needs of others, and the secondary wrong of profiting from one's own transgression (or a transgression in which one is complicit). With regards to PTP, Siegel notes that "in principle, a pharmaceutical company can refuse to provide a successful intervention or other posttrial [sic] benefits without displaying indifference

⁴⁹ Mitra (2013), p. 116. I discuss Mitra's arguments in greater detail in chapter 5, as they primarily concern community benefit (from which participants' post trial access is to be derived).

to the population in which the intervention was tested.”⁵⁰ If the sponsor cannot afford to provide post-trial benefits such as PTP, or if the sponsor is already doing its fair share of aid in order to fulfill its duties of beneficence, then failing to offer PTP to participants does not amount to indifference, and hence cannot entail exploitation. On the other hand, if the sponsor can afford PTP and is not sufficiently discharging its duties of benevolence elsewhere, then the failure to offer PTP *could* amount to indifference, depending on what other benefits are being offered to participants for taking part in the trial. In order to amount to exploitation, the sponsor would have to demonstrate indifference towards the participants and the sponsor’s gains from the trial would have to also be partly or fully contingent on a transgression in which the sponsor is complicit. As a result, it will be very difficult to say, on Siegel’s account, whether avoiding exploitation entails a requirement to ensure that participants have post-trial access to beneficial trial interventions.

On Sample’s account, matters are somewhat clearer. A sponsor’s failure to ensure PTP for participants will amount to moral disrespect, and hence exploitation, if two conditions are met. Firstly, PTP must constitute a genuine need for participants. Secondly, it must be possible for that genuine need to be satisfied in a way that maintains the mutually beneficial status of the research interaction – sponsors need not lose money to fulfill their obligations of beneficence. With regards to the method of ensuring PTP, any of the following would be entirely consistent with a sponsor’s obligations under Sample’s account: means testing, direct sponsor provision or some form of third party agreement. Means testing involves ensuring that only those potential participants with the means to access the tested intervention following the trial, are selected for inclusion (including, but not limited to, access through a sufficiently-funded public health system.) A direct sponsor provision scheme would involve the donation by the sponsor of (e.g.)

⁵⁰ Siegel (2008), p. 195.

drugs, in a manner that ensures participants have post-trial access to the tested intervention, for either a specified or an indeterminate period of time. Third party agreements are similar in effect to direct sponsor provision, but involve third parties who agree to take responsibility for buying and/or administering the tested intervention.

Chapter 5

Exploitation and Communities

There have been a number of claims in the literature that benefits to host communities are important to avoiding exploitation in off-shored clinical trials.¹ The guidelines for international research put forward by CIOMS stipulate that this benefit ought to take the form of tested interventions being made reasonably available to host communities following trial completion.² Advocates of the fair benefits approach to avoiding exploitation in offshored research agree with the importance of providing benefits to the host community, although they dispute the claim that reasonable availability is the only appropriate benefit.³ Such claims raise two important questions: how should we define the term “host community” with reference to determining which community or communities ought to be receiving benefits from hosting trials; and who is being exploited in a trial that fails to provide (sufficient) benefits to the host community?

With regards to the first question, concerning defining host communities, there are a number of difficulties with determining how the relevant community or communities to be benefitted should be identified and demarcated. Firstly, it will be necessary to determine which types of communities could be considered host communities; Weijer and Emanuel offer a typology of communities that is of some use in this regard.⁴ This will be discussed in some detail in section 5.1.1. Secondly, there is the question of whether host community benefits are necessary

¹ See, for example: CIOMS (2002); Participants (2002), p. 2134; Participants (2004), pp. 22-23; Hughes (2012); Gbadegesin & Wendler (2006); Mitra (2013).

² CIOMS (2002).

³ Participants (2002), p. 2134; Participants (2004), pp. 22-23.

⁴ Weijer & Emanuel (2000).

to avoid exploitation in all trials, or only in offshored trials conducted in LMICs. This issue is the focus of section 5.1.2. Thirdly, there is the ontological consideration of whether a host community is to be conceived of as merely a collection of individual members, or as a separate entity (albeit one that is at least partly composed of individual members). This distinction will be discussed in section 5.1.3.

With regards to the second question, are community benefits necessary to avoid exploitation of the individual participants in the trial, or the community itself? I will take up this question within the context of discussing the connection between community benefits and each type of exploitation. In section 5.2, the connection between host community benefits and avoidance of micro fairness exploitation will be discussed, both in terms of the potential exploitation of individual participants and of the host community. In particular, I will discuss the arguments for the possibility of communities being victims of micro fairness exploitation, put forward by Segun Gbadegesin and David Wendler. Section 5.3 concerns macro fairness exploitation and community benefits, including Agomoni Ganguli Mitra's reciprocity constraint arguments, which suggest that individual participants can be macro fairness exploited by their involvement in a trial that fails to provide sufficient benefits to the participants' community. In section 5.4, I will discuss the connection between host community benefits and mere use exploitation, drawing on an argument from Robert Hughes to suggest that host community benefits may be necessary to avoid mere use exploitation of individual participants. I will also discuss the reasons that communities are not, in general, potential victims of mere use exploitation.

5.1 Defining Communities

“Community,” as a concept, is something of a quagmire. Communities are often heterogeneous and changing; one person can simultaneously be a member of several communities; there are difficult issues surrounding the drawing of community boundaries (both in geopolitical terms and in terms of membership); communities can not only overlap but also can be nested, so that one community is completely contained within a larger community. Furthermore, there may be questionable “modes of representation of some indigenous communities”⁵ (and non-indigenous communities), in that there may not be any community leadership, or if there is, it may be corrupt, unaccountable or not truly representative of the community. And this is leaving aside issues concerning collective agency. In terms of identifying a “host community” for a given clinical trial, it is difficult to find a non-arbitrary basis for choosing which “community” is the relevant host, even if we were to arbitrarily stipulate from the outset that only geographically-defined communities will be considered (as opposed to religious, ethnic, linguistic, or other communities). Is the host community the village where the clinic is located? Or is it the surrounding district from which participants are drawn? Or perhaps it is the region, province, state, territory, or country within which the village is situated? A case could be made for any of these candidates, and perhaps more besides. There may be different implications depending on which community is deemed to be the “host community”. It is important to recognize these issues and how thorny they are, even though, for the purposes of the present discussion, many of these issues can be bracketed. Without presuming any particular answer to such questions, it should be possible to proceed with a fairly abstract discussion about the

⁵ Schüklenk & Kleinsmidt (2006), p. 132.

connection between benefits to host communities and avoidance of exploitation (in all its forms) in clinical research on human subjects. Before proceeding with this abstract discussion, however, it may be helpful to survey some of these issues; in section 5.1.1, I will survey some of the general types and characteristics of communities. Next, in section 5.1.2, I will briefly address the question of whether the connection between host community benefits and avoidance of exploitation is categorically different in LMICs than it is in HICs. Finally, in section 5.1.3, I will draw an important distinction between two conceptions of “community”.

5.1.1 Types of Communities

In the present section, I will examine the term “host community”, in an attempt to clarify what counts as a community involved in research, such that the community may be owed something in addition to any benefits that might accrue to individual members of the community. One issue, which I will be largely bracketing in this discussion, is the question of the collective agency of communities as it relates to community consent to a trial. I will be setting this aside not just because it is a particularly sticky wicket, but because it is effectively orthogonal to the question at hand (since exploitation can occur with or without the consent of the exploited party, as discussed in chapter 3.) Weijer and Emanuel identified a number of morally relevant characteristics of communities, and used these in delineating seven different *types* of communities relevant to biomedical research.⁶ These are aboriginal communities, geographical/political communities, religious communities, disease communities, ethnic/racial communities, occupational communities and virtual communities. Within this typology, many of the issues mentioned above persist. An aboriginal community, for instance, could also be a

⁶ Weijer & Emanuel (2000), table 1.

geographical/political community. Geographical/political communities are often nested—as the Queen’s University community is nested within the Kingston community, which is nested within the eastern Ontario community, which is nested within the Ontario community, which is nested within the Canadian community. So how are we to determine which community (or communities) are the host(s) of a given clinical trial, for the purposes of determining whether or not they might be exploited? The answer to this question will depend on a number of factors, including the type of trial being conducted and the population being targeted for recruitment. For instance, in the case of genetic research, the “community” potentially at risk of being exploited is comprised of those who share a common genetic lineage, regardless of where they live.⁷ In other cases, the relevant community might be defined geographically by the catchment area within which participants are being recruited.

The literature on exploitation in off-shored clinical trials tends to focus primarily on geopolitical communities⁸. However, there are at least two relevant levels of geopolitical community to consider: the local community where the research site is located, and the host country. For instance, in elaborating the Fair Benefits Framework, its authors describe ten different kinds of potential benefits to participants and the population from which participants are drawn; while some of these benefits (such as post-trial availability of the tested intervention) might accrue to the population of the host country, others (such as collateral health services) would be limited to the population of the local community where the study actually takes place.

⁷ This is a simplification of matters; for instance, in the previously mentioned genetic studies, the risk of stigma and discrimination is borne by all (and only) those who are identified as belonging to that community. So a community member who does not share the genetic lineage may bear the risk, while a person who does share the genetic lineage but is not seen as a member of the community may not bear the risk of stigma and discrimination.

⁸ See Participants (2002); Participants (2004); Wertheimer (2010).

In spite of the focus on examples of geopolitical communities, there is no principled reason to think that other types of communities could not be considered host communities if, for example, they were specifically targeted for recruitment.

5.1.2 Benefits to Host Communities: a Concern Unique to LMICs?

While many people have negative moral intuitions about off-shored trials (for-profit clinical trials on drugs intended for HIC markets but conducted in LMICs by or on behalf of HIC sponsors), they often do not have such negative intuitions about “off-shore” trials (such as a trial conducted in one HIC on a drug that will primarily be marketed in another HIC.) If LMIC host communities must be assured benefits to avoid exploitation, why would such a requirement of community benefit not apply in other cases? The only response given seems to be the one provided by the proponents of the fair benefits approach:

“The potential for clinical research to exploit populations is not a major concern in developed countries since there are processes, albeit haphazard and imperfect, for ensuring that interventions proven effective are introduced into the health-care system and benefit the general population.”⁹

This response is not particularly satisfactory for three reasons. Firstly, it actually constitutes a tacit acknowledgement of the importance of host community benefits to the avoidance of exploitation, even in trials conducted within HICs; the fact that such benefits often accrue to HIC host communities only indicates that this requirement is met in many cases. Secondly, as the proponents of the fair benefits approach themselves point out, post-trial availability of tested interventions is only one possible benefit, and is neither necessary nor sufficient to ensuring a fair level of benefits. Thirdly, given the diversity of types of communities, it is not implausible to

⁹ Participants (2002), p. 2133.

think that some communities within HICs could be described as hosting research that primarily benefits people outside of the community. Indeed, some of the most ethically problematic studies of the 20th century were conducted on members of marginalized communities within HICs, such as the Tuskegee syphilis experiments. Marginalized communities within HICs may also have limited access to the health care system, so that they are denied even the benefit of post-trial availability of the tested intervention. Therefore, a principled investigation into the importance of host community benefits to avoiding exploitation in clinical trials should begin without assuming that such benefits are only important to avoiding exploitation in research conducted in LMICs.

5.1.3 Two Conceptions of “Community”

An important distinction, necessary even for an abstract discussion of the connection between host community benefits and exploitation, is the distinction between two different metaphysical conceptions of “community.” On the ontologically minimalist “thin” conception of the term, “community” is essentially just shorthand for the collection of individuals who are members of the community. Conversely, on the more ontologically demanding “thick” conception, “community” refers to an entity that is distinct from the individual members who comprise it. Except where otherwise noted, I will be discussing communities only in the former, more limited, sense; any moral obligations to ensure benefits to a host community *qua* collection of individuals should also apply, *a fortiori*, to a host community *qua* discrete entity. It may be wondered whether requiring benefits to a host community in this former sense actually differs from requiring benefits to individual participants; it does, as not all host community members will be participants.

5.2 Community Benefits and Micro Fairness Exploitation

Recall that, according to Wertheimer’s account of micro fairness exploitation, “*A exploits B when A takes unfair advantage of B.*”¹⁰ In this formulation, “A” and “B” could represent individuals, groups, institutions or organizations. With regards to benefits for host communities, there are therefore two possible scenarios where host community benefits will be necessary to avoid micro fairness exploitation. Let “A” represent the trial sponsor and researchers in both scenarios. In the first scenario, “B” represents an individual trial participant, and host community benefits are (somehow) a necessary component of any benefit-sharing arrangement that is to be fair to B. In the second scenario, “B” represents the entire host community, and hence host community benefits are inherently necessary to any fair benefit-sharing arrangement. The first scenario is mentioned (in passing) by the advocates of the fair benefits approach, while the second scenario has been discussed in detail by Segun Gbadegesin and David Wendler. In this section, I will review each of these scenarios in turn, in order to determine the nature of the connection between host community benefits and avoidance of micro fairness exploitation.

5.2.1 Host Community Benefits and Micro Fairness Exploitation of Individual Participants

As proponents of the fair benefits approach note, a number of benefits from research might accrue to host communities, such as “collateral health services to members of the population not enrolled in the research,” public health measures during or after the research, economic activity, local research and medical care capacity development, reasonable local

¹⁰ Wertheimer (2010), p. 198.

availability of tested interventions, or profit-sharing from research results.¹¹ However, it does not follow from this that provision of such community benefits is either necessary or sufficient to ensure that individual trial participants are not exploited in the micro fairness sense. The Participants point out that, on their account,

“determination of whether the distribution of benefits is fair depends on the level of benefits received by those members of the community who actually participate in the research, for it is they who bear the burdens of the interaction.”¹²

Community benefits are thus a permissible means of (indirectly) benefitting trial participants, but “the important question is how much the participants will benefit from these measures.”¹³ So long as participants get sufficient benefits from the research interaction to satisfy the requirements of the selected account of micro fairness, there is no need to provide any benefits at all to the host community in order to avoid the micro fairness exploitation of individual participants. As a result, the scenario where host community benefits are necessary to avoid micro fairness exploitation of individual participants will only ever obtain in rare cases, such as where it is not possible to sufficiently benefit participants except by inclusion of benefits to the entire host community. For instance, one example of a potential benefit given by the fair benefits proponents is the digging of a borehole for clean water. If this was the only way for researchers and/or sponsors to provide a fair level of benefits to participants in a particular trial, it might seem as though this host community benefit was necessary to avoid micro fairness exploitation of the trial participants. However, even in such a case, the benefit to the rest of the host community is entirely superfluous to the requirements of avoiding micro fairness exploitation of the participants. In theory, the

¹¹ Participants (2002), p. 2134.

¹² Participants (2004), p. 22.

¹³ Ibid.

researchers could erect a fence around the borehole and lock the gate, only providing keys to the trial participants, and the participants would still not be exploited in a micro fairness sense. In general, benefits to host communities are not necessary to avoid micro fairness exploitation of individual trial participants.

