MAKING PARTICIPATION WORK: A GROUNDED THEORY DESCRIBING PARTICIPATION IN PHASE I DRUG TRIALS FROM THE PERSPECTIVE OF THE HEALTHY SUBJECT

by

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Abstract

Making Participation Work: A Grounded Theory Describing Participation in Phase I Drug Trials from the Perspective of the Healthy Subject

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A qualitative research study was conducted with people who had participated as healthy subjects in phase I drug trials at commercial research facilities, in order to develop a better understanding of their perspective regarding research participation. The participants were recruited using online advertisements posted on the University of Toronto student website (www.my.utoronto.ca) and NOW Magazine online. Thirty-one subjects were interviewed. The audiotaped interviews were transcribed and analyzed using grounded theory methods. A grounded theory was developed that describes the process of participation and the main factors affecting the experience of participation, from the perspective of healthy subjects. The theory, called Making Participation Work, explains how healthy subjects frame participation as an income earning opportunity, and how this framing shapes their behaviour with regard to participation. Participants expressed a range of attitudes about the experience of participation, from very positive to very negative. The main factor affecting the experience is the perceived net burden, which is in turn affected by the degree to which subjects find personal control over their participation. Net burden and finding personal control were both affected by the degree to which subjects felt valued by research staff, and by whether subjects had trust in the research enterprise. Although subjects framed participation as work, the relationship with the study doctors and nurses was viewed as clinical. Most subjects are generally trusting...
that participation in phase I drug trials is safe. These findings suggest that models of
research participation assuming participation motivated by altruism or potential
therapeutic benefit cannot accommodate the attitudes and behaviours of healthy subjects
in phase I drug trials. New models must be developed which account for the framing of
participation as work, while being sensitive to the trust that healthy subjects place in the
research enterprise.
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# Table of Contents

1 INTRODUCTION .................................................................................................................. 1  
1.1 OVERVIEW ......................................................................................................................... 1  
1.2 PURPOSE OF THE STUDY .................................................................................................. 3  
1.3 RATIONALE ....................................................................................................................... 3  
1.4 ORGANIZATION ............................................................................................................... 6  

2 PHASE I STUDIES .............................................................................................................. 7  
2.1 TYPES OF TRIALS ............................................................................................................ 7  
2.2 RESEARCH ENVIRONMENT AND CONDITIONS ............................................................. 9  
2.3 COMPENSATION ............................................................................................................... 10  
2.4 SUMMARY ....................................................................................................................... 10  

3 ETHICAL CONCERNS REGARDING THE USE OF HEALTHY SUBJECTS IN PHASE I DRUG TRIALS .................................................................................................................. 11  
3.1 OVERVIEW ....................................................................................................................... 11  
3.2 ETHICAL JUSTIFICATION FOR THE ENROLMENT OF HEALTHY SUBJECTS IN PHASE I DRUG TRIALS ........................................................................................................... 12  
3.3 DETERMINING REASONABLE RISK .............................................................................. 13  
3.4 PAYMENT ....................................................................................................................... 18  
3.4.1 Decision Making .......................................................................................................... 18  
3.4.1.1 Understanding ......................................................................................................... 19  
3.4.1.2 Voluntariness .......................................................................................................... 21  
3.4.2 Deception by Subjects ................................................................................................. 25  
3.4.3 Exploitation ................................................................................................................. 26  
3.4.4 Justice ........................................................................................................................ 32  
3.5 ETHICAL ISSUES SUMMARY ......................................................................................... 34  

4 REVIEW OF EMPirical STUDIES ABOUT HEALTHY SUBJECTS AND PARTICIPATION IN NON-THERAPEUTIC RESEARCH ...................................................................................... 36  
4.1 MOTIVATION .................................................................................................................. 36  
4.2 DECEPTION BY SUBJECTS ............................................................................................ 40  
4.3 INFORMED CONSENT ..................................................................................................... 42  
4.3.1 Risk Assessment ......................................................................................................... 44  
4.4 THE EXPERIENCE OF BEING A RESEARCH SUBJECT .................................................. 48  
4.5 SUMMARY ....................................................................................................................... 51  