5.2.2 Host Community Benefits and Micro Fairness Exploitation of Host Communities

Turning to the second possible scenario, straight away it becomes clear that host community benefits are much more likely to be necessary to avoid the micro fairness exploitation of the host communities themselves, as opposed to the individual community members who actually participate in a given trial. Naturally, the first step will be to determine when a particular community is involved in a trial. According to Segun Gbadegesin and David Wendler,

“[A] research study involves the community itself, when, in addition to involving individual community members, the study: 1) relies on the community’s resources, including economic, social, knowledge base, or political resources; 2) focuses on the community’s customs, traditions or practices; or 3) focuses on a health feature of the community.”¹⁴

This is because the community’s resources, including its social and political structures as well as physical infrastructure, belong to the community as a whole rather than to individual community members. For the purposes of evaluating exploitation claims, a community can potentially be exploited if it is involved in the research interaction, as it is when the community either bears some risks or burdens, or contributes in some other way to the research. On a micro fairness model of exploitation, the community’s contribution to the interaction means that it should be

¹⁴ Gbadegesin & Wendler (2006), p. 250.

entitled to a fair¹⁵ share of the resultant benefits (if any). Robert Hughes argues that this will only justify compensation in some cases, thus generating only a weak obligation for off-shored clinical trials to benefit host communities.¹⁶ Gbadegesin and Wendler seem more optimistic but do not rule out such an outcome. According to them, the benefits to a community should be proportional to the risks and burdens it will bear, as well as the extent of benefits to other parties.¹⁷

“Individuals are exploited when they engage in transactions with others, but fail to receive a fair level of benefits. This suggests that the potential exploitation of communities arises when the communities are involved in health research, and others benefit from the community’s involvement.”¹⁸

They argue, following advocates of the Fair Benefits Approach, that benefits should not be restricted to communities involved in phase-III trials, since communities involved in early-stage research also contribute to the value of research, and that benefits other than reasonable availability of the tested intervention may be sufficient.

There are at least five types of cases in which host communities can be said to be involved in research, by Gbadegesin and Wendler’s criteria, and which therefore hold potential for the micro fairness exploitation of communities. The different types of cases either involve whole communities being exposed to risks (even if not all community members participate in the research), or communities having a direct claim to a share of the benefits of research. One of these types of cases is research conducted on a community partnership model, where the community is actively engaged by the sponsor or researchers from the design stages of the project and forward, and helps to determine the direction and content of the research. Such cases clearly

¹⁵ Subject to the usual caveats about determining what counts as fair.

¹⁶ Hughes (2012), p. 627.

¹⁷ Gbadegesin & Wendler (2006) p. 251.

¹⁸ Ibid., p. 250.

meet the community involvement criteria, but they are also much less likely to raise concerns about exploitation of the host community. Therefore, I will be focusing on four other types of cases: physical or financial community contribution, indirect risk to the community, direct risk to the community, and intellectual property community contribution. The first type of case involves research that relies on public infrastructure or other community resources. The second type of case, indirect risk, has the potential to eventuate in negative social consequences, such as stigmatization or discrimination, for a specific identifiable community. Most indirect risk cases involve genetic studies. The third type of case, which I will refer to as a direct risk case, involves research that imposes direct health risks on a community. Direct risk cases include live vaccine trials, and studies that alter some aspect of the community's local environment. Finally, the fourth type of case involves research intended to commercialize a community's traditional knowledge, such as trials of traditional medicines.¹⁹ I will refer to such cases as community ownership cases. In each of these cases, there is a clear sense in which an entire community bears risks or burdens, or is arguably entitled to a share of any financial benefits resulting from the success of a trial, in order to avoid micro fairness exploitation of the community.

Physical or Financial Community Contribution

A community may be said to contribute to a clinical trial in a fairly straightforward way when the trial relies on community resources such as a public hospital or clinic. In such cases, say

¹⁹ It could be argued that by the time compounds derived from a traditional medicine are brought to trial, they are no longer traditional medicines that are being tested – as suggested by Udo Schüklenk (personal communication). However, it does not follow from this that the traditional knowledge in question is not a significant contribution to the research program – without the traditional knowledge, the compound in question might never have been identified as a potential drug candidate. So there is at least a case to be made for the source community being owed some compensation in such cases.

Gbadegesin and Wendler, the community ought to be compensated in some manner for the contribution it has made.

“By relying on the community’s physical infrastructure, or its social or political structures, the investigators involve the community itself in the research. For these structures, processes, and organizations are common resources that belong to the community as a group, not to individual members of the community.”²⁰

The community’s involvement suggests that benefits to the community will be necessary to avoid micro fairness exploitation of the community (rather than of individual members of the community.) The need for community benefits to avoid micro fairness exploitation of the community in such cases would be entirely contingent on the trial’s reliance on community resources; on this basis, a trial conducted by a CRO in a private clinic may not need to provide much or indeed any benefit to the host community. Benefits to the community could be financial, perhaps taking the form of a community trust to fund beneficial community projects, or they could take other forms, such as the donation of hospital equipment at the conclusion of the trial. In many instances, the requisite level of benefits to avoid micro fairness exploitation of the community will be quite limited for cases of this type; as Hughes puts it, “this argument supports at most a weak obligation to benefit the host community.”²¹ Advocates of the fair benefits approach agree with this conclusion, noting that on a micro fairness understanding of exploitation, “there is no justification for including everybody in an entire region or country in the distribution of benefits... unless the whole region or country is involved in bearing the burdens of the research and at risk for exploitation.”²²

²⁰ Ibid.

²¹ Hughes (2012), p. 627.

²² Participants (2004), p. 23.

Indirect Risk to a Community

Indirect risks to a community usually arise when a study targets community features, as in genetic research, and are less likely to crop up with typical drug trials. Genetic research has been highlighted in the literature as having the potential to exploit communities.²³ Charles Weijer gives the example of studies of anonymized genetic samples from Ashkenazi Jews, which led to the identification of mutations that predispose people to breast, ovarian, and colon cancer. Weijer notes that although these studies posed no risks to individuals (since the samples were anonymous and in an existing databank), “the results of these studies may have a substantial impact on the community of Ashkenazic Jews. These two research reports may give further credence to the suggestion that Jews are more susceptible to malignancies... and this in turn may engender discrimination.”²⁴ Given that the community of Ashkenazi Jews was exposed to risk (namely, the risk of stigma or discrimination) by these studies, it follows that the community could have been exploited (in the micro fairness sense) if the studies produced benefits for others and the community did not receive a fair share of the benefits. Since the genetic mutations identified are not unique to Ashkenazi Jews, the research could potentially produce benefits for others outside of the community in question. It might be objected that since the stigma or discrimination in this example would affect individuals, then micro fairness should only require benefits to those individuals who actually suffer the stigma or discrimination. However, the *risk* of stigma and discrimination accrues to all members of the community, not only those who participate in the trial or those for whom the risk eventuates into actual harm, and as discussed in chapter 3, avoidance of micro fairness exploitation requires us to consider risks and potential benefits from

²³ Weijer & Emanuel (2000); Gbadegesin & Wendler (2006).

²⁴ Weijer (1999), p. 502.

an *ex ante* perspective. Hence, genetic studies of this type have the potential to exploit (genetic) communities, even on the ontologically minimal interpretation of a community as merely a collection of individual community members. As usual with avoidance of micro fairness exploitation, the benefits in question can take any form so long as they are sufficient to be fair.

Direct Risk to a Community

In the case of a live vaccine trial, the host community is also exposed to risk, in the more direct sense of the potential for increased risk of infection spread from those who are vaccinated. Live vaccines (nowadays) are attenuated – the microbes have been altered in the lab to render them non-virulent. However, because they are still living, it is possible for mutations to occur, including mutations that make the microbes virulent again. If this were to occur, participants dosed with the mutated live vaccine could not only become ill, they could also become contagious. Thus live vaccine trials pose a (typically very small) risk of contagion, which is primarily borne by the local population in the host community. The community bears risks in such cases (in this example, the relevant group is the geographic community, meaning all those who live or work in the same geographical area as the participants and are likely to come into close contact with them.)²⁵ Therefore the community could be micro fairness exploited if the trial results in benefits for others and the community does not receive a fair share of those benefits. Similarly, a trial that alters some aspect of the local environment, such as an environmental release trial of mosquitoes that have been genetically modified to make them less effective disease vectors,²⁶ can potentially impose risks on a community. In both examples, the risks, while

²⁵ While it is possible for the infection to spread beyond the host community, those in the host community are subjected to an elevated risk in a way that can be identified *ex ante*, which is the basis of the claim that the host community could be owed something.

²⁶ Lavery, Harrington & Scott (2008) discuss site selection considerations for such trials. While their project (at that point in time) did not involve releasing genetically modified mosquitoes into

small, are directly borne by all those who live or work in a particular area, regardless of whether they are participants in the research trial or not. Since the entire community bears these risks, it follows that there must be some prospective benefit for the entire community in order to avoid the community's being micro fairness exploited; however, since the risks are very small, so too the level of benefits needed to avoid micro fairness exploitation of the community will be minimal. In many direct risk cases, it could be argued that community access to the knowledge gained from the research would be a sufficient benefit to ensure micro fairness.

Community Ownership

The fourth type of case, community ownership, is perhaps the most unusual. In such cases, the potential for micro fairness exploitation of a community is not contingent on the community actually hosting the trial. This is because rather than the community bearing risks or burdens, the community's involvement in the trial is that the experimental intervention is based in the community's traditional knowledge or traditional medical practices. In such cases, there are grounds for a claim that the community has contributed in some way to the research, and hence should receive some benefits from the research. For instance, consider an aboriginal community, *A*, whose traditional medical knowledge advises the treatment of some condition, *L*, with an extract from a particular plant, *P*, which is commonly (though not exclusively) found in the traditional territory of *A*. Now imagine that following the popular reporting of some anthropological research on *A*'s traditional medical practices, Farmako, a multinational pharmaceutical company, decides to investigate the *P* extract as a potential treatment for *L*. Farmako is able to procure *P* from outside of *A*'s traditional territory, and the published anthropological research is sufficiently detailed that they are able to reproduce the traditional

the wild, the ultimate goal of their research (to use genetic modification of insects as a disease control strategy) would require such a trial.

extract of *P*, without needing to contact anyone from *A*. Farmako then conducts some chemical analyses to identify *Q*, the specific chemical compound in the *P*-extract that they believe to be the active ingredient. The company files for a patent on compound *Q*, proceeds to conduct clinical trials on *Q*, and on the basis of the success of those trials, receives regulatory approval to bring the new drug to market. In this scenario, community *A* is not directly involved in the trials process at all (the trials are conducted in another country). Nonetheless, it could be argued that unless Farmako works out a fair benefit-sharing arrangement with *A*, then the community has been exploited in the micro fairness sense.²⁷ This is so even if Farmako seeks official permission from the leaders of *A* to conduct the trial. Since community *A* has majorly contributed to the trial interaction (in the form of its traditional knowledge), community *A* has a claim to some share of the benefits of that interaction (in this case, presumably in the form of a royalty or share of the profits).

It has been objected, by Udo Schüklenk and Anita Kleinsmidt, that benefit-sharing arrangements in bio-prospecting schemes are well intentioned but misguided, because the patent system is not designed to handle traditional knowledge, and such arrangements often result in negligible benefit to the communities and do little to address the problems of lack of access to essential medicines and lack of research into treatments for tropical diseases. Patent protection is inappropriate for traditional knowledge, they argue, since it is not novel by definition,²⁸ and ironic, given that drug patents are a major contributing factor to the lack of access to essential medicines in LMICs. As mentioned in section 5.1, there are also issues regarding the quality and

²⁷ In this example, it is perhaps also possible that *A* has been exploited by the anthropologists, but I will bracket this concern for the purposes of the present discussion. In any event, the anthropologists are not essential to the example: for instance, a vacationing Farmako employee, who observes the traditional medical practice while visiting the area, could fill the anthropologists' role.

²⁸ Schüklenk & Kleinsmidt (2006), p. 129.

legitimacy of a community's representatives, and problems with determining community membership.²⁹ In spite of these objections, even Schüklenk and Kleinsmidt acknowledge "a sense of fairness necessitates that the holders of knowledge are compensated when that knowledge is used to generate financial gain for commercial operators."³⁰ While I am sympathetic to their argument that patent protection is inappropriate in cases of treatments derived from traditional community knowledge, so long as such patents continue to be given out, avoidance of micro fairness exploitation of the communities whose traditional knowledge is commercialized seems to require that the communities receive a fair level of benefits as compensation for their contribution.

5.3 Community Benefits and Macro Fairness Exploitation

Macro fairness accounts of exploitation, as discussed in Chapter 3, share micro fairness accounts' focus on fairness of the distribution of benefits from an interaction, but contend that background conditions such as structural injustice are relevant to determinations of fairness. Avoiding macro fairness exploitation does not require individual agents to singlehandedly undo the damage caused by structural injustice, but it may impose limits on how they can interact for advantage with parties who are the victims of such injustice,³¹ or it may involve a political responsibility to help address structural injustice.³² Community benefits may be necessary to avoid macro fairness exploitation of host communities in those cases where they are also

²⁹ *Ibid.*, p. 132.

³⁰ *Ibid.*, p. 129.

³¹ Pogge (2008), p. 113.

³² Young (2006), p. 102.

necessary to avoid micro fairness exploitation of host communities, though the two accounts may differ with regards to the level of benefits required. Recall that on Thomas Pogge's view, one must treat the victims of injustice "as [one] would have to treat them if this injustice did not exist."³³ Effectively, this means that when proposing to interact with victims of injustice, one ought not to offer terms of interaction that are only made acceptable to them by their unjust circumstances. Conversely, avoiding macro fairness exploitation of host communities may be less a matter of benefit distribution and more a matter of increased political responsibility to address the underlying structural injustice one is profiting from, according to Iris Marion Young's account. Agomoni Ganguli Mitra, on the other hand, addresses the question of community benefits head-on, advancing an argument that host community benefits are necessary to avoid the macro fairness exploitation of individual trial participants. It is this argument that is the focus of the present section.

Mitra argues that individual participants can be exploited in a macro fairness sense by clinical trials that violate what she calls the "reciprocity constraint."³⁴ Although her argument makes claims that are initially counterintuitive, further examination shows that there may be something to the notion that an individual participant can be macro fairness exploited by a clinical trial that does not sufficiently benefit the host community.

The argument in question, linking insufficient host community benefit with macro fairness exploitation of individual participants, is advanced by Mitra in her article "Off-Shoring Clinical Research: Exploitation and the Reciprocity Constraint." Mitra begins by critiquing and rejecting Alan Wertheimer's micro fairness approach in favour of a macro fairness approach. This critique allows for consideration of the larger context surrounding research interactions, including

³³ Pogge (2008), p. 113.

³⁴ Mitra (2013), p. 111.

the norms of the enterprise of clinical research. The justification for the research enterprise, according to Mitra, depends on its integration within a health system “from which participants regularly benefit.”³⁵ Participation in clinical research therefore ought to be a way to reciprocate the benefits one receives from the health system as a patient. Therefore, off-shored research can macro fairness exploit participants by having them contribute to a health system that does not benefit them.

Mitra’s critique of Wertheimer focuses on Wertheimer’s view that micro fairness exploitation is the only type of exploitation, his modeling of exploitation as a feature of two-party transactions, and the level of abstraction in Wertheimer’s account. Ultimately, all of her criticisms boil down to an insistence that in questions of exploitation, context is relevant in ways that Wertheimer’s account does not recognize. On a macro fairness view (and contrary to Wertheimer’s micro fairness view) the background conditions of all parties are relevant to exploitation claims; Mitra argues (following Jeremy Snyder) that both micro fairness and macro fairness accounts of exploitation have validity, and need not be exclusive.³⁶ Similarly, Mitra claims, Wertheimer’s transaction model of exploitation obscures the number and variety of agents involved in research interactions, and the ways that their various roles and interests can have a net effect of disadvantaging participants.³⁷ Finally, she alleges that the abstractness of Wertheimer’s account obscures relevant features such as the norms of the enterprise in question. In response to these issues, Mitra proposes to provide the missing context by “emphasising the nature and

³⁵ Mitra (2013), p. 112.

³⁶ *Ibid.*, p. 113.

³⁷ *Ibid.*, p. 114.

justification for the enterprise of research itself,”³⁸ in order to clarify some of the exploitation claims that arise with regards to off-shored clinical research.