5 METHODS ................................................................................................................................ 54  
5.1 OVERVIEW ..................................................................................................................... 54  
5.2 RELATIONSHIP BETWEEN EMPIRICAL AND NORMATIVE ETHICS ................................ 54  
5.3 STUDY DESIGN ............................................................................................................... 55  
5.4 STUDY POPULATION ...................................................................................................... 57  
5.5 RECRUITMENT ................................................................................................................ 58  
5.6 THEORETICAL SAMPLING ............................................................................................ 60  
5.7 INTERVIEWS .................................................................................................................. 62  
5.8 ANALYSIS ....................................................................................................................... 64  
5.9 ROLE OF PUBLISHED LITERATURE AND ETHICAL THEORY ......................................... 67  

6 RESULTS: MAKING PARTICIPATION WORK—THE PROCESS OF PARTICIPATION ........................................... 70  
6.1 OVERVIEW ..................................................................................................................... 70  
6.2 SUBJECT CHARACTERISTICS ....................................................................................... 71  
6.2.1 Demographic Information Summary ......................................................................... 75  
6.3 MAKING PARTICIPATION WORK: THE PROCESS OF PARTICIPATION ................................... 75  
6.3.1 Overview .................................................................................................................... 75
7 RESULTS: FACTORS AFFECTING THE EXPERIENCE OF PARTICIPATION .............105
7.1 OVERVIEW ...........................................................................................................105
7.2 NET BURDEN .....................................................................................................107
  7.2.1 Stigma .............................................................................................................107
  7.2.2 Risk ................................................................................................................109
  7.2.3 Physical Discomfort .......................................................................................109
  7.2.4 Deprivation of Control ...............................................................................111
    7.2.4.1 Voluntariness .........................................................................................113
    7.2.4.2 Deprivation of Choice ..........................................................................114
      7.2.4.2.1 Boredom .........................................................................................114
      7.2.4.2.2 Feeling Uncomfortable ..................................................................115
    7.2.4.3 Deprivation of Privacy ..........................................................................117
    7.2.4.4 Deprivation of Power ............................................................................120
    7.2.4.5 Factors Affecting the Degree of Burden Associated with Deprivation of Control ..........................................................................................................................122
      7.2.4.5.1 Lack of Information .........................................................................122
      7.2.4.5.2 Arbitrary Deprivation of Control ......................................................122
      7.2.4.5.3 Reluctant Participation ..................................................................123
    7.2.4.6 Deprivation of Control Summary ............................................................124
  7.3 FINDING PERSONAL CONTROL .....................................................................125
    7.3.1 Overview ......................................................................................................125
      7.3.1.1 How Subjects Finding Personal Control ............................................127
    7.3.2 Accepting ......................................................................................................127
      7.3.2.1 Accepting Overview ...........................................................................127
      7.3.2.2 Mechanisms for Accepting ..................................................................130
        7.3.2.2.1 Buying into Study Requirements ..................................................130
        7.3.2.2.2 Normalizing ..................................................................................131
        7.3.2.2.3 Excusing Staff ...............................................................................132
      7.3.2.3 Accepting Summary ..............................................................................133
    7.3.3 Rationalizing Risk ..........................................................................................134
      7.3.3.1 Health Beliefs .......................................................................................135
        7.3.3.1.1 Washout of Drug Effects ...............................................................135
        7.3.3.1.2 Differential Susceptibility ..............................................................136
        7.3.3.1.3 Protective Behaviours ....................................................................137
      7.3.3.2 Reducing Exposure to Risk ...................................................................138
        7.3.3.2.1 Choosing Safe Studies .................................................................138
        7.3.3.2.2 Limiting Participation ....................................................................139
      7.3.3.3 Becoming Philosophical .......................................................................140
      7.3.3.4 Rationalizing Risk Summary .................................................................141
    7.3.4 Emphasizing Autonomy ...............................................................................141
      7.3.4.1 Emphasizing Autonomy Summary ......................................................144
List of Tables

Table 1. Subject Education Level .............................................................................................................72
Table 2. Participation Experience at Commercial Research Facilities ...................................................72
Table 3. Income Level .................................................................................................................................73
Table 4. Importance of Study Earnings ....................................................................................................74
List of Figures

Figure 1. Making Participation Work .................................................................77
List of Appendices

Appendix A. Online Advertisement, University of Toronto ................................................................. 216
Appendix B. Online Advertisement, NOW Magazine ................................................................. 217
Appendix C. Advertisement. Poster Distributed by Research Subject ........................................... 218
Appendix D. Information and Consent Form ......................................................................................... 219
Appendix E. Audiotaping Consent Form ............................................................................................... 223
Appendix F. Demographic Questionnaire .............................................................................................. 226
1 Introduction