On Mitra’s account, research is one of three arms of a health system, with the others being health care and public health. The three arms are interdependent, each having different goals and methods: health care benefits individuals, public health benefits populations, and research makes it possible for them to do this — but does so at a cost to participants. Clinical research, Mitra claims, must have social value in order to be justified, and this social value comes in the form of improved capabilities of the health care and public health arms of the health system. “Clinical progress and medical innovation have a true *raison d’être* only in a society where access to their fruits are a reality.”³⁹ Her idea is that the enterprise of clinical research is justified as a form of reciprocity: it is a way for people to contribute (as participants) to the health system that benefits them (as patients). Since off-shored research does not generally benefit participants in terms of health care or host communities in terms of public health, the reciprocity justification fails in such cases. Hence off-shored clinical research can be macro fairness exploitative of participants when it disregards this reciprocity principle, because in such cases LMIC participants are contributing to the health systems of HICs, but the health care and public health benefits of these systems are not afforded to the LMIC participants. As Mitra puts it, “the exploitative nature of such transactions lies in asking participants to contribute to a system from which they derive little or no benefit as patients.”⁴⁰

To the extent that it is successful, Mitra’s argument reveals a way in which ensuring sufficient host community benefits may be necessary to avoid macro fairness exploitation of

³⁸ Ibid.

³⁹ Ibid., p. 115.

⁴⁰ Ibid.

individual participants. If LMIC participants are being asked to contribute to a health system that benefits others but not themselves, there may be macro fairness exploitation occurring. It is worth noting that while Mitra talks about a health *system*, this is a simplification and in reality there are many health *systems*. Each country has its own health system, and indeed some countries (such as the USA) have multiple systems. One wrinkle that arises from this distinction is that it is not necessarily problematic if a participant's contribution to research benefits a health system of which the participant is not a beneficiary – so long as that contribution *also* benefits a health system of which the participant *is* a beneficiary. For instance, if a clinical trial conducted in France demonstrates the efficacy of a new drug, and that new drug subsequently becomes widely available in all HIC markets, the trial participants have effectively contributed not only to the French health system, but also to the health systems of the other HIC countries. So long as the French health system is among the beneficiaries of the research, and the participants are beneficiaries of the French health system's health care and public health arms, then Mitra's reciprocity principle has not been violated. Conversely, if the same trial were conducted in Malawi, and the new drug subsequently made widely available in HIC markets but not in Malawi, then the trial would run afoul Mitra's reciprocity principle. The Malawian trial would be macro fairness exploitative of its participants, while the French trial would not, on Mitra's account. This is the sort of result that is clearly the intended outcome of Mitra's argument, but it also points towards some (presumably) unintended consequences of her argument. Although in some particular cases, application of her reciprocity principle yields the result that host community benefit is necessary to ensure that individual participants are not exploited, this connection between community benefit and individual exploitation is contingent on the fact that health systems are typically organized at the national level. Reciprocity only requires that *participants*

benefit from a health system that benefits them as patients; any benefits to non-participant members of the host community are “collateral benefits”. Although it would certainly go against the spirit of her proposal, there is nothing in her arguments to preclude the possibility of novel health system arrangements that would technically respect the reciprocity principle while providing little or no collateral benefit to the participants’ fellow LMIC citizens. For instance, imagine that Mitra’s reciprocity principle were to become widely enshrined in policy and regulation. Keen to maintain their competitive advantage, a consortium of CROs in India band together to build a small testing village with a hospital. Prospective participants are offered residence in the village, and the consortium sets up and pays for health care and public health systems that serve the village. So long as the village’s health care and public health systems keep up with the innovations that are researched in the village, Mitra’s reciprocity principle remains inviolate. This remains true if we stipulate that the village’s health system is exclusive to residents, all of whom are trial participants; it is unclear how Mitra could object even if the consortium made it a condition of continued village residency that residents must participate in a minimum number of trials each year. To Mitra’s credit, although this testing-village scenario is unlikely to sit well with people concerned about benefits to host communities, it might still represent a significant improvement from the current state of affairs for many prospective trial participants in LMICs.

5.4 Community Benefits and Mere Use Exploitation

The third type of exploitation, mere use exploitation, involves the wrongful use of another rational agent. On Andrew Siegel’s strict Kantian account, this wrongful use of another

rational agent involves agent A benefitting from acting toward agent B on a maxim that “fails to acknowledge needs that are essential to B qua rational agent.”⁴¹ Such action violates A’s duty of beneficence. On Ruth Sample’s account of mere use exploitation, it is a kind of failure of respect for the inherent value of persons, which in turn thwarts human flourishing. Mere use exploitation thus “involves interacting with another being for the sake of advantage in a way that degrades or fails to respect the inherent value in that being.”⁴² Like Siegel, Sample links the wrongness of exploitation with a failure of the duty of beneficence, but unlike Siegel, she argues that this imperfect duty becomes a specified duty when one proposes to interact with particular others who have unmet genuine needs. Although he does not specify an account of exploitation, both of these mere use accounts are compatible with Robert Hughes’ argument that host community benefits are necessary, in at least some cases, in order to avoid the mere use exploitation of individual trial participants. However, it is implausible to claim that a lack of host community benefits could constitute mere use exploitation of the host communities, on either account of mere use exploitation. In this section, I will begin by explaining and evaluating Hughes’ argument that host community benefits may be necessary to avoid mere use exploitation. I will then proceed to briefly explain the difficulties with making any mere use exploitation claims on behalf of host communities.

5.4.1 Community Benefits & Mere Use Exploitation of Individual Participants

Hughes advances an argument that can be used to demonstrate that, in at least one type of case, an off-shored clinical trial must have prospective benefits for the host community in order to

⁴¹ Siegel (2008), p. 181.

⁴² Sample (2003), p. 57.

avoid exploiting individual participants. According to Hughes, “when research involves substantial net risk to subjects, individual risk and community benefit are ethically linked.”⁴³ This is because trials that pose substantial net risk to subjects must be justified at least partly by appeal to altruism, and historical facts as well as current relations between LMICs and HICs make it inappropriate and disrespectful to ask LMIC citizens to take on substantial risks in order to altruistically benefit HIC citizens. This disrespect constitutes mere-use exploitation of LMIC subjects, according to Ruth Sample’s account of mere-use exploitation.

After noting his assumption that the term “community” is to be understood geographically for the purpose of his argument, Hughes begins by explaining what he means by substantial net risk. Whenever the potential for medical benefit to subjects is less than the risks (broadly construed) of the intervention,⁴⁴ there is a net risk to subjects; in such cases, subjects “could not rationally choose to receive this intervention for their own medical benefit.”⁴⁵ Hughes focuses on cases of *substantial* net risk because it is clearest in these cases that subjects’ participation cannot be justified solely by the prospect of personal medical benefit. In order for such trials to be ethical, the net risk posed to subjects by the intervention must be balanced by other benefits, either to subjects or to others. Additional benefits to subjects (i.e., benefits not resulting from the trial intervention) would be sufficient if, all things considered, participation yields net benefits or at least approaches a “break even” point between risk and benefit, thus rendering participation in the interest of prospective participants. Hughes considers two potential additional types of benefits: medical benefits and financial benefits. Medical benefits could include ancillary care or screening that would not otherwise be available to participants. Hughes

⁴³ Hughes (2012), p. 626.

⁴⁴ For more on quantifying such risks, see Wendler & Miller (2006).

⁴⁵ *Ibid.*, p. 627.

notes that there is some controversy as to whether ancillary care should be counted in risk/benefit evaluation of a trial, with for instance Kenya's official guidelines specifying that it must not be counted; in any event, he claims, not all substantial risks can be justified by ancillary care or screening.⁴⁶ As for financial benefits, while they may be effective recruitment tools, Hughes accepts the dominant view that payments are not risk-justifying benefits.⁴⁷ He concludes that if a trial poses substantial net risk to participants, and this is not offset by additional medical benefits such as ancillary care or screening (whether because such benefits cannot justify risks to participants in general, or because the benefits are insufficient in a particular instance), then "researchers must be justified in asking prospective subjects to participate at least partly out of altruism."⁴⁸

The problem for off-shored trials that pose substantial net risk to participants, according to Hughes, is that it is sometimes unreasonable (and therefore disrespectful) to ask certain parties for help. In particular, he claims, otherwise reasonable requests for help can be made unreasonable by a negative relationship between parties, or by past refusals to help the other party from the party currently asking for help.⁴⁹ Since one or both conditions will generally obtain in cases of off-shored research, it is generally unreasonable (and therefore disrespectful) to ask prospective participants from LMICs to participate altruistically in research that will primarily benefit HIC citizens. (Either condition's obtaining would be sufficient to render the request for altruistic help from LMIC citizens disrespectful.) With regards to the first condition, Hughes points to the cosmopolitan view of distributive justice and to Pogge's argument that HICs actively

⁴⁶ Ibid.

⁴⁷ Ibid., p. 628.

⁴⁸ Ibid.

⁴⁹ Ibid.

perpetuate inequality between HICs and LMICs; if either of these views is correct, then the first condition obtains. While cosmopolitanism is very controversial, as Hughes acknowledges, Pogge makes a fairly compelling case that HICs actively perpetuate poverty in LMICs.⁵⁰ Even if one remains skeptical about Pogge's conclusions, Hughes can fall back on the second condition. The second condition indisputably obtains, according to Hughes, because of the collective lack of generosity on the part of HIC citizens towards LMICs. Though it may be permissible, "the collective refusal of high-income countries' citizens to make even modest financial sacrifices to save lives in LMICs makes it unreasonable to ask people in LMICs to risk their health for the sake of people in rich countries."⁵¹ If researchers do unreasonably ask people in LMICs to take on such risks, such requests demonstrate a failure of respect for the prospective participants.

Although Hughes does not explicitly make the connection to exploitation, this sort of disrespectful interaction could potentially qualify as mere-use exploitation. It appears to fit the bill of mere-use exploitation on Sample's account, which she describes as "disrespect toward a person in pursuit of our own advantage – the disrespect of merely using another person."⁵² Mere use of a person, according to Sample, means refusing to take that person's genuine interests seriously. It follows that Hughes' argument shows that it is at least *possible*, in certain types of cases and on a certain understanding of exploitation, for individual participants to be exploited by their participation in a clinical trial that fails to provide sufficient benefits to the host community. Note that this is possible even if participants are compensated financially as recommended in Chapter 6. That there are grounds for exploitation claims on behalf of individuals based on a lack

⁵⁰ Pogge makes a number of similar arguments to this effect in various places. For an example, see Pogge (2005).

⁵¹ Hughes (2012) p. 628.

⁵² Sample (2003), p. 70.

of community benefits is an interesting result, but it is limited in scope. Most significantly, it only applies to trials with substantial net risk to subjects. Additionally, there is no necessary connection to the host community in particular – which is to say, the community benefit requirement can be satisfied by benefits to *any* LMIC community that does not have a negative relationship with the host community and has not previously refused requests for help from the host community. Furthermore, this argument only demonstrates the possibility of mere use exploitation of individuals by failing to benefit communities, and mere-use exploitation is perhaps the most controversial of the three types of exploitation discussed in Chapter 3 (although it may just be the least-widely accepted, judging by the relative paucity of citations of Sample’s book in the literature in comparison with other authors). Nonetheless, Hughes’ argument offers a novel account of the connection between exploitation and community benefits in off-shored clinical trials.

5.4.2 Community Benefits and Mere Use Exploitation of Host Communities

As discussed in section 5.2, there are several types of cases in which a host community could potentially be micro fairness exploited by a clinical trial. It likely follows that a host community could potentially be macro fairness exploited by a clinical trial, as discussed in section 5.3, since both types of exploitation concern unfairness, and micro fairness is more stringent in terms of which factors enter into the equation.⁵³ It remains to be seen, however, whether there are any grounds for claims that a community can be mere-use exploited by a trial.

⁵³ I say that it *likely* follows, because one would expect most cases of micro unfairness to also be macro unfair, though not necessarily vice versa. If factory owner A pays worker B \$0.30 per day, which we shall assume is micro-unfair, it is unlikely that taking into account B’s vulnerability, A’s privilege, and the structural and historical injustices at play will yield the result that B’s wage is macro fair.

There are some *prima facie* reasons to think that a mere use account of exploitation would be applicable here. A host community's lower standards of care, lax regulations, low cost of labour, and adherence to the TRIPS treaty could all be used by a foreign research sponsor, it seems, and this could all be done with minimal benefit to the host community. For example, in the proposed Bolivian Surfaxin trial, one could argue that Discovery Labs' planned study would have used Bolivia as a mere means. Bolivia was chosen as a study site only because the local standard of care would have allowed for the use of a placebo-control trial design (and hence the trial would arguably have involved Bolivia, as it focused on a particular health feature of the community). Had the planned trial gone ahead and been successful, Discovery Labs stood to gain, as did some HIC patients and even the prospective individual participants (since the "placebo" in question was not a true placebo, as it was known to be better than the non-treatment otherwise available to prospective participants). Bolivia, however, would have gained little from hosting the trial.

However, the *prima facie* case quickly falls apart upon further consideration, because the mere use account of exploitation is only applicable to interactions with a certain kind of entity, namely a being with inherent value and worthy of moral respect. On Siegel's account, it is only possible to mere use exploit rational agents.⁵⁴ Similarly, on Sample's account it is only possible to mere use exploit persons, beings with inherent value.⁵⁵ These definitions leave the door open for potential claims about the mere use exploitation of artificial intelligences and perhaps certain non-human animals, but it would be a very contentious account of the nature of communities that satisfied either definition. Certainly the minimalist reading I have been using thus far, of communities as collections of individuals, would not provide a basis for mere use exploitation

⁵⁴ Siegel (2008), p. 181.

⁵⁵ Sample (2003), p. 57.

claims on either of these accounts. On this reading, any mere use exploitation would have to be mere use exploitation of the individual community members, so there would be no grounds for claiming the necessity of community benefits unless every single member of the community (including those who were not trial participants) would otherwise be mere use exploited. The only way that I can see for a case to be made for the possibility of mere use exploitation of communities would be to argue for a *very* “thick” conception of community, such that a community is not just a collection of individual members, or even the set of its members plus their customs and language and institutions, but a rational agent (which is the source of the inherent moral value of persons on Sample’s account). I am very skeptical that a plausible and convincing case can be made for such a conception of community, and in the absence of such a case, there is no real basis to claim that communities can be mere use exploited.

5.5 Community Benefits and Avoiding Exploitation

Host community benefits have been mentioned as potentially being important to avoiding exploitation in clinical trials. Setting aside the thorny issues of defining, identifying and delineating host communities in clinical research, and focusing on a “thin” conception of community, this chapter has analysed the connection (or lack thereof) between host community benefits and the avoidance of each of the three types of exploitation, as well as determining the potential victims of exploitation in cases where such benefits do not accrue to host communities. In certain types of cases, avoidance of micro and macro fairness exploitation of host communities will require that host communities receive a fair level of benefits, or that researchers and sponsors

support collective efforts to address structural injustice, respectively. Host communities are not generally the right type of entity—inherently morally valuable rational agents—to be a possible victim of mere use exploitation. From a micro fairness perspective, host community benefits are completely incidental to avoiding the exploitation of individual trial participants. In contrast, there may be some types of cases, respectively argued by Mitra and Hughes, where community benefits are necessary to avoid the macro fairness exploitation or mere use exploitation of individual participants.

Chapter 6

Participation, Compensation, and Exploitation

In chapter 2, I reviewed the recent history of the debate about exploitation as an ethical concern in clinical trials. In chapter 3, I discussed several theoretical accounts of exploitation and provided a rough working description of exploitation. In this chapter, I turn my attention to the question of how to avoid exploiting individual clinical trial participants. The overarching argument of this chapter is as follows. Firstly, I will argue that clinical trial participation (whether by healthy volunteers or patients) is properly thought of as a form of labour. Secondly, I will argue that compensation, in the form of monetary payments to participants, is generally appropriate to commercial exchanges of labour, and that compensation can help avoid or minimize exploitation. Thirdly, I will review several competing concerns, which could be argued to support the limiting of compensation offers. Finally, I will outline a compensation model for participants in commercial clinical trials, which I will argue provides better protection of participants against exploitation than the status quo, while remaining feasible and not worsening the situation of the badly-off.

6.1 Clinical Trial Participation As Labour

In this section, I will argue that clinical trial participation is properly thought of as a form of labour. I will begin by outlining and defending a general definition of “labour.” Next I will make a *prima facie* case for thinking of clinical trial participation as labour. Then, I will argue

against the distinction between healthy volunteers and patient participants in terms of whether their participation should be thought of as labour. I will briefly touch on some difficult cases that may appear to run counter to my general claim that participation is labour. Finally, I will address some potential objections to my general claim that participation is labour.

6.1.1 What Counts as Labour?

Although it is not exactly like manufacturing production-line work, which is still the implicit archetype for the idea of “labour” (in spite of the fact that this type of work accounts for a small and diminishing proportion of employment in most developed economies), I will argue that participation in a clinical trial is nonetheless a form of labour. In economics, “any resource used in the production of goods or services” is called a factor of production, and these “can be broadly classified into three main groups: labour, or human services; capital, or man-made means of production; and land, or natural resources.”¹ In other words, labour is the use of human beings in the production (or attempted production) of something of value. Under this definition, labour can be done for oneself, for the benefit of another, or as part of an exchange with one or more other parties; hence the DIY home-improvement project, the volunteer litter clean-up, and the 9-to-5 office job all comfortably fit within the concept of labour, as they should. The product of labour could be a physical object like a chair, but it need not be an object at all – it could be a service rendered, or in the case of intellectual property, a non-material good. This is necessary to distinguish between actions that do not aim at value-production and are typically not thought of as labour (for instance, scribbling absent-mindedly on each page in a stack of papers) from otherwise similar actions that are thought of as labour (such as grading and commenting on a

¹ Black, Hashimzade and Myles (2009), “Factor(s) of Production”.

stack of essays.) It is worth noting that an unsuccessful attempt at production does not negate the status of the factors of production that went into the attempt: when a chef makes a dish that is then sent back, the preparation of the replacement dish is labour but so was the preparation of the original dish.

6.1.2 A *Prima Facie* Case For Clinical Trial Participation as Labour

On the basis of the preceding account of labour, I offer the following *prima facie* argument for thinking of clinical trial participation as a form of labour. According to this definition, the hallmarks of labour are present in clinical trial participation: the trial participant's body and time are used in an attempt to produce something of value. In this instance, that product is scientific knowledge rather than a car, a chocolate bar, or a load of coal. Much like the production line worker, the trial participant may have very limited knowledge of the process of which their efforts form a part, and the efforts of the individual participant, taken in isolation, would not amount to anything useful; it is only when the whole production line is taken into account that the addition of value becomes evident.

The clinical trial is a mode of production, and the good it produces is scientific knowledge. The financial value of this good arises from the legal frameworks of patents and intellectual property, combined with the regulation of the drug market. To promote pharmaceutical innovation, new drugs can be patented, effectively providing a temporary (20-year) period of state-enforced monopoly for the new drug's patent-holder. This monopoly gives the patent-holder the power to charge an arbitrarily high price for the drug during the life of the patent, because there is no competitive pressure for the patent-holder to bring the price closer to the cost of making the drug. However, prescription drugs cannot simply be sold to consumers;

they must first be prescribed by a doctor. Doctors can only prescribe drugs that have been approved by the local drug-regulating authority, and drug-regulating authorities only approve drugs that have been proven safe and effective by clinical trials on human subjects. So while clinical trial participants do not make the tested drugs, they are a necessary factor in the production of the scientific knowledge that enables the tested drugs to be sold.

6.1.3 Objections to Participation as Labour

As there has been relatively little argumentation in the literature to support the notion that clinical trial participation (CTP) is a form of labour,² it may be helpful to consider a number of potential objections to this notion,³ as well as possible responses to those objections. In the following section, I will examine several such objections in turn.

Health Benefit Objection

One might object that CTP should not be thought of as a form of labour on the grounds that, unlike other forms of labour, CTP can offer the prospect of personal health benefits. That is to say, participation can sometimes directly improve a participant's health (as in the case where they are randomized to the active arm of a trial for a drug that turns out to be effective).

² Dickert & Grady (1999) make a very brief argument that participation is similar to unskilled labour, which argument is cited by others such as Phillips (2011), Lemmens & Elliott (1999). Cooper & Waldby (2014) also provide a very detailed account of what they refer to as clinical labour.

³ As Benjamin Sachs notes, few attempts have been made in the literature to identify disanalogies between the investigator-subject relationship in clinical research and the employer-employee or volunteer organizer-volunteer relationships. Sachs locates and (rightly) dismisses only two such attempts, both centred on the riskiness of clinical research and both disputing the propriety of monetary compensation for participation, rather than disputing that clinical trial participation is a form of labour. See: Sachs (2010), p. 73.

This objection is easily dismissed, as there are other (undisputed) forms of labour that can also offer direct health benefits to the labourer. For instance, letter carriers get outdoor exercise every working day in the course of their duties. Physical activity (and walking especially) can confer an array of health benefits. While it is true that not every letter carrier will get all of the potential benefits, and indeed they are all simultaneously exposed to concomitant risks (such as joint wear, increased exposure to air pollution, and increased sun exposure), this only serves to further cement the analogy between letter carrying and CTP.

Motivation Objection

Another potential objection to conceiving of CTP as a form of labour is that the motivational structures of CTP and undisputed forms of labour are too dissimilar.⁴ In traditional forms of labour, both the labourer and the employer are motivated primarily by financial concerns. Conversely, on this objection, in CTP neither the participant nor the researcher is primarily motivated by prospective financial gain (though admittedly the sponsor might be.) According to this objection, the researcher is (or at least ought to be) motivated by the prospect of creating new scientific knowledge and by the prospect of helping people who might suffer from the relevant condition in the future. The participant is also (or at least ought to be) motivated by these same prospects, and may also (permissibly) be motivated by the prospect of direct health benefit. A difference in motivation can make a difference to the meaning of an action, and such is the case here, says the objection: since participants are not motivated by economics, their participation is not a form of labour.

However, this objection fails because the motivational structure of CTP is not so different from other forms of labour in practice. Straight away, this objection has a credibility problem,

⁴ A version of this argument is made by Lemmens & Elliott (1999), p. 4.

since both individual researchers and CROs *are* typically paid – often handsomely – to conduct the research. This is compounded by the fact that commercial research sponsors are transparently motivated primarily by prospective financial gain. Even if the *ideal* motivational structure of a clinical trial is different from typical forms of labour, it is unclear that this matters given the similarity in practice. If the objection is modified so that it only claims that the *participants'* motivation is dissimilar from the motivations of people undertaking recognized forms of labour, it still falls flat, as can be seen in the following example.

To see how similar CTP is to other forms of labour in terms of motivation, let us consider an example. Imagine a film studio hiring a very serious filmmaker to produce a film of real artistic significance. The studio is primarily motivated by the prospect of financial gain, much like the commercial sponsor of a clinical trial. (For an analogy with a non-commercial trial, imagine that the film has been commissioned from the filmmaker by the national film board, which is motivated primarily by the film's cultural significance.) The studio (or film board) is analogous to the research sponsor in both role and motivation. The filmmaker herself is motivated by the prospect of making an artistic cultural contribution, personal career advancement, and the cultural benefits the film may have for people who see it in the future. She is thus analogous to the researcher in both role and motivation. Finally, the filmmaker casts hundreds of extras for the film. Due to the abstract nature of the film, the extras require no real acting skill – they just show up and follow the directions they are given. Many of the extras are motivated by the potential artistic and cultural significance of the film, and some are also motivated by the chance to potentially get some artistic benefits from their participation (such as inspiration for their own work, or learning by observing a skilled filmmaker, et cetera). So the motivations and role of the extras are analogous to those of the clinical trial participants. But it is not controversial to say that

what the extras contribute to the film is their labour (as well as their likenesses). So even the idealized motivational structure of CTP is not unlike that of a labour relationship. Furthermore, the recognition that the extras are labourers, and that they should be paid as such, need not have a corrupting influence on the artistic integrity of the film – even if some of the extras now count financial gain as their primary motive for participation. Similarly, we might infer that recognizing participants as labourers need not have a corrupting influence on the scientific integrity of the study (but more on this later).

Passivity Objection

Another objection to the notion of CTP as a form of labour is that labour is essentially active, but CTP is essentially passive; a labourer does something, while a participant has something done to them. Therefore, according to this objection, CTP cannot be a form of labour.

Although *prima facie* appealing, both of this objection's premises turn out to be questionable. Let us begin by examining the second premise, that CTP is essentially passive. It is certainly true that CTP *may* be passive; for instance, consider the Surfaxin trials that were eventually conducted on infants in respiratory distress.⁵ The infants in that study were hardly active participants. Similarly, one might conduct a trial of a new resuscitation device, which would necessitate the use of non-responsive (and hence utterly passive) subjects. However, it is another matter entirely to say that CTP is *essentially* passive – this is to say that passivity is a *sine qua non* condition of CTP.⁶ Yet in many instances, CTP requires active involvement. Participants may be asked to follow a drug regimen, record and/or report symptoms, answer questions about

⁵ For a thorough summary of the details of this case, see Hawkins & Emanuel (2008b), pp. 58–62.

⁶ In order for the objection to work, three conditions must obtain:

- 1) Labour must necessarily be active
- 2) CTP must necessarily be passive
- 3) It must not be possible for an action to be both active and passive.

their history, condition and symptoms, or present themselves to the clinic for follow up, among other things. So participation can also be active.

Next, let us examine the first premise, namely that labour is essentially active. Once again, it is certainly the case that labour can be active. Indeed, the archetypal forms of labour all seem to be active, such as manufacturing, resource collection, and agriculture. Even less-traditional forms of labour, such as office work, involve mental activity, if not much in the way of physical activity. However, when we are talking about essences — as this objection must do in order to succeed — it is not enough for most cases to fulfill the essential property, and so a single counter-example is sufficient to demonstrate that a putatively essential condition is not really essential. Modelling provides us with such a demonstration. At least sometimes, a model's labour consists of little more than being present and having certain physical characteristics. For example, imagine a photo shoot for a print advertisement for a wristwatch, where only the model's hands will be photographed. The model is required to show up at a certain time, allow the crew (makeup and wardrobe artists, lighting and camera operators) to work on him, and hold still in specified positions for specified periods of time while the photos are taken. The model in this case has no role in the planning of the photo shoot or the design of the advertisement: his contribution begins when he shows up at the start of the shoot, and ends when the shoot ends. In this example, the model's involvement is largely passive – at least as passive as the involvement of a clinical trial participant. And yet the model's contribution, like that of the clinical trial participant, is still a (minimal) form of labour because in both cases, they are factors in the production of a good or service. Even if the objector were to revise their notion of activity to accommodate the model's work, the objection would still fail because any such revision would also capture the work of some trial participants, whose involvement can be more active than that of the model.

No Free Labour Objection

One might object that CTP cannot be labour on the grounds that, unlike labour, CTP is willingly undertaken free of charge by many. There are two possible readings of this objection that lend it some plausibility. The first reading assumes a certain level of economic rationality (i.e. self-interested maximizing rationality) in people, such that it would be unlikely to find many people participating in clinical trials for free if that were really a form of labour. However, there are two shortcomings of this reading. Firstly, people may freely give their labour for rational but non-economic reasons, such as to further a cause they support. Secondly, it does not follow that even economically rational (self-interested maximizing) agents would not “give away” labour. Under certain circumstances, such a course of action may represent an agent’s least worst option, which is the fertile soil in which exploitation grows. For instance, a young graduate may take an unpaid internship if it appears to be their best opportunity to break in to a desirable industry.⁷ Similarly, a cancer patient may enrol in an unpaid clinical trial if it appears to be their best opportunity to get effective treatment (despite the fact that they could be randomized to a placebo arm, and that the investigational intervention may prove not to be effective.) In neither case does a willingness to forgo compensation indicate that there is no exchange of labour.

On the second reading, the objection is not about actual agents but the expected actions of idealized rational economic agents (again, self-interested maximizers). On this reading, the objection posits that such idealized agents would still sometimes agree to participate in clinical trials without fiscal compensation. The reason for this willingness is that trials can offer the prospect of non-monetary benefits that may be highly valued by the idealized agents, such as potential medical benefits. Of course, this reading only has a patina of plausibility, because the

⁷ In fact, there have even been reports of graduates paying for the “privilege” of an unpaid internship placement. See, e.g., Shih (2009); Johnson (2010); Olen (2013); Patty (2014).

idealized rational agents are not really participating for free – they are doing so for non-monetary (but nonetheless valuable) benefits. So it does not follow that the idealized agents do not view participation as valuable labour, only that the benefits of exchange (CTP) are sometimes sufficient to motivate them.

Unique Nature of Medicine/Medical Research Objection

It might be objected that medicine and/or medical research are different in nature to other value-producing activities, and that for this reason, the contributions of research participants should not be considered labour.⁸ However, if the medical research enterprise's unique nature precludes participation in that enterprise from counting as labour, then it would seem to follow that researchers' contributions should also not count as labour. This would be an absurd suggestion. Recall that labour is the use of humans as factors of production of a good or service, and that clinical trials produce the good of scientific knowledge. Thus the contributions of researchers and participants alike are labour, in economic terms. There remains the question of whether (and what type, and how much) compensation is appropriate for such labour, and the alleged unique nature of medical research may be relevant to that discussion, but it makes no difference to the question of whether or not trial participation is labour.

Double Toiler Objection

This objection to the notion of CTP as labour claims that CTP cannot be labour because it is possible to do other forms of labour while participating in a trial. For instance, a writer could plausibly churn out copy during an extended observation period of an overnight stay drug study. While it has a whiff of initial plausibility, it is ultimately a spurious objection. Of course it is possible to do two forms of labour at once – on the pitch, the professional soccer player is at once

⁸ This objection was suggested by Udo Schüklenk (personal communication). A similar argument was put forward as an objection to paying research participants by McNeill (1997), p. 391.

an athlete and a human billboard; a knitting nanny makes garments while minding children. So too the writer-participant is able to do two forms of labour at once.

No Product Objection

According to this objection, CTP cannot be a form of labour because the participant is not the one making the product. This too is a spurious objection. The test pilot does not make the airplane, yet her efforts are both vital to the process and clearly a form of labour.

Naïve Advantage Objection

Unlike most forms of labour, there is a naïve advantage in CTP – greater experience as a clinical trial participant can actually make one a worse participant. This may show that CTP is not a craft in the Aristotelian sense,⁹ but then not all forms of labour are crafts, so it does not follow that CTP is not labour.

6.2 Exploitation and Compensation for Participation

Having established that clinical trial participation is a human factor in the production of the good of scientific knowledge, and hence a form of labour, the next step is to determine whether and how that labour ought to be compensated.¹⁰ It has been argued in the literature that while compensation is (or at least may be) appropriate for “healthy” subjects, it would be inappropriate for “patient” subjects;¹¹ in this section, I will argue against this distinction, and

⁹ Aristotle (1999), p. 88.

¹⁰ For the purposes of this argument, I will primarily be discussing compensation in terms of monetary payments to participants, as this is the clearest and most controversial form of compensation.