1.1 Overview

The first human testing in the development of new investigational drugs takes place in Phase I clinical trials. These trials are carried out to examine the acute, dose-related toxicities of new drugs. Phase I trials are often conducted in healthy subjects, though it is common to involve patients who have exhausted current therapies and who might theoretically benefit from interventions that are known to be toxic, as is the case with many cancer drugs (1). A healthy subject is

\[ \text{an individual who is not known to suffer any significant illness relevant to the proposed study, who should be within the ordinary range of body measurements such as weight, and whose mental status is such that he is able to understand and give valid consent to the study (2).} \]

While the actual number of healthy subjects who take part in phase I drug trials is not known, the available data suggest that this research involves a significant number of people each year. Of the 1724 new Clinical Trial Applications received by Health Canada in 2007\(^1\), 1069 were for phase I trials involving healthy subjects. Using a conservative estimate of 20 subjects per protocol\(^2\) would suggest that a minimum of 21,380 subjects participated in phase I drug trials in Canada in 2007. It is expected that some portion of subjects take part in more than one study each year, so this number would reflect the minimum number of participations, rather than number of individuals. Phase I research facilities are found throughout the US, the UK (3), Europe (4) and there is an effort to expand into developing countries (5). It is therefore likely that worldwide, tens if not hundreds of thousands of healthy subjects take part in phase I drug trials each year.

At first glance, clinical research involving healthy, competent adults might appear to represent the ideal research scenario. The decision-making capacity of healthy subjects is

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\(^1\) In Canada, research in human subjects involving investigational drugs must be approved by Health Canada before commencing. A CTA is the application form which must be submitted to Health Canada for approval of each clinical trial.

\(^2\) Phase I trials generally involve 20 to 80 subjects, but can include as few as 3 subjects.
not compromised by physical or mental illness. In addition, while patients taking part in clinical research often show difficulty differentiating clinical care from research—the so-called “therapeutic misconception”—healthy subjects, who are not seeking care for a medical condition, are not vulnerable to this confusion. Similarly, for the most part, healthy subjects are not in a therapeutic relationship with the investigator, and are therefore free from pressure to please their doctor (6).

Despite these apparent advantages, however, phase I trials with healthy subjects raise a number of ethical concerns. The fundamental ethical concern is that phase I trials offer healthy subjects no prospect of therapeutic benefit to balance the risks of participation. The term “risks” refers to the possible adverse health effects of study drugs or procedures. For research ethics boards (REBs) assessing the ethical acceptability of a clinical trial, a favourable risk-benefit ratio is a critical requirement for approval. In the absence of therapeutic benefit, research with healthy subjects is considered in terms of whether the risk is balanced by the potential knowledge to be gained, with society as the potential beneficiary of the knowledge. This balancing of two such different entities (i.e. health risk to individual subjects versus knowledge to society) poses many practical and philosophical challenges, including the challenge of making risk assessments in the face of limited to no prior human testing of a new drug.

In addition to the risks of phase I drug trials, participation also often involves burdensome study requirements such as multiple blood samples, restrictions on consumption of substances including caffeine, alcohol, and certain nutritional supplements, and confinement for one to many days at a research facility. In the absence of therapeutic benefits, healthy subjects are commonly offered payment in exchange for participation. Significant concern has been raised about the impact of payment on voluntary and informed decision making with regard to participation.

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3 In the REB calculation of risk-benefit ratio, “benefit” is defined as therapeutic benefit to the subject. See Chapter 3 for a more detailed examination of this issue.
4 Other parties may also benefit, as noted in Chapter 3. This simplified view focuses on the parties whose interests should be considered by REBs in their weighing of the risks and potential benefits associated with a research protocol.
These ethical concerns have been discussed extensively among ethicists and regulators of human subjects research, but there is no consensus with regard to how these issues are to be addressed, or even how to define the issues (see Chapter 3 for a detailed examination of this discussion).

To date, the ethics discussions regarding what is in the best interests of healthy subjects have been based on theoretical principles and assumptions about the attitudes and behaviours of those who take part in phase I drug trials. The perspective of the subjects themselves, however, has been largely absent from this discussion. Without the perspective of actual subjects regarding the process of decision making and the experience of participating in research, the assumptions that underlie the ethical discussions will remain merely assumptions. Empirical data are needed regarding the perspective of the healthy subject, to allow for an evidence-based approach to ethical oversight of phase I clinical trials.