¹¹ For example, see Lemmens & Elliott (1999). Scare quotes are used here because “healthy” subjects are just participants who do not have the condition that the investigational agent is

propose instead distinguishing between commercial and non-commercial research. On this account, the profit orientation of research makes a difference to the moral necessity (but not the moral permissibility) of compensating participants.¹² I will then examine the case for (or against) compensating clinical trial participants on the basis of three types of exploitation considerations. Micro fairness exploitation concerns speak unequivocally in favour of compensating participants, I will argue. Macro fairness exploitation concerns could be interpreted as weighing against compensating participants, but I will argue that such an interpretation is mistaken. Meanwhile there is a mere use exploitation concern about compensating clinical trial participants, but this is based on a general concern with commodification of persons, a concern that, if taken seriously, calls for a radical transformation of the current research system rather than a strengthening of proscriptions against compensating participants. Overall, then, exploitation concerns weigh in favour of offering compensation to clinical trial participants, particularly those participating in commercial research.

It has been suggested by Trudo Lemmens and Carl Elliott (among others) that “healthy” subjects should be treated differently from “patient” subjects in clinical trials with regards to compensation for their participation. Lemmens and Elliott argue that while research on “patient” subjects is properly governed by a humanitarian model, research on “healthy” subjects is a commercial transaction, which should therefore be treated like any other exchange of labour for money.¹³ In support of this claim, they cite the rise of professional “guinea pigs” for whom trial participation is their primary source of income. Due to the unpleasantness associated with trial

intended to treat, and while “patient” subjects do have the relevant condition, they are still participants rather than patients *per se*. I will continue to use these terms for the sake of brevity, and maintain the use of scare quotes for the sake of clarity.

¹² Sachs draws a similar distinction between commercial employment and altruistic volunteering: Sachs (2010), p. 70.

¹³ Lemmens & Elliott (1999), p. 5.

participation, they argue, “few healthy subjects would consider taking part without payment.”¹⁴ Those “healthy” subjects who do participate are often motivated by the prospect of financial compensation, and in practice their participation is often a nakedly commercial transaction. Since “patient” subjects are not typically paid, and are often motivated by hope for personal medical benefit, Lemmens and Elliott argue that the humanitarian model of governance is appropriate for them; in effect, the two types of subjects should be treated differently because their interactions fall into different spheres of justice.¹⁵ In a similar vein, David Resnik argues that while “healthy” subjects should be paid for their participation, “patient” subjects “expect to get some medical benefit from participation,” which makes their participation “more like a fiduciary relationship than a contractual one.”¹⁶ As a result, Resnik argues, it is appropriate to draw a distinction between “healthy” and “patient” subjects with regards to compensation for participation.

Lemmens and Elliott are on to something with their reference to different spheres of justice, but they have drawn the distinction in the wrong place. The contributions made by participants, whether they are “healthy volunteers” or “patient subjects”, are a form of labour in the production of a good, which is scientific knowledge. Instead of focusing on the health status or motivations of the participants, the distinction should be drawn between commercial research and non-commercial research.¹⁷ This is just another instantiation of the familiar distinction we

¹⁴ Ibid., p. 13.

¹⁵ Ibid., p. 14. There is also a suggestion both here and elsewhere in the literature, for example in Grady (2001), that “patient” subjects are more susceptible to “undue inducement.” I am bracketing this question at present, but discuss undue inducement in detail in the following section.

¹⁶ Resnik (2001), p. 55. Notably, unlike Lemmens and Elliott, Resnik argues that it might be permissible to offer some (lower, standardized) payment to “patient” subjects. However, he still maintains that the two groups ought to be treated fundamentally differently.

¹⁷ By “commercial research”, I mean research in the service of a profit-seeking enterprise; “non-commercial research”, on the other hand, refers to research that does not aim to serve a profit-seeking enterprise. Thus, a trial of a treatment for a rare disease (which will never be

draw between commercial labour transactions (i.e. salaried or wage labour) and non-commercial ones (i.e. unpaid volunteering). Although the labour contribution made by a volunteer cashier to a charity fundraising event is in many ways identical to the labour contribution made by an employee cashier to a retail store, the difference in the natures of the respective enterprises is salient to determining the compensation owed to each. It would be unreasonable to *require* the charity to pay the volunteer cashier minimum wage (although the charity certainly *may* offer some form of compensation, even an honorarium), just as it would be unreasonable to *allow* the retail store to compensate the employee cashier with a hearty thanks and a free t-shirt.

Participation in clinical trials, like other forms of labour, can be done in service of a commercial enterprise or a non-commercial one, and it is appropriate to have different norms and governing rules depending on the type of enterprise.

The motivation of participants is irrelevant to determining which norms of compensation ought to apply, as can be seen by returning to the example of the two cashiers. Whether the volunteer cashier is motivated primarily by altruism, by the offer of the free t-shirt and hearty thanks, or any other motive, it is the fact that he is volunteering for a charity that determines which norms regarding compensation apply. Similarly, it would be inappropriate to apply the non-commercial norms of compensation to the exchange between the employee cashier and the for-profit retail store, even if the employee cashier were primarily motivated by something other

commercially viable due to the rarity of the condition) would count as non-commercial research, even if a for-profit pharmaceutical corporation were the sponsor. Likewise, a trial of a new drug to treat high cholesterol, for instance, could count as commercial research even if it were sponsored by a not-for-profit entity such as a public hospital or university. The reasoning here is that the cholesterol drug (if it proves to be safe and effective) could be a blockbuster drug, generating a massive windfall for the patent-holder and/or licensee. In practice, most commercial research is sponsored by for-profit companies and most non-commercial research is sponsored by not-for-profit entities, but the point is that it is the (potential) profitability of the experimental intervention that is relevant to determining appropriate compensation for participants, rather than the nature of the sponsoring institution.

than the prospect of financial compensation. If the store compensated the employee cashier in a way that fell short of the requirements of commercial labour exchange norms, the store would be micro fairness exploiting the employee cashier, even if the employee agreed to the arrangement and the offer was in keeping with the norms of non-commercial labour.

The health status of participants is not completely irrelevant, but is also no basis for applying non-commercial norms to a commercial enterprise. Health status can be relevant in the following way. It need not violate the norms of commercial labour exchange for the commercial labourer to be compensated (partly) with benefits in kind. In the case of a clinical trial, this could include provision of medical treatment (above and beyond that which forms an integral part of the research protocol, or to which the participant is otherwise normally entitled — otherwise it would not be compensation). However, this provision of medical treatment (generally speaking) only constitutes a benefit to “patient” subjects, and hence would not be a legitimate benefit in kind if offered to “healthy” subjects. So there may be cases where it is appropriate to offer benefits in kind to “patient” subjects but not to “healthy” subjects, but this does not imply that there ought to be a fundamental distinction drawn between “patient” and “healthy” subjects for the purposes of determining appropriate compensation. As argued by the proponents of the Fair Benefits framework, it is the amount of benefits rather than the type of benefits that is relevant to fairness. There is no principled reason to stipulate a different amount of benefits for “patient” and “healthy” subjects in the same trial, even when there may be reason to offer the two groups different types of benefits.

6.2.1 Micro Fairness Exploitation and Compensation

As alluded to above, compensation for CTP in commercial trials is needed to avoid micro fairness exploitation of participants. Recall that, on Wertheimer’s account of micro fairness

exploitation, A exploits B when B does not receive a sufficient (fair) level of benefits from their interaction. In the case of a clinical drug trial, “A” stands for the researcher(s), sponsor(s), and CRO(s) (in outsourced trials), while “B” is the participant.¹⁸ Recall also that the benefits to each party are to be viewed from an *ex ante* perspective. We cannot definitively say exactly how much benefit each participant (B) must receive, because there is no agreed standard of fairness.

However, it is clear that in a commercial drug trial where the sponsor stands to make many millions of dollars and the researchers stand to gain wages and capitation fees (for instance), any plausible account of fairness will demand significant benefits to the participants as well. Since commercial sponsors aim to profit from their research, and the researchers also benefit financially, it seems that participants are being (micro fairness) exploited. As Savulescu puts it, “one might argue that fairness requires participants should have a share in the (very large) financial rewards of commercially sponsored biomedical research, and to fail to pay them is to exploit them.”¹⁹

While the lack of an agreed account of fairness does prevent the specification of what would constitute a fair distribution of benefits between sponsors, researchers and participants, such an account is not needed to determine that the greater the benefits to participants, the less likely it is that they are being (micro fairness) exploited.

6.2.2 Macro Fairness Exploitation and Compensation

¹⁸ Wertheimer (2010). Technically, if the benefits to A are being considered as a whole, then the benefits to B should be described in terms of the collective benefits to all the participants; alternatively, the total benefits to A could be divided by the number of participants in order to compare like to like. However, given that there is no agreed standard of fairness, these calculation issues are of little immediate concern.

¹⁹ Savulescu (2001), p. 1g.

While micro fairness considerations support the notion of compensation for CTP in commercial research, it could be argued that macro fairness considerations weigh against the practice. In the present subsection, I will summarize this argument, before explaining why it is mistaken. I will then argue that macro fairness considerations actually favour compensation for CTP.

It might be objected that offering compensation for clinical trial participation in commercial research would worsen, rather than ameliorate, macro fairness exploitation. The products of commercial research primarily benefit the well off, those who have prescription drug coverage or can otherwise afford to buy new drugs during the life of the patent. By offering compensation for participation, commercial clinical research could preferentially recruit individuals with little or no income and few alternatives, and this disproportionate burden on the poor only exacerbates inequity as the products of commercial research primarily benefit the rich. On this objection, offering compensation to participants in commercial research only serves to further entrench the unjust social structures that selectively privilege some while disadvantaging others. “The offering of financial inducement... adds further to the risks for those disadvantaged people,”²⁰ according to Paul McNeill, because they are more likely to be induced to accept risks, since they need the money and have fewer alternatives available to them. Offering money for participation in research could be said to be macro fairness exploitative, then, by selectively pressuring poor people to assume the risks and burdens of trial participation, the products of which selectively benefit rich people.

While this objection does have some *prima facie* appeal, it rests on a misconception of macro fairness exploitation. Recall that macro fairness exploitation takes into consideration

²⁰ McNeill (1997), p. 394.

background structural injustices when determining the fairness of a transaction. As I explained in chapter 3, unjust social structures constrain and enable actors in a way that limits the opportunities of certain groups and expands the opportunities of others. But offering payment in exchange for CTP does not limit the opportunities of any group. If anything, it expands the opportunities for the disadvantaged by giving them a means to earn money. If the adoption of the practice of offering monetary compensation for CTP somehow led to the removal of existing options for the disadvantaged, that would increase structural injustice, but it is unclear how this could happen.

Indeed, the more plausible macro fairness exploitation concern is that failing to compensate clinical trial participants for their labour is to take advantage of existing structural injustices. As Ezekiel Emanuel writes, “if the worry is attracting a disproportionate number of poor people to participate in research, the solution would seem to be to raise the incentives to make the rich deem it worthwhile to participate too.”²¹ Margaret Brazier echoes this sentiment, arguing that “putting your health at risk in medical research demands substantial reward, at a level high enough to ensure that poverty alone does not motivate participation.”²² Paying participants in commercial research would reduce, rather than increase, macro fairness exploitation of the participants.

6.2.3 Mere Use Exploitation and Compensation

²¹ Emanuel (2004), p. 103.

²² Brazier (2008), p. 183.

The third type of exploitation in Snyder's typology, mere use exploitation, poses a potential problem for the argument that monetary compensation for participants in commercial research reduces (rather than causes or increases) their exploitation. The source of this problem, in Sample's account of mere use exploitation, is her controversial third way in which a person's inherent value²³ can be disrespected, namely by having some aspect of themselves inappropriately commodified.²⁴ According to some commentators, monetary compensation for research participation is problematic precisely because "such compensation transforms the research subject into a commodity."²⁵ If this allegation is correct, and one accepts Sample's claims about inappropriate commodification, it would seem to follow that offering monetary compensation to participants in commercial clinical trials could constitute mere use exploitation of those participants. I will argue that, on the contrary, in many cases a *failure* to offer compensation for participation would be a more serious disrespect for the inherent value of participants. Furthermore, I will contend that participants in commercial research are already thoroughly commodified even without being offered compensation, so any prohibition of compensation for participants would not undo this commodification.

In many cases of offshored commercial research, the prospective LMIC participants will have unmet "genuine needs", to use Sample's terminology, meaning (roughly) those needs that are essential to maintaining their status as rational agents.²⁶ Recall that on Sample's account, we have obligations not only to refrain from harming others, but also to help those with whom we

²³ For Sample, and indeed for most Kantians, people have inherent value because they are rational agents.

²⁴ Sample (2003), p. 57.

²⁵ Chambers (2001), p. 48.

²⁶ One side issue, which I do not address in the present work, is the moral status of humans who (temporarily or permanently) fall short of rational agency. This is a general problem for Kantian ethics, and not specific to questions about exploitation.

interact. As she puts it, “ignoring the needs of others can be just as disrespectful as harming them and can also be exploitative when we profit from the interaction.”²⁷ Since CROs and sponsors of commercial research do profit (*ex ante*) from the interaction with participants, it follows that they also mere-use exploit any participants who have unmet genuine needs, unless they take measures to help address those needs. One obvious way to help address the genuine needs of impoverished persons is to offer them significant monetary compensation in exchange for their contribution to your interaction with them. On Sample’s account, there will be an upper bound on the amount of compensation that sponsors of commercial research are required by beneficence to offer, because beneficence does not require them to operate at a loss. Nonetheless, there is strong reason to think that offering monetary compensation to participants in commercial research would help reduce the incidence of mere use exploitation of participants, particularly among impoverished populations.

The concern about commodification of participants also rings hollow on its own merits, even setting aside the issue of unmet genuine needs of certain participants, and granting Sample’s controversial assumptions about proper and improper commodification of aspects of a person. The reason for this is simply that participants in commercial clinical research are no less commodified for not being paid. The prevalence of CROs and offshoring both point to the fact that participants are treated as commodities (or at least their participation is treated as a commodity.) Doctors may be paid capitation fees for each participant they successfully recruit to a commercial study.²⁸ And as I have argued above, trial participation is a form of labour like any other. So if it is problematic for clinical trial participation to be commodified—and I am not convinced that it is inherently problematic—then the problem runs much deeper than whether or

²⁷ Sample (2003), p. 67.

²⁸ Savulescu (2001), p. 1g.

not participants are offered monetary compensation. Meanwhile, the fact is that participation in a commercial clinical trial *is* a commodity, and whether or not that commodification is appropriate, it is difficult to see how the situation is improved by ensuring that participants never receive any part of the price that commercial sponsors currently pay to CROs, researchers, and referring doctors for that commodity. Likewise, it is difficult to see how offering compensation to participants could worsen their commodification: the wrong of commodification, on Sample's account, is that it constitutes a failure (on the part of the commodifier) to respect the inherent moral value of the person who is commodified. Imagine two scenarios: in scenario A, the sponsor of a commercial clinical trial treats participants like commodities, paying incentives to those who recruit participants; in scenario B, the sponsor does the same thing, but also pays an incentive to those who are recruited. It is very difficult to see how the participants in scenario B are respected less than those in scenario A; if anything, it seems more plausible that the reverse is true and the participants in scenario B are *more* respected than those in scenario A. But if this is so, then offering compensation to participants cannot make their mere-use exploitation worse.²⁹

To summarize, micro fairness exploitation concerns suggest that all participants in commercial trials should be compensated. Although mere use and macro fairness exploitation concerns might, at first blush, appear to bolster the case against offering compensation to commercial trial participants, compensation would actually help reduce both types of exploitation. Payment of commercial trial participants is indicative of the commodification of their participation, but this is just a reflection of the fact that their participation *is* a commodity: namely, it is labour. Therefore, in order to avoid (or at least minimize) the exploitation of participants in commercial clinical research, compensation (including financial compensation)

²⁹ This example may actually constitute a reason to reject Sample's concept of mere use exploitation by commodification, although I am not taking any position on that issue here.

ought to be offered to participants. In the next section, I will address a number of competing concerns that are claimed to provide reasons against requiring (or even allowing) compensation for participation in commercial clinical trials. In the subsequent section, I will then argue for a specific model of compensation for participation in commercial clinical trials.

6.3 Competing Concerns

Concerns related to all three types of exploitation provide reasons in favour of offering compensation to clinical trial participants in commercial research. However, there are a number of competing concerns that have been raised in the literature, which seem to provide reasons against offering such compensation. The primary objection to offering compensation to clinical trial participants is the spectre of undue influence. Others have suggested that offering compensation may incentivize certain undesirable behaviours among prospective and actual participants. Finally, I will consider two prudential concerns that have been claimed to provide reasons to prohibit (or at least minimize) compensation offers to commercial trial participants.

6.3.1 Undue Inducement as a Reason to Limit Compensation

Monetary payments as compensation for participation in commercial research “may be undue if they alter patients’ decision-making processes such that they do not appropriately consider the risks of participating.”³⁰ Much ink has been spilled on this subject,³¹ but what

³⁰ Halpern et al., (2004), p. 801.

evidence there is suggests that inducements do not prevent prospective participants from understanding the risks of participating, and there are persuasive conceptual arguments that undue inducement is not a serious concern for research that has passed ethics review.

With regards to the empirical question of whether inducements can blind prospective subjects from the risks of participation in a clinical trial, there is not a great deal of evidence available due to the fact there are protections against undue inducements being offered to participants in research. This makes it very difficult to conduct an empirical study into whether or not inducements are (or can be) undue,³² since any such study must be able to demonstrate that it will not offer undue inducements to participants. However, there have been some studies done on attitudes towards compensation and participation, which do shed some light on the subject. Halpern et al. asked patients about their willingness to participate in a number of (hypothetical) trials; the trials were identical except for the variables of risk and amount of payment. The main finding from this study was a negative one: “There were no significant interactions between payment level and either risk variable. This suggests that increasing payments do not alter peoples’ [sic] perceptions of these risks.”³³ Bentley and Thacker also examined whether the amount of payment offered would affect participant perceptions of risks, and came to a similar conclusion: “Higher monetary payment, at least in this study, did not appear to blind respondents

³¹ For arguments that payment constitutes undue inducement, see (e.g.) Macklin (1981), McNeill (1997). Even those who think undue inducement is a serious problem are bound to admit, however, that the concept is rather nebulous.

³² Although I am personally skeptical of the very concept of “undue” inducement, for present purposes I am bracketing the question of whether inducement can *ever* be undue. My concern at present is to demonstrate that offering monetary compensation to clinical trial participants does not constitute undue inducement, regardless of whether or not anything else does constitute undue inducement.

³³ Halpern et al. (2004), p. 803.

to risks.”³⁴ One study actually found greater comprehension of risk among participants who reported money as their primary motivation for participating than among those who did not.³⁵

Another study posited, and found evidence to support the claim, that offers of large payments to participants serve as a signal of the study’s riskiness:

“Instead of blinding participants to potential risks, higher payments actually seemed to make participants more vigilant. [...] We observe that participants not only rate high-paying studies as riskier, but that they spend more time studying potential risks when study payments are large.”³⁶

In short, the (admittedly limited) empirical evidence seems to cast doubt on, rather than reinforce, concerns about undue inducement.

Such concerns are cast further into doubt by some fairly compelling arguments put forward by Julian Savulescu and Ezekiel Emanuel. As Savulescu notes, other parties to the research project are often paid cash incentives. Doctors may be paid capitation fees for each participant they recruit to a study, but this is not thought to impair the doctors’ judgment; it is therefore “paternalistic not to offer patients the same rewards from research as doctors receive.”³⁷ Proponents of undue inducement argue that money can cause people to take risks against their better judgment, but Savulescu counters that “in many cases, it will merely be that the financial reward makes the risk worth taking.”³⁸

In a similar vein, Emanuel argues that undue inducement plays no role in clinical research. In order to pass ethics review, research must demonstrate that it will contribute social value, have a scientifically rigorous design to generate valid and reliable data, recruit fairly, have

³⁴ Bentley & Thacker (2004), p. 297.

³⁵ Stunkel et al. (2010), p. 6.

³⁶ Cryder et al. (2010), p. 460.

³⁷ Savulescu (2001), p. 1g.

³⁸ Ibid., p. 2g.

a favourable risk-benefit ratio, and garner participants' informed consent. The fundamental function of independent review of research, according to Emanuel, is to ensure that these requirements are fulfilled, and to prevent any studies from going forward if they are "likely to pose excessive discomforts or risks, and would be imprudent for a reasonable person to participate in."³⁹ Importantly, review bodies also do not take any incentives into account in their risk-benefit assessments, so there is no possibility of an excessively dangerous trial being permitted just because it offered large monetary compensation to participants. Given all these facts, then, Emanuel argues that no inducement could actually be undue, in the sense of causing participants to act against their best interests, since trials are not allowed to proceed if they pose unreasonable risks. As he puts it, "How can it be reasonable to invite people to enrol in a particular trial for no money, but unreasonable—even unethical—to invite them to enrol in the same trial for \$100, \$1,000 or even \$10, 000?"⁴⁰

In light of these arguments and the available empirical evidence, it seems that concerns about undue inducement in clinical research trials causing prospective participants to ignore the risks associated with participation are ill founded.

6.3.2 "Bad Incentive" Reasons to Limit Compensation

By definition, inducements (such as offers of compensation for participation) are intended to incentivize people. Even if there is nothing wrong with incentivizing people to participate in commercial clinical research, it is still possible that the particular inducement of monetary compensation might also incentivize behaviours that are undesirable from the

³⁹ Emanuel (2004), p. 102.

⁴⁰ Ibid.

perspectives of scientific validity or participant safety. In particular, participants who need the money offered as compensation may be motivated to lie about or conceal facts in order to secure and/or maintain their enrolment in a trial. In order to secure their own enrolment, prospective participants might engage in omission and/or deception to convince researchers that they meet inclusion criteria and/or do not meet exclusion criteria, which could potentially undermine the study's scientific validity and, in certain cases, endanger the participant. Once enrolled, a participant who needs the money might be motivated to hide side effects for fear of being removed from the study, thereby also endangering themselves. According to Christine Grady, these concerns give reasons to keep payments modest.⁴¹ If these concerns are valid, it would seem to suggest that the need to avoid exploitation by offering sufficient compensation ought to be balanced against the need to avoid incentivizing bad behaviours by keeping compensation low. With regards to deception about inclusion and exclusion criteria, the limited data available do not rule out these concerns. Bentley and Thacker found that "higher levels of monetary payment may influence subjects' behaviours regarding concealing information about restricted activities," although this effect might be "more likely to occur in lower risk studies."⁴² With regards to side effects from study participation, Bentley and Thacker found payments had no significant effect on participants' propensity to report negative consequences.⁴³

While the (very limited) data do not rule out such concerns, they are not unique to trials that offer monetary compensation. As Grady notes, money is not unique with respect to distorting judgment or encouraging deception; the prospect of potential personal medical benefit might have the same effects for people with little to no alternative in terms of promising options for treatment

⁴¹ Grady (2001), p. 43. Ruth Macklin (1981) also makes a similar argument.

⁴² Bentley & Thacker (2004), p. 297.

⁴³ Ibid.

of a serious illness.⁴⁴ Similarly, LMIC participants in offshored trials may be motivated by inducements such as access to care or medications. Arguably such motives would be more likely to lead desperate prospective participants to lie about exclusion criteria. Furthermore, if paid participants' understanding of risks is as good as or better than unpaid participants' understanding of risks, as suggested previously, then it may be overly paternalistic to assume that financial motivations would cause them to make bad judgments about reporting exclusion criteria, side effects or trial-related injuries. Finally, there are more direct ways to address the problem of participant deception than to remove or minimize compensation for participation. Wilkinson and Moore argue that participant deception is not really an ethical concern for studies without harm-related exclusion criteria, and that for studies with harm-related exclusion criteria, researchers ought to be required to use methods "independent of subject self-report, for checking subject eligibility."⁴⁵ If there is a harm-related exclusion criterion but no adequate independent method of confirmation, then they argue that the study should probably not be allowed to proceed at all, because excluded subjects might still participate. Financial motives to hide side effects could also be minimized by an appropriately-structured compensation model that does not make payment contingent on study completion. For instance, participants could be paid on a pro rata basis for the portion of the protocol they complete before dropping out, or paid the full amount of offered compensation if the researchers remove them partway through the trial for medical reasons. Measures such as independent confirmation of eligibility criteria and tailoring of financial incentives would potentially address concerns about study validity and even sponsor liability as well as participant safety.

⁴⁴ Grady (2001), p. 43.

⁴⁵ Wilkinson & Moore (1997), p. 388.

6.3.3 Prudential Reasons to Limit Compensation

Some prudential, rather than ethical, reasons might also be suggested for limiting the amount of monetary compensation offered to participants in commercial clinical research.⁴⁶ A requirement to financially compensate these participants might increase new drug prices; discourage offshoring (potentially making people in LMICs worse-off); or “crowd out” non-commercial research.

With regard to the first concern, it is unlikely that compensation for participants would have an appreciable effect on the price of new drugs, since during the patent-protected monopoly period these are already priced as high as is possible without reducing total sales revenue. The absence of competition during the life of the patent means that new drug prices are limited only by what the market will bear, and not tied to the cost of production. For argument’s sake, imagine that the cost of compensating participants in trials of a new drug would add \$1 to the drug company’s unit cost to produce the drug, and that without this added cost, the company would sell the drug at \$100 per unit. If the company could sell the drug for \$101 per unit without hurting the bottom line by a reduction in sales, then there is no reason for it not to charge \$101, regardless of whether it incurred the additional costs of participant compensation or not. Besides which, there may be good arguments for the redistribution of that money from those who benefit from the drug to those who assumed the risks of participating in the trials. So concerns about increasing prices for new drugs do not provide a compelling reason to limit amounts of compensation offered to commercial clinical trial participants.

Given that the opportunity to participate in offshored trials, with or without compensation, may represent the best available option for some prospective LMIC participants, it

⁴⁶ As they are prudential concerns rather than ethical ones, these would only provide reasons to limit the amount of compensation offered, not to eliminate such offers outright.

could be argued that requiring compensation would be counter-productive if it ended up discouraging offshoring. Commercially sponsored offshored research is voluntary, and so “to retain an incentive for commercial companies to invest in international research, [offshoring] must remain more efficient than conducting the research in a developed country.”⁴⁷ However, this concern can be allayed by a properly designed model of compensation. So long as compensation for participation in commercial research is required across the board, and does not make offshored trials less efficient than HIC trials, offshoring will not be discouraged.

Finally, Trisha Phillips argues that there is legitimate reason to be concerned about the potential effects of high payments to commercial research participants on recruitment prospects for non-commercial research, a problem she refers to as “crowding out”.⁴⁸ The concern is that non-commercial researchers, including researchers working on treatments for neglected or rare conditions, will not be able to compete for participants given the resources available to commercial researchers. As Phillips puts it:

“If [non-commercial] researchers do not have the funding to make such payments, and presumably many would not, then they would not be able to recruit with offers of money. Commercially sponsored studies would still have an advantage when recruiting subjects, and non-commercial studies would suffer from poor enrollment.”⁴⁹

While it may be true that commercially sponsored studies have recruitment advantages over non-commercial studies, this does not in and of itself provide a sufficient reason to restrict the amount or kind of inducements that commercial studies can offer. The threat of exploitation in commercial studies, on the other hand, does provide an ethical reason to require such studies to

⁴⁷ Ballantyne (2010), p. 29.

⁴⁸ Phillips (2011), p. 243.

⁴⁹ *Ibid.*, p. 247.

offer compensation to participants. In other types of labour, it is not thought that wages for commercial labour ought to be restricted in order to limit the recruitment advantage of commercial employers over non-commercial institutions seeking employees or volunteers. This is despite the fact that this will hinder recruitment for many non-commercial institutions doing what is considered to be very important work with significant societal benefits, while benefitting commercial endeavours that may have comparatively little to recommend them. Similarly, the potential effects on non-commercial research do not provide a sufficient reason to restrict compensation for participants in commercial research.

6.4 Towards a Model for Compensation of Commercial Trial Participation

Thus far, I have argued that clinical trial participation is a form of labour. I have argued that while it is ethically permissible (but not mandatory) to offer compensation for non-commercial labour, it is ethically mandatory to offer compensation for labour contributions to a commercial endeavour. Furthermore, I have argued that exploitation concerns suggest that such compensation for participation in commercial clinical trials should be significant. In order to avoid micro fairness exploitation, compensation should be fair relative to the burdens and potential risks borne by participants as well as the prospective benefits to others.⁵⁰ To avoid macro fairness exploitation, compensation offers should be high enough that they would be acceptable to participants in the absence of any structural injustices, to ensure that sponsors are

⁵⁰ The risks borne by phase I trial participants may seem difficult to quantify from an *ex ante* perspective, since the rate of side effects would not yet be known. However, it may be possible to generalize about the risks of phase I trial participation by looking at the rates of negative outcomes in past phase I trials on similar treatments, where such data is available. Where no such data is available, the very absence of information implies a high degree of risk from an *ex ante* perspective.

not taking advantage of existing structural injustices. To avoid mere use exploitation, compensation should be high enough to address the unmet essential needs of any prospective participants, to the extent that this is possible without making the trial cost-prohibitive for the sponsor. I have argued that the alleged competing concerns, which might otherwise be thought to be reasons to limit compensation offers to participants in commercial clinical trials, do not warrant the imposition of such restrictions. I have also noted that, in order to avoid worsening the situation of the worst-off prospective participants in LMICs, any proposed compensation model for clinical trial participation should maintain the efficiency advantage of offshoring.

In light of all these considerations, I suggest the following as a potential model for compensating participation in commercial clinical trials. Participants in commercial clinical trials should be offered, as a minimum, the equivalent of a locally indexed living wage.⁵¹ A living wage, unlike a market-determined wage, ensures that participants' unmet essential needs will be met, and that sponsors are not taking advantage of structural injustices to offer less compensation than would be acceptable in the absence of such injustices. Because living wages are calculated relative to local conditions and costs of living, and compensation would be mandatory regardless of setting, offshored studies will retain their efficiency advantages over HIC studies due to the

⁵¹ It might be objected that this would lead to a “race to the bottom”-type situation (Udo Schüklenk, personal communication), with sponsors searching for the cheapest possible locations for their trials. This is a potential outcome of implementing the proposed model, perhaps even a probable outcome, but it is not problematic in the same way as the “race to the bottom” scenario described by London & Zollman (2010), for three reasons. Firstly, the search for cheaper trial locations is no different from what is currently happening in terms of offshoring. Secondly, by setting a minimum level of compensation (relative to local conditions), an artificial “bottom” is put in place to ensure at least enough compensation for participants to live on. Thirdly, it is a design feature of such a system that it would encourage offshoring to locations with the lowest standards of living. By paying living wages in such settings, the local standards will gradually increase, and the cost of living along with them. So the “race to the bottom” becomes a process that actually *raises* rather than lowers the “bottom”; offshoring is transformed from an exploitative practice to an engine for development of LMICs.

lower costs of living in LMICs, but participants' resulting purchasing power (with regard to essential needs at least) will be roughly equivalent regardless of study location. Finally, the use of a living wage as a minimum level of compensation, without specifying any maximum, allows for participants to benefit when market conditions warrant higher compensation offers, thus avoiding micro fairness exploitation. At the same time, it also protects participants from market conditions that would lead to minimal benefits,⁵² thus avoiding macro fairness and mere use exploitation.