1.2 Purpose of the Study

The purpose of the original empirical study described in this thesis was to begin to address the above information gap by developing a grounded theory about the experiences, perspectives and concerns of healthy subjects taking part in phase I drug trials.

1.3 Rationale

In the extensive discussion regarding how to address the above ethical concerns the views of a key stakeholder—the research subject—have been missing. This thesis will begin to address this information gap by examining the experiences, perspectives and concerns of healthy subjects taking part in Phase I drug trials. This information can inform the discussion of concerns about phase I research with healthy subjects discussed above, allowing a more evidence-based approach to the issues. The results of the current study
will also be helpful for guiding the direction of future studies, to ensure that they are focussed on issues important to research subjects.

This study focused on participation in phase I drug trials because these trials are the most demanding of subjects, in terms of study procedures, time commitment, and study restrictions (see Chapter 3). In addition, as will be described more fully in Chapters 2 and 3, some phase I study designs lead to increased risk of adverse drug reactions. Finally, because phase I drug trials represent the earliest human testing of new drugs, the trials involve the highest degree of uncertainty regarding possible drug effects, including adverse drug reactions. Thus any concerns healthy subjects may have about participation in non-therapeutic research are likely to be more apparent in phase I drug trials. Similarly, it is these trials that are most commonly the topic of ethical concern regarding involvement of healthy subjects. Moreover, as a result of their demanding nature these trials offer the highest payment to research subjects, allowing exploration of the ethical issue of payment for participation.

This study focused specifically on the experience of healthy subjects at commercial research facilities, also known as Contract Research Organizations “CROs”, for two reasons. First, most of the phase I drug trials involving healthy subjects are now conducted at these facilities. A 2000 report states that in the US, major CROs are growing by an estimated 15 to 20% annually (7). In 2005, CROs conducted 70% of Phase I drug trials in the US, up from 45% in the early 1990’s (8). In the UK, a 1999-2000 survey found that 82% of phase I drug trials were CRO-based (3). Biovail, a Toronto, Ontario based CRO specializing in early phase I trials, boasts on its web site that in its over 25 years of services they have conducted more than 3,000 clinical studies, and have over 80,000 healthy subjects in their database (9). Including Biovail, there are at least seven CROs doing phase I trials in the Greater Toronto Area (GTA) alone. This growth reflects a response to the rapid increase in both government and industry-sponsored research, and the ability of CROs to offer cost-effective, efficient services (7,10).
The second reason for focusing on research conducted at CROs is that, despite the thousands of healthy subjects that participate at these facilities each year the empirical data regarding this population is limited. The handful of empirical studies that have examined the research participation experience in the CRO setting have used written questionnaires, limiting data collection to short answers and pre-defined topics (11). As discussed in detail in Chapter 5, the qualitative approach used in this empirical study allows in-depth exploration of topics identified as important by the research subjects. To the best of my knowledge, the only other qualitative study of healthy subjects in phase I drug trials at CROs was an ethnographic study focussing specifically on a group of self-described anarchists who worked as “professional guinea pigs” in the Philadelphia area (12). This research study was therefore set in commercial research facilities in the hopes of helping to address the gap in the current knowledge.

This study has specifically focused on healthy subjects because although thousands of healthy subjects take part in phase I trials each year as noted above, there is limited empirical data regarding their perspectives and experiences (13). A number of studies have examined the experiences and attitudes of patients in phase I and later phase research, but patients differ from healthy subjects in important ways. The most significant difference is that patients have the potential for therapeutic benefit from research participation, or to contribute to knowledge about a condition that they have. Concern about one’s condition and getting appropriate treatment are a significant aspect of the research participation experience of patient-subjects (14). This is particularly true for research involving patients with serious conditions such as cancer (15-17), one of the patient populations most often involved in phase I drug trials. Such condition-related motivations and concerns are generally not applicable to research with healthy subjects. In addition, patients are less likely to be involved in phase I studies with lengthy periods of confinement, or to engage in repeat participation in many phase I trials. Thus, it seems likely that healthy subjects will have perspectives and experiences that differ from those of patient subjects.
1.4 Organization

This thesis is organized into nine chapters. This first chapter provides an introduction to and overview of the thesis. Chapter 2 provides a description of the nature of phase I drug trials. It includes a list of the various study designs used in phase I research, and descriptions of the environment at commercial phase I research facilities and the general requirements associated with participation as a healthy subject. These descriptions are provided to give the reader a sense of the context in which participation of healthy subjects takes place.

Chapter 3 examines some of the ethical concerns that have been raised regarding the participation of healthy subjects in medical research and describes the differing opinions regarding both the defining of the issues and appropriate measures for addressing them. Chapter 4 reviews the empirical literature that is of potential relevance to the experience of healthy subjects. Findings from a variety of populations related to issues such as motivation for participation and the impact of payment on decision making are described. The possible implications for research ethics are considered, and the lack of data specifically addressing the attitudes and experiences of healthy subjects in phase I drug trials is noted.

The original empirical research study is described in Chapters 5 through 8. Chapter 5 describes the methods used. Chapters 6, 7 and 8 describe the study results. In Chapter 6 I introduce the grounded theory developed through this research, *making participation work*, and describe the *process of participation*. Chapter 7 describes *net burden*, and *finding personal control*, the main factors affecting the participation experience. Chapter 8 considers the impact of *feeling valued* and *trust* on the experience. The impact of trust on subject framing of research participation is considered.

Chapter 9, the final chapter, describes the contribution of this research to current knowledge about the experience of healthy subjects in phase I drug trials, and discusses several ethical implications arising from the research findings.
2 Phase I Studies

Phase I drug trials represent the first phase of human testing of new investigational drugs. Chapter 1 provided a brief introduction into the ethical issues regarding this research, and the rationale for focusing on the experience of healthy subjects participating at CROs. The purpose of this chapter is to provide an overview of the nature and location of phase I drug trials, which is the setting for this thesis research, and the context in which many healthy subjects experience research participation.

2.1 Types of Trials

Phase 1 trials are designed to determine the metabolic and pharmacological actions of the drug in humans, the side effects associated with increasing doses (to establish a safe dose range), and, if possible, to gain early evidence of effectiveness; they are typically closely monitored. The ultimate goal of Phase 1 trials is to obtain sufficient information about the drug’s pharmacokinetics and pharmacological effects to permit the design of well-controlled, sufficiently valid Phase 2 studies. Other examples of Phase 1 studies include studies of drug metabolism, structure-activity relationships, and mechanisms of actions in humans, as well as studies in which investigational drugs are used as research tools to explore biological phenomena or disease processes. The total number of subjects involved in Phase 1 investigations is generally in the range of 20-80 (18).

The term phase I drug trial is often associated only with the very first administration of a new drug in humans (first in humans), and with ascending dose studies intended to determine the maximum tolerated dose (MTD) of a new drug. For example, in a review of the ethical issues of phase I drug trials it was noted that “all phase one studies involve considerable risks to the subjects because all such studies escalate the dose of the drug to the point of toxicity.” (19) In reality, dose escalation studies to determine MTD are but one of the designs used for phase I trials involving healthy subjects. An accurate understanding of the nature of phase I drug trials is necessary before the ethical aspects of this research can be considered.
A variety of study designs are employed in meeting the objective of determining the toxicity, pharmacokinetics and pharmacodynamics of new drugs. Phase I drug trials include:

- bioavailability studies, which examine the extent and rate of absorption of a drug or one of its metabolites;
- bioequivalence studies, which compare the pharmacokinetics or blood levels of marketed drugs with new generic formulations;
- drug interaction studies, which examine whether the metabolism or action of the test drug is altered when co-administered with other drugs;
- abuse-liability studies, which examine the “likeability” or abuse potential of drugs that affect the central nervous system;
- and studies which attempt to elucidate the mechanism of action of new drugs, for example by locating their binding sites via PET scans.

Subjects in phase I studies may take a single dose of a drug or comparator, a single dose of various drugs at different time points, multiple administrations of a fixed dose, multiple escalating doses, or multiple drugs concomitantly. Administration may be topical, inhaled, oral, subcutaneous or intravenous, with oral dosing being the most common. Study design may require subjects to be in a fasted or fed state for dosing, and in some cases may require consumption of specific foods, such as a high fat breakfast. In Canada, bioequivalence studies are the most common type of phase I trial, and indeed the most common type of clinical trial. Of the 1724 applications for approval of clinical trials (Clinical Trial Applications or CTAs) received by Health Canada in 2007, 948 were for bioequivalence studies. (Annual Drug Submission Report—TPD 2007)

Thus, it would erroneous to associate phase I drug trials with a single design, and to make generalizations about associated risks. The risk of a given trial will depend on the nature of the drug being tested, the dose being used, the mode of administration, and physiological characteristics of individual subjects, such as pharmacogenetic variations affecting drug metabolizing enzymes, or psychological characteristics that might affect the subjective experience of drug effects. The degree of uncertainty regarding risk will
vary with the extent of previous human experience with the study drug or related molecules. Bioequivalence studies, for example, involve the testing of drugs that have been previously marketed, so that in contrast to first-in-human studies, there is considerable information about the risks associated with the active ingredient.

2.2 Research Environment and Conditions

Although traditionally carried out in a university or hospital setting, as discussed in Chapter 1, the majority of phase I drug trials now take place at specialized commercial units. These units are equipped for sample collection (mostly blood and urine), monitoring of vital signs and ECGs, and emergency resuscitation. As many phase I trials require confinement of subjects for 24 hours or more, facilities for sleeping, meals and showers are located on the premises. Sleeping quarters are gender-specific, dormitory-like rooms, with anywhere from 1 to 52 subjects per room (9,20). In some cases bunk beds are used.

Highly demanding study conditions are often used to maximize the reliability of the phase I data. Collection of this information usually requires many blood samples over several hours to several days. To avoid confounding of data with effects of other substances, subjects are usually required to adhere to strict study restrictions, such as abstinence from caffeine, alcohol, smoking, strenuous physical activity, and other drugs, including vitamin supplements and herbal products. In some cases subjects are confined to the study facility for periods ranging from several hours to several weeks, where the timing and content of meals are highly regulated and other activities, such as sleep times and levels of physical activity are controlled to meet the requirements of the research protocol. Subjects may, for example, be required to sit up in bed—not lie down and not get up and walk about—for several hours after drug administration. Privacy is limited, as subjects are supervised constantly, even during washroom visits, and must share mealtimes and sleeping quarters.

Although the general design and requirements of phase I drug trials are dictated by scientific requirements, there is a great deal of variation in the operation and physical
environment among individual research facilities. While some clinics are spacious, with comfortable furnishings and delicious, plentiful meals, others are crowded with few amenities, serving “tasteless, meager meals”; most clinics fall somewhere in between these two extremes (20,21).

2.3 Compensation

As noted in Chapter 1, healthy subjects are generally paid as compensation for research participation. As will be discussed in Chapter 3, there are no regulations regarding specific rates of payment, and the issue of what is reasonable compensation is highly contentious. A study of healthy subjects in the Philadelphia area found that payments averaged $200 to $400 per day (12). Interviews with healthy subjects in the current study as well as my experience reviewing phase I drug trials as an REB member, indicate that payments of $1200.00 to $1600.00 are common for studies involving several 2 day confinement periods plus short return visits with single drug dosing in each period, and payments of $4000.00 to $6000.00 or higher are offered for more onerous studies involving lengthier confinement periods and multiple dosing over a confinement period.

2.4 Summary

Phase I trials involve a variety of study designs, with the general purpose of characterizing new investigational drugs. The risks and burdens associated with participation vary with the design, the specific drug(s) being tested and the physical environment and operation of individual research facilities. This chapter provided an overview of the nature of phase I drug trials in commercial research facilities. The following two chapters will examine respectively the ethical and the empirical literature regarding phase I research with healthy subjects.

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5 During the 1990’s, Guinea Pig Zero, a “zine” aimed at healthy subjects, published consumer reports of specific research facilities, grading them on details such as compensation, the skill of the venipuncturist, cleanliness, amenities and food. As a result of these publications, the author, Robert Helms was banned from several research units and was sued by one facility when some of the reports were reprinted in Harper’s (12).
3 Ethical Concerns Regarding the Use of Healthy Subjects in Phase I Drug Trials

Research with healthy volunteers has particular ethical interest because it places in bold relief the moral context of all clinical research: Some individuals are exposed to risks of harm for the potential benefit of future patients and society.

-Franklin G Miller (2003)

3.1 Overview

This chapter provides an overview of some of the main ethical concerns associated with the participation of healthy subjects in phase I drug trials. In this review I will describe how the ethical issues affect current approaches to human subjects protection in the context of research with healthy subjects, and will identify areas of concern that remain controversial. The potential contribution of empirical data to the debate regarding various issues will be considered and some alternative views will be suggested.

This review of the ethical issues is intended to support the rationale for carrying out the empirical study described in Chapters 5 through 8, and to provide background for the discussion, in Chapter 9, of the ethical implications of the empirical findings. This chapter will focus on the question of what is a reasonable level of risk for research involving healthy subjects, and on the issue of payment and its influence on subject decision making and behaviour. Concerns about exploitation and justice arising from payment of subjects will also be examined. The chapter begins with a brief review of the ethical justification for the enrolment of healthy subjects in phase I drug trials.
3.2 Ethical Justification for the Enrolment of Healthy Subjects in Phase I Drug Trials

The use of healthy volunteers to test new drugs in phase I trials has been the source of much ethical concern. This concern stems from the fact that healthy subjects bear the burden of the risk in these trials, without the prospect of therapeutic benefit. The ethical principal of justice requires a fair distribution of the benefits and burdens of research (22). This includes that subject selection is based first on the scientific goals of the research and not on the vulnerability, convenience or privilege of various populations (23). Fairness also requires that study subjects are selected according to criteria that minimize risk and enhance benefits to individual subjects and to society (23).

The first requirement for justice listed above appears not to be met for healthy subjects in phase I drug trials, as they have no prospect of therapeutic benefit, yet bear all of the burdens of the research. Thus, distribution of benefits and burdens do not appear fair. Research with healthy subjects is widely accepted, however, on the grounds that this group is scientifically appropriate and may be at lesser risk than patients with medical conditions of suffering the ill effects of investigational drugs. Thus, the use of healthy subjects satisfies the other requirements of justice, namely, selection based on the scientific goals of the research, and selection according to criteria that will minimize risk and enhance benefits to society.

Use of healthy subjects in phase I drug trials is justified scientifically because, in contrast to the situation with patients, interpretation of study results are not expected to be confounded by the effects of other medication or pre-existing medical conditions. Healthy subjects may also be more able to cooperate with demanding study requirements. In addition, the requirements of phase I trials—such as stopping all usual medication, use of sub-therapeutic doses, and comparison with placebo—could put patients at risk of worsening of their condition, but this is not a concern with healthy subjects (2). Finally, if

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6 Although healthy subjects are not expected to be taking other medications or have pre-existing medical conditions, in reality this may not always be the case, as discussed in the section on deception in this chapter and in Chapter 4.
an investigational drug does cause an adverse reaction, it is anticipated that in most cases a healthy subject will be better able to tolerate and recover from the event than a patient whose health is already compromised.

Despite this justification of research with healthy subjects, a number of specific concerns remain, based on the fundamental imbalance that healthy subjects bear all of the research risks, with no potential for direct therapeutic benefit. For example, what level of risks to the individual can be balanced by benefits to society? Furthermore, as healthy subjects receive no benefit for bearing risks and enduring demanding study conditions, they commonly receive financial compensation for participation. This payment raises concerns about undue influence on the informed consent process and exploitation of economically disadvantaged populations. In this chapter I will review the discussion regarding these concerns about healthy subjects. In Chapter 9 of this thesis, I will revisit these issues and consider the implications of my empirical research findings for the discussion regarding these ethical concerns.

3.3 Determining Reasonable Risk

It is generally accepted that to be ethically acceptable, research studies involving human subjects must have, among other things, a “favourable risk-benefit ratio”. This includes that risks must be minimized, potential benefits to the subject maximized, and the potential benefits to individuals and society must outweigh the risks (23). As discussed above, phase I research involving healthy subjects offers no medical benefits to the individual, leaving only potential societal benefits to outweigh the risks. While research subjects may construe the receipt of payment for participation to be a benefit, it is generally accepted that payment should not be viewed as a benefit in any risk-benefit calculations used by REBs or other regulators to determine the ethical acceptability of a given study. If payment or other extraneous benefits not related to the research procedures, such as additional medical services, were used in risk-benefit calculations, unlimited levels of research risk could be justified by increasing payment or adding more unrelated services (23).
There is a consensus among national and international guidelines and regulations that for non-therapeutic research, the risk must be justified or balanced by the importance of the knowledge to be gained (23), which Weijer distinguishes from individual benefit with the term “risk-knowledge calculus.” (24) If it is accepted that it is ethically permissible to ask healthy subjects to assume risk for the benefit of society⁷, how is this risk-knowledge calculus to be performed? A thorough examination of this question would require consideration of how to carry out the risk assessment, assessment of potential knowledge arising from the research, and how to balance the two. This will not be undertaken in this thesis. In this chapter, I will focus on one aspect of this question, namely, is there an upper limit to the level of risk that can be justified by potential increased knowledge? The following section examines the extent to which this issue has been addressed in regulations, guidelines, and the research ethics literature.

Subject protection through placement of limitations on the level of allowable risk has been applied to non-therapeutic research involving several different subject populations as a result of their being classified as vulnerable. US Food and Drug Administration (FDA) regulations, for example, state that for non-therapeutic research involving children, the risk must be no more than minimal or a minor increment over minimal, except under special circumstances (25). For research involving prisoners, US Federal Regulations 45CFR46.306(a) places a limit of no more than minimal on research investigating criminal behaviour and incarceration, but not on non-therapeutic medical research in this population. No limits have been explicitly placed on non-therapeutic research involving free-living competent adults. This lack of a defined upper limit on risk for non-therapeutic research suggests that, if the knowledge to be gained is very

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⁷ Of course, in addition to society in general, various individuals or groups also benefit from the participation of healthy subjects, such as the pharmaceutical companies sponsoring the research, the commercial research organization being paid to conduct the research and their staff, and, where applicable, the private REB employed to provide ethical oversight of the research. These benefits to specific groups, however, are not used by REBs in the balancing of risks and benefits of a particular research study. Indeed, these benefits to specific third parties, which are primarily financial, are generally viewed as conflicting interests which may compete with interest in subject well-being.
important, a very high level of risk is acceptable. Some regulatory statements, however, suggest that special protections for healthy subjects may be warranted.

US federal regulations section 45CFR46.111(b) (26), which addresses Criteria for IRB Approval of Research indicates that

When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects (emphasis added).

Similarly, the Declaration of Helsinki (27) states

Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence (emphasis added).

Although healthy subjects are not specifically identified as vulnerable in these statements, there is concern that healthy subjects tend to be economically disadvantaged, and therefore vulnerable to coercion\(^8\) or undue influence. (28) Of relevance to the consideration of acceptable risk, is the question of what “additional safeguards” or “special protection” might be required. In the Frequently Asked Questions section of their web site, the US Office for Human Research Protections (18) indicates that additional safeguards may include restriction of financial incentives, and careful review of information describing incentives to subjects. These considerations focus exclusively on the informed consent process and the impact of payment on that process. There is no reference to limiting the level of permissible risk for studies involving capable subjects. Thus, limitation of risk levels appears to be invoked only for vulnerable subjects who

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\(^8\) The term “coercion”, which is commonly used in discussions regarding voluntariness of informed consent, refers to threats which diminish available choices to the subject. It is often used inappropriately to refer to various factors that may impact voluntariness, but which do not involve threats and do not limit choices. The offer of payment, for example, does not involve a threat and does not limit the available choices. This issue has been thoroughly examined elsewhere (eg.(44,177)).
lack the capacity for informed consent, rather than for subjects who may be vulnerable simply to threats to voluntariness.

The Nuremberg Code states, “No experiment should be conducted where there is an *a priori* reason to believe that death or disabling injury will occur” (29). This limitation, however, applies to all subjects, and it is not clear from this statement what probability of death or disabling injury is acceptable (6).

An upper limit on risk was recommended by the Royal College of Physicians of London in their 1986 report, “Research on Healthy Volunteers”, which states that “A risk greater than minimal is not acceptable in a healthy volunteer study.” For pharmacological studies, minimal risk is defined in the report as either “a small chance of a trivial reaction, such as lethargy or headache”, or a “very remote chance of a serious disability or death”, comparable to the risk “of flying as a passenger in a scheduled aircraft” (2).

Recommendations for ensuring minimal risk in pharmacological studies include the testing only of those drugs predicted to have low toxicity as determined in animal studies, and the use of “low and graded doses”. It is further noted that drugs that have been previously tested on many patients may be regarded as posing minimal risk, “provided that proper procedures and adequate safeguards are followed.” (2)

Ackerman (30) supports an upper threshold for risk in non-therapeutic research, but suggests that the limit be no more than a minor increase over minimal, such as the risk associated with “endoscopies” and “bone marrow aspirations”. Given that the risk of death from being a passenger on a domestic flight—the example suggested as acceptable by the Royal College of Physicians and Surgeons—is approximately 1 in 1,000,000 to 1 in 10,000,000 (31) and the risk of serious harm or death from endoscopy is in the order of 1 in 1500 to 1 in 5000 (32), these two determinations of acceptable risk thresholds are very different. These differences illustrate the difficulties in defining risk thresholds for research.
Variability in defining research risks has been observed previously. Significant variability was found among REB Chairpersons in a study where they were asked to rate the risk of a blood draw for research in children (33). Considering that in phase I of drug development, probability and severity statistics