Of course, there are details to be worked out with such a model. In particular, there is a need for a fair and reliable method to measure the contribution made by participants, which is often primarily their assumption of risks rather than their time spent in protocols,⁵³ and to convert this into a living-wage equivalent. This is not an insignificant problem and it is one that is beyond my remit as a philosopher. Nonetheless, there is much to recommend further research into a compensation model based on equivalency to a locally indexed living wage as a universal minimum standard of compensation.

⁵² For an example of how market-determined benefit levels would be minimized in the current climate of offshoring, see London & Zollman (2010).

⁵³ As pointed out by Menikoff (2001), p. 56.

Chapter 7

Conclusion

In the introduction to this thesis, two main questions were identified about exploitation within the context of clinical trials on human subjects. The first question concerned the nature of such exploitation: what is—and by extension, what is not—exploitation in this context? The second question concerned practical responses to the implications of the first question: how can exploitation in clinical trials on human subjects be avoided (or at least minimized)? Although I do not presume to have definitive answers to either question, in the intervening chapters, I have endeavoured to provide an outline of what an answer to each of these questions might look like. I began by describing the real-world circumstances that triggered the present debate about exploitation in clinical trials, as well as examining the approaches to this problem espoused by the two main camps in the literature—proponents of the reasonable availability approach and proponents of the fair benefits approach—and arguing that both approaches were importantly flawed. I proceeded to outline a more comprehensive theoretical account of exploitation, based on Jeremy Snyder’s typology of exploitation accounts.¹ I then used this tripartite theory of exploitation to critically evaluate some of the exploitation claims made in the literature. Firstly, I investigated the claim that trials are exploitative if they use a local standard of care (which is lower than the global “gold standard” of best practice) to justify a placebo-controlled design, despite the (non-local) availability of proven effective treatment. Next, I investigated the claim that clinical trials exploit their participants if there is no reasonable prospect of those participants

¹ Snyder (2010a); Snyder (2010b); Snyder (2012).

having post-trial access to the tested intervention, should it prove to be effective. I then turned my attention to claims that trials can be exploitative if they fail to provide sufficient benefits to the host community. Finally, I examined the question of benefits (other than access to novel interventions) to participants, focusing on financial compensation of participants in commercial research. In reviewing these discussions, several general considerations are brought to light regarding practical measures to avoid exploitation in clinical research on human subjects, and a number of areas for further research are highlighted.

As discussed in Chapter 2, the roots of the current debate about exploitation in clinical trials can be traced back to the fallout of several controversial cases in the 1990s, especially the post-Protocol ACTG 076 placebo-controlled trials of short course zidovudine. A number of questions about avoiding exploitation in clinical trials arose from this discourse, such as questions about the appropriate standard of care against which experimental interventions should be tested; questions about the necessity of ensuring participants would have post-trial access to (successfully) tested interventions; questions about sufficient benefits to host communities; and questions about sufficient benefits to participants other than post-trial access to tested interventions. Two main approaches to these problems were identified: the reasonable availability approach, and the fair benefits approach. The reasonable availability approach aimed to avoid exploitation by proscribing research that fails to ensure tested interventions, if successful, will eventually be made reasonably available to the population of the community where the trial takes place.² Unfortunately, this approach failed to offer an account of what exploitation is, and hence could not satisfactorily explain why ensuring reasonable post-trial availability of tested interventions would be necessary or sufficient to prevent exploitation. The exclusive focus on

² CIOMS (2002).

post-trial availability of tested interventions ignored the possibility of exploitation being avoidable by provision of other important benefits, even when participants and/or host communities might prefer such benefits.³ The exclusive focus on offshored research ignored the possibility of exploitation in non-offshored trials, despite the fact that many of the most egregious ethical violations in the history of clinical research have occurred in trials conducted entirely within HICs, often on participants from disadvantaged or marginalized groups. In contrast to the reasonable availability approach, the fair benefits approach emphasised a particular account of exploitation as micro level unfairness in the distribution of benefits and burdens of an interaction.⁴ Proponents of the fair benefits approach argued that on this account, avoiding exploitation becomes a matter of ensuring a fair level of benefits to participants and host communities, rather than specifying a particular type of benefit to be ensured in all cases. However, this approach also had a number of problems. The account of exploitation used as a foundation for this approach is overly narrow, failing to capture many of the pre-theoretic connotations of the term. While a clear definition of exploitation was furnished, the concept was essentially defined in terms of fairness; but no account of fairness was initially given,⁵ and the account of fairness that was eventually given⁶ turned out to be implausible and to have unintended and highly counterintuitive consequences.⁷ Like the reasonable availability approach, the fair benefits approach also failed to address the possibility of exploitation in non-offshored research. Taken together, the failings of both approaches led to the conclusion that, while exploitation does seem to be a relevant concern for the ethics of clinical trials on human subjects,

³ Participants (2004).

⁴ Participants (2002).

⁵ Ibid.

⁶ Participants (2004).

⁷ London & Zollman (2010).

no real progress on questions about avoiding exploitation can be made without a more complete theoretical account of exploitation.

As a first step towards addressing this need for a more complete theoretical account of exploitation, Chapter 3 discussed some generally-agreed features of exploitation before detailing three main types of exploitation accounts in the literature, endorsing Jeremy Snyder's assertion that these accounts are mutually compatible because they actually describe three different types of exploitation.⁸ All the main contemporary accounts of exploitation agree on several points, such as that exploitation must involve some benefit or advantage (prospective or actual) for someone other than the exploited party.⁹ There is also general agreement that exploitation is distinct from both coercion and harm, meaning that an exploitative interaction may be consensual or non-consensual, and that the exploited party may or may not be harmed by the interaction. Indeed, an interaction may be fully voluntary and mutually beneficial, yet still exploitative.¹⁰ Beyond these broad areas of agreement, accounts of exploitation can be divided into fairness-based accounts (which hold that exploitation is about unfairness) and mere use accounts (which hold that exploitation is about the merely instrumental use of persons). Fairness-based accounts can be further divided between micro fairness accounts, which focus on micro level unfairness particular to a given interaction,¹¹ and macro fairness accounts, which focus on macro level unfairness resulting from background conditions such as structural injustice.¹² Mere use accounts of exploitation concern themselves with whether interacting agents treat each other in ways

⁸ Snyder (2012).

⁹ Wertheimer (2010).

¹⁰ Ibid.

¹¹ Wertheimer (2010).

¹² Mitra & Biller-Andorno (2013).

compatible with appropriate respect for the inherent value of persons.¹³ While many of these accounts have been put forward in the literature as comprehensive standalone accounts of exploitation, a more complete picture of the concept is afforded by Snyder's approach, which holds that each of these accounts describes a particular *type* of exploitation, and that there are thus (at least) three types of exploitation possible. These three types of exploitation can also intersect in particular cases, so that an interaction can be exploitative in multiple senses.¹⁴ Importantly, different types of exploitation may require different solutions, as became evident in the discussion of particular exploitation claims in the subsequent chapters. With this account of exploitation(s) in place, it then became possible to fruitfully discuss some of the original questions about trial design, host community benefits, and non-medical benefits to participants.

Two particular aspects of trial design have been singled out in the literature as potential sources of exploitation: the use of local (rather than global) standards of care to justify a placebo-controlled trial of an experimental intervention when another (locally unavailable) intervention is already known to be effective; and the recruiting of participants who are unlikely to have post-trial access to the tested intervention if it turns out to be effective. In Chapter 4, I critically evaluated such claims using the accounts of the different types of exploitation described in Chapter 3. With regards to appeals to local (rather than global) standards of care to justify placebo use, I argued that while this practice might be impermissible for reasons unrelated to exploitation, using a local standard of care is not *inherently* micro fairness exploitative, so long as participants and host communities receive a sufficient level of benefits overall. Using a local standard of care can be macro fairness exploitative in some cases, as it arguably would have been

¹³ Sample (2003).

¹⁴ Snyder (2012).

in the proposed Bolivian Surfaxin trial, but not be macro fairness exploitative in other cases, as in the short-course AZT trials; the relevant distinction between these cases being that the former proposed to take advantage of a structural injustice for the further benefit of those already privileged by social structures, while the latter aimed to benefit those who were disadvantaged by structural injustice (albeit in a possibly misguided manner). Using local standards of care to justify a placebo-controlled trial design may or may not constitute mere use exploitation of participants, but for different reasons than in macro fairness exploitation, such that verdicts regarding these two types of exploitation may diverge in particular cases. For instance, the short-course AZT trials could be described as mere use exploitative because participants' unmet genuine or essential needs were not addressed by the interaction with researchers, which furthered the researchers' own (well-intentioned) ends. The verdicts about macro fairness and mere use exploitation also diverge in the case of the proposed Bolivian Surfaxin trial: the trial would not have been mere use exploitative, as the proposed "placebo" was actually better than the local standard of care (even though it was not as good as the global standard of care), meaning that researchers would arguably not have been failing their obligations of beneficence. In the second half of Chapter 4, the same method of analysis was applied to the question of whether prospective participants' post-trial access to successfully tested interventions must be ensured in order to avoid exploiting them. The results were broadly similar to those in the first half of the chapter. Failure to ensure participants' post-trial access to tested interventions is not inherently micro fairness exploitative, provided that the overall distribution of benefits and burdens is fair. Failure to ensure such post-trial access for trial participants may be macro fairness exploitative, particularly if the product of the research is intended to benefit people who are more privileged by structural injustices than are the participants. Finally, failure to ensure post-trial access for

participants will generally make research mere use exploitative if the condition being targeted is severe enough that post-trial access constitutes a genuine or essential need for participants.

In Chapter 5, I turned from questions about exploitation and study design to questions about exploitation and host community benefit. Once again, the tripartite account of exploitation was used in the analysis, although a number of claims in this realm had been argued—with reference to an account of a type of exploitation—in the literature. Convincing and parallel arguments were made in the literature for the conclusions that ensuring post-trial availability throughout the host community might be necessary to avoid the macro fairness exploitation of participants¹⁵ and the mere use exploitation of participants.¹⁶ A central tenet of the fair benefits approach is that benefit to host communities is often necessary to avoid (micro fairness) exploitation,¹⁷ the implications of which were considered in a number of different scenarios. Avoidance of macro fairness exploitation of host communities (as opposed to individual participants) similarly may require benefits to host communities. However, I argued that host communities probably could not be the victims of mere use exploitation, unless one adopts a very unusual view of communities as persons.

Finally, Chapter 6 looked at a consideration (at least implicitly) suggested by the fair benefits approach, namely that provision of other (non-medical) benefits to participants may be helpful or sometimes even necessary to avoid exploiting them. In particular, I focused on the potential benefit to participants of financial compensation for taking part in commercial research trials. I argued for conceiving of trial participation as a form of labour, and that as in other forms of labour, it was appropriate to draw a distinction between labour exchanges in commercial and

¹⁵ Mitra (2013).

¹⁶ Hughes (2012).

¹⁷ Participants (2002); Participants (2004). See also Ballantyne (2010).

non-commercial settings with regards to compensation requirements. I argued that it might be necessary to pay participants in commercial research in order to avoid micro fairness exploiting them, given that the other parties to the interaction (particularly the sponsors and researchers) stand to make significant financial gains. I also argued that such payment would not constitute macro fairness or mere use exploitation of participants, and that avoidance of these forms of exploitation might require that the sums paid to commercial research participants are at least equivalent to a living wage, particularly if the participants are structurally disadvantaged and/or have unmet essential needs.

In summary, then, I have argued that there are (at least) three types of exploitation, each of which is relevant to the ethics of clinical trials. Perhaps the most interesting implication of this position is that avoidance of each type of exploitation may require different strategies; in other words, just as there are different forms of exploitation, there are different requirements for avoiding each form of exploitation. Avoidance of micro fairness exploitation may require ensuring adequate (sufficient levels of) benefits to host communities, as well as payment of participants in commercial research. Avoidance of macro fairness exploitation may require trials to adhere to a uniform global standard of care and to ensure the post-trial availability of tested interventions to host communities, as well as paying participants in commercial research. Avoiding macro fairness exploitation may also mean that sponsors and researchers involved in offshored research have strengthened obligations to work towards or support collective actions to address structural injustices. Avoidance of mere use exploitation may also require using a global standard of care and ensuring post-trial availability to host communities, as well as paying living wages to participants in commercial research who have unmet essential needs.

Of course, I have not solved the problem of exploitation in clinical trials, and there are a number of areas where further research is needed. Perhaps most glaringly, there is a need for a plausible and non-controversial account of micro level fairness to be used in accounts of micro fairness exploitation. There is much more work to be done on developing a model for determining appropriate payment structures for participants in commercial research, as my own suggestions in this area are necessarily vague due to a lack of expertise in economics. Another promising area for future research would be looking into means to address the structural injustices undergirding macro fairness exploitation concerns, particularly through research industry support of collective action. This includes two broad categories of initiatives: those that seek to improve global health and reduce structural injustice through application of existing technology, and those that seek to do the same by researching novel technologies. Examples of the former might include micro-loan programs to help break the cycle of poverty, infrastructure initiatives to provide clean water in areas where there is none, and programs that deliver existing interventions (such as essential medicines or mosquito nets) in areas where there is need. An example of the latter is the proposed Health Impact Fund,¹⁸ which would incentivize commercial research into treatments for the conditions that account for the majority of the global disease burden, in order to help reduce the so-called 90/10 gap (whereby 90% of research funding is spent on conditions that only account for 10% of the global disease burden.) There has also been some discussion in the literature of the collaborative partnership model for research in LMICs and disadvantaged communities within HICs;¹⁹ while this has tended to focus on non-commercial research, even within that sphere it may be helpful as a means to avoiding mere use exploitation.

¹⁸ Hollis & Pogge (2008).

¹⁹ See, e.g., Buchanan et al. (2008); Diallo et al. (2005); Godard, Hunt, and Moube (2014).

Bibliography

- Abrams, S. L. (2005). Clinical trials headed for IPOs, M&A trend to outsourcing by big Pharma leads to financing activity. *The Investment Dealers' Digest*, (Feb. 25, 2005), 12-13.
- Alva, M. (2008). Drug companies look to outsource for oversight of clinical trials. *Investor's Business Daily*, (Aug 5, 2008).
- Angell, M. (1997). The ethics of clinical research in the third world. *New England Journal of Medicine*, 337(12), 847-849.
- Annas, G. & Grodin, M. (1998). Human rights and maternal-fetal HIV transmission prevention trials in Africa. *American Journal of Public Health*, 88(4), 560-563.
- Aristotle. (1999). *Nichomachean ethics* (T. Irwin Trans.). (2nd ed.). Indianapolis: Hackett.
- Avorn, J. (2005). *Powerful medicines: The benefits, risks, and costs of prescription drugs* (2nd ed.). New York: Vintage Books.
- Ballantyne, A. (2010). How to do research fairly in an unjust world. *The American Journal of Bioethics*, 10(6), 26.
- Bayer, R. (1998). The debate over maternal-fetal HIV transmission prevention trials in Africa, Asia, and the Caribbean: Racist exploitation or exploitation of racism? *American Journal of Public Health*, 88(4), 567-570.
- Bentley, J. P. & Thacker, P. G. (2004). The influence of risk and monetary payment on the research participation decision making process. *Journal of Medical Ethics*, 30(3), 293-298.
- Biotech Business Week. (2003). Market analysis; Eastern Europe emerges as new hub of low-cost clinical trials. *Biotech Business Week*, (Nov. 24, 2003), 108.
- Black, J., Hashimzade, N., & Myles, G. (2009). Factor(s) of production. *A dictionary of economics* (3rd ed.,) Oxford University Press.
- Brazier, M. (2008). Exploitation and enrichment: The paradox of medical experimentation. *Journal of Medical Ethics*, 34(3), 180-183.
- Buchanan, D., Sifunda, S., Naidoo, N., James, S., & Reddy, P. (2008). Assuring adequate protections in international health research: A principled justification and practical recommendations for the role of community oversight. *Public Health Ethics*, 1(3), 246-257.
- Chambers, T. (2001). Participation as commodity, participation as gift. *The American Journal of Bioethics*, 1(2), 48-48.

- CIOMS (2002). *International ethical guidelines for biomedical research involving human subjects*. Geneva: Council for International Organizations of Medical Sciences.
- Connor, E. M., Sperling, R. S., Gelber, R., Kiselev, P., Scott, G., O'Sullivan, M. J., et al. (1994). Reduction of maternal-infant transmission of Human Immunodeficiency Virus type 1 with Zidovudine treatment. *New England Journal of Medicine*, 331(18), 1173-1180.
- Cooper, M. & Waldby, C. (2014). *Clinical labor: Tissue donors and research subjects in the global bioeconomy*. Durham: Duke University Press.
- Cryder, C. E., London, A.J., Volpp, K. G., & Loewenstein, G. (2010). Informative inducement: Study payment as a signal of risk. *Social Science & Medicine*, 70(3), 455-464.
- de Zulueta, P. (2001). Randomised placebo-controlled trials and HIV-infected pregnant women in developing countries. Ethical imperialism or unethical exploitation? *Bioethics*, 15(4), 289-311.
- Denny, C., & Grady, C. (2007). Clinical research with economically disadvantaged populations. *Journal of Medical Ethics*, 33(7), 382-385.
- Diallo, D. A., Doumbo, O. K., Plowe, C. V., Wellems, T. E., Emanuel, E. J., & Hurst, S. A. (2005). Community permission for medical research in developing countries. *Clinical Infectious Diseases*, 41(2), 255-259.
- Dickert, N. & Grady, C. (1999). What's the price of a research subject? Approaches to payment for research participation. *New England Journal of Medicine*, 341(3), 198-203.
- Edwards, B. (2008). How should you safely outsource pharmacovigilance to an Indian contract research organization? *Indian Journal of Pharmacology*, 40(7), 24-27.
- Elliot, C. (2008). Guinea-pigging. *The New Yorker*, 83.42(Jan. 7, 2008), 36. Retrieved Feb. 23, 2015 from <http://go.galegroup.com.proxy.queensu.ca/ps/i.do?id=GALE%7CA173132205&v=2.1&u=q ueensulaw&it=r&p=AONE&sw=w&asid=35f6db5c72df9aad10bf6a978de57d17>
- Emanuel, E. (2004). Ending concerns about undue inducement. *Journal of Law, Medicine & Ethics*, 32(1), 100-105.
- Emanuel, E., Wendler, D., & Grady, C. (2000). What makes clinical research ethical? *Journal of the American Medical Association*, 283(20), 2701-2711.
- Emanuel, E., Wendler, D., Killen, J., & Grady, C. (2004). What makes clinical research in developing countries ethical? The benchmarks of ethical research. *Journal of Infectious Diseases*, 189(5), 930-937.

- Freedman, B. (1987). Equipoise and the ethics of clinical research. *New England Journal of Medicine*, 317(3), 141-145.
- Gbadegesin, S. & Wendler, D. (2006). Protecting communities in health research from exploitation. *Bioethics*, 20(5), 248-253.
- Godard, B., Hunt, M., & Moube, Z. (2014). Éthique de la recherche en santé mondiale: La relation Nord–Sud, quel partenariat pour quelle justice sociale ? *Global Health Promotion*, 21(2), 80-87.
- Goodin, R. (1988). *Reasons for welfare: The political theory of the welfare state*. Princeton, N.J.: Princeton University Press.
- Grady, C. (2001). Money for research participation: Does it jeopardize informed consent? *The American Journal of Bioethics*, 1(2), 40-44.
- Gwynne, P. (2002). Companies take the outside route for clinical trials. *Drug Discovery & Development*, 5(11), 71.
- Halpern, S. D., Karlawish, J. T., Casarett, D., Berlin, J. A., & Asch, D. A. (2004). Empirical assessment of whether moderate payments are undue or unjust inducements for participation in clinical trials. *Archives of Internal Medicine*, 164(7), 801-803.
- Hawkins, J. & Emanuel, E. (2008). Introduction: Why exploitation? In J. S. Hawkins & E. J. Emanuel (Eds.), *Exploitation and developing countries: The ethics of clinical research* (pp. 1-20). Princeton, NJ: Princeton University Press.
- Hawkins, J. & Emanuel, E. (2008). Two case studies: The Havrix trial and the Surfaxin trial. In J. S. Hawkins & E. J. Emanuel (Eds.), *Exploitation and developing countries: The ethics of clinical research* (pp. 55-62). Princeton, NJ: Princeton University Press.
- Hollis, A. & Pogge, T. (2008). *The Health Impact Fund: Making new medicines accessible for all*. New Haven, CT: Incentives for Global Health.
- Hughes, R. (2012). Individual risk and community benefit in international research. *Journal of Medical Ethics*, 38(10), 626-629.
- Hurst, S. (2008). Vulnerability in research and health care; describing the elephant in the room? *Bioethics*, 22(4), 191-202.
- Johnson, J. (2010). *More would-be interns paying thousands to land a coveted spot*. Retrieved Apr. 7, 2015, from <http://www.washingtonpost.com/wp-dyn/content/article/2010/08/29/AR2010082903743.html>

- Kant, I. (1993). *Grounding for the metaphysics of morals* (J. Ellington Trans.). (3rd ed.). Indianapolis: Hackett.
- Labonté, R., Blouin, C., & Chopra, M. (2007). *Towards health equitable globalisation: Rights, regulation and redistribution* (Final Report of the Globalization Knowledge Network of the WHO Commission on Social Determinants of Health). Geneva: World Health Organization.
- Lavery, J., Harrington, L., & Scott, T. (2008). Ethical, social, and cultural considerations for site selection for research with genetically modified mosquitoes. *The American Journal of Tropical Medicine and Hygiene*, 79(3), 312-318.
- Lemmens, T. & Elliott, C. (1999). Guinea pigs on the payroll: The ethics of paying research subjects. *Accountability in Research*, 7(1), 3-20.
- Lie, R. (2010). The fair benefits approach revisited. *Hastings Center Report*, 40(4), 3-3.
- London, A. J. & Zollman, K. J. S. (2010). Research at the auction block. *Hastings Center Report*, 40(4), 34-45.
- Lurie, P. & Wolfe, S. M. (1997). Unethical trials of interventions to reduce perinatal transmission of the Human Immunodeficiency Virus in developing countries. *New England Journal of Medicine*, 337(12), 853-856.
- Macklin, R. (1981). 'Due' and 'undue' inducements: On paying money to research subjects. *IRB: Ethics and Human Research*, 3(5), 1-6.
- McNeill, P. (1997). Paying people to participate in research: Why not? *Bioethics*, 11(5), 390-396.
- Menikoff, J. (2001). Just compensation: Paying research subjects relative to the risks they bear. *The American Journal of Bioethics*, 1(2), 56-58.
- Mitra, A. G. (2013). Off-shoring clinical research: Exploitation and the reciprocity constraint. *Developing World Bioethics*, 13(3), 111-111-118.
- Mitra, A. G. & Biller-Andorno, N. (2013). Vulnerability and exploitation in a globalized world. *International Journal of Feminist Approaches to Bioethics*, 6(1), 91-102.
- Nozick, R. (1974). *Anarchy, state, and utopia*. New York: Basic Books.
- Olen, H. (2013, June 04, 2013). Today's internship economy is widening the wealth gap in America. *The Guardian*, Retrieved Apr. 7, 2015 from <http://www.theguardian.com/money/us-money-blog/2013/jun/04/unpaid-internship-paying-for-experience-lebron-james>

- Pace, C., Miller, F., & Danis, M. (2003). Enrolling the uninsured in clinical trials: An ethical perspective. *Critical Care Medicine*, 31(3 Suppl.), S121-S125.
- Participants in the 2001 Conference on Ethical Aspects of Research in Developing Countries. (2002). Fair benefits for research in developing countries. *Science*, 298(5601), 2133-2134.
- Participants in the 2001 Conference on Ethical Aspects of Research in Developing Countries. (2004). Moral standards for research in developing countries from "reasonable availability" to "fair benefits". *The Hastings Center Report*, 34(3), 17-27.
- Patty, A. (2014). Young jobless pay for internships. *Sydney Morning Herald*, (August 11, 2014).
- Petryna, A. (2007). Clinical trials offshored: On private sector science and public health. *Biosocieties*, 2(1), 21-40.
- Petryna, A. (2009). *When experiments travel : Clinical trials and the global search for human subjects*. Princeton, NJ: Princeton University Press.
- Phillips, T. (2011). A living wage for research subjects. *Journal of Law, Medicine & Ethics*, 39(2), 243-253.
- Pogge, T. (2005). Human rights and global health: A research program. *Metaphilosophy*, 36(1-2), 182-209.
- Pogge, T. (2007). Montréal statement on the human right to essential medicines. *Cambridge Quarterly of Healthcare Ethics*, 16(1), 97-108.
- Pogge, T. (2008). Testing our drugs on the poor abroad. In J. S. Hawkins & E. J. Emanuel (Eds.), *Exploitation and developing countries: The ethics of clinical research* (pp. 105-141). Princeton, NJ: Princeton University Press.
- Resnik, D. (2001). Research participation and financial inducements. *The American Journal of Bioethics*, 1(2), 54-56.
- Resnik, D. (2006). Access to medications and global justice. In J. Cohen, P. Illingworth & U. Schüklenk (Eds.), *The power of pills: Social, ethical & legal issues in drug development, marketing & pricing* (pp. 88-97). London: Pluto Press.
- Rowland, C. (2004). Clinical trials seen shifting overseas. *International Journal of Health Services*, 34(3), 555-556.
- Sachs, B. (2010). The exceptional ethics of the investigator-subject relationship. *Journal of Medicine and Philosophy*, 35(1), 64-80.

- Sample, R. (2003). *Exploitation: What it is and why it's wrong*. Lanham, MD: Rowman & Littlefield.
- Savulescu, J. (2001). The fiction of "undue inducement": Why researchers should be allowed to pay participants any amount of money for any reasonable research project. *The American Journal of Bioethics*, 1(2), 1g-3g.
- Schüklenk, U. (2004). The standard of care debate: Against the myth of an "international consensus opinion". *Journal of Medical Ethics*, 30(2), 194-197.
- Schüklenk, U. & Ashcroft, R. (2000). International research ethics. *Bioethics*, 14(2), 158-172.
- Schüklenk, U. & Kleinsmidt, A. (2006). North–South benefit sharing arrangements in bioprospecting and genetic research: A critical ethical and legal analysis. *Developing World Bioethics*, 6(3), 122-134.
- Shaffer, D. N., Yebei, V. N., Ballidawa, J. B., Sidle, J. E., Greene, J. Y., Meslin, E. M., et al. (2006). Equitable treatment for HIV/AIDS clinical trial participants: A focus group study of patients, clinician researchers, and administrators in Western Kenya. *Journal of Medical Ethics*, 32(1), 55-60.
- Shih, G. (2009, August 8, 2009). Unpaid work, but they pay for privilege. *The New York Times*, pp. A16.
- Siegel, A. (2008). Kantian ethics, exploitation, and multinational clinical trials. In J. S. Hawkins & E. J. Emanuel (Eds.), *Exploitation and developing countries: The ethics of clinical research* (pp. 175-205). Princeton, N.J.: Princeton University Press.
- Snyder, J. (2010). Exploitation and sweatshop labor: Perspectives and issues. *Business Ethics Quarterly*, 20(2), 187-213.
- Snyder, J. (2010). Multiple forms of exploitation in international research: The need for multiple standards of fairness. *The American Journal of Bioethics*, 10(6), 40.
- Snyder, J. (2012). Exploitations and their complications: The necessity of identifying the multiple forms of exploitation in pharmaceutical trials. *Bioethics*, 26(5), 251-258.
- Steiner, H. (1984). A liberal theory of exploitation. *Ethics*, 94(2), 225-241.
- Stobie, M. & Slack, C. (2010). Treatment needs in HIV prevention trials: Using beneficence to clarify sponsor-investigator responsibilities. *Developing World Bioethics*, 10(3), 150-157.
- Stunkel, L., Benson, M., McLellan, L., Sinaii, N., Bedarida, G., Emanuel, E., et al. (2010). Comprehension and informed consent: Assessing the effect of a short consent form. *IRB: Ethics & Human Research*, 32(4), 1-9.

- Sunder Rajan, K. (2007). Experimental values: Indian clinical trials and surplus health. *New Left Review*, (45), 67-88.
- Valdman, M. (2008). Exploitation and injustice. *Social Theory and Practice*, 34(4), 551-572.
- Varmus, H. & Satcher, D. (1997). Ethical complexities of conducting research in developing countries. *New England Journal of Medicine*, 337(14), 1003-1005.
- Weijer, C. (1999). Protecting communities in research: Philosophical and pragmatic challenges. *Cambridge Quarterly of Healthcare Ethics*, 8(04), 501.
- Weijer, C. & Emanuel, E. (2000). Protecting communities in biomedical research. *Science*, 289(5482), 1142-1144.
- Weijer, C. & LeBlanc, G. J. (2006). The balm of Gilead: Is the provision of treatment to those who seroconvert in HIV prevention trials a matter of moral obligation or moral negotiation? *Journal of Law, Medicine & Ethics*, 34(4), 793-808.
- Wendler, D., Emanuel, E., & Lie, R. (2004). The standard of care debate: Can research in developing countries be both ethical and responsive to those countries' health needs? *American Journal of Public Health*, 94(6), 923-928.
- Wendler, D. & Miller, F. (2007). Assessing research risks systematically: The net risks test. *Journal of Medical Ethics*, 33(8), 481-486.
- Wertheimer, A. (1999). *Exploitation*. Princeton, NJ: Princeton University Press.
- Wertheimer, A. (2010). *Rethinking the ethics of clinical research: Widening the lens*. Oxford: Oxford University Press.
- Wilkinson, M. & Moore, A. (1997). Inducement in research. *Bioethics*, 11(5), 373-389.
- Young, I. M. (2006). Responsibility and global justice: A social connection model. *Social Philosophy and Policy*, 23(01), 102-130.
- Zong, Z. (2008). Should post-trial provision of beneficial experimental interventions be mandatory in developing countries? *Journal of Medical Ethics*, 34(3), 188-192.
- Zwolinski, M. (2007). Sweatshops, choice, and exploitation. *Business Ethics Quarterly*, 17(4), 689-727.

Appendix A

Abbreviations Used

ACTG	AIDS Clinical Trials Group
AIDS	Acquired Immunodeficiency Syndrome
AZT	Zidovudine
CIOMS	Council for International Organizations of Medical Sciences
CRO	Contract Research Organization
CTP	clinical trial participation
FDA	Food and Drug Administration
HIC	High Income Country
HIV	Human Immunodeficiency Virus
IRB	Institutional Review Board
LIC	Low Income Country
LMIC	Low or Middle Income Country
LMICs	Low and Middle Income Countries
MIC	Middle Income Country
OPC trials	Trials Offshored to enable use of Placebo Controls
Participants	Participants in the 2001 Conference on Ethical Aspects of Research in Developing Countries
PTP	Post-trial provision of experimental interventions to Trial Participants
RDS	Respiratory Distress Syndrome
TRIPs	Agreement on Trade-Related Aspects of Intellectual Property Rights
USA	United States of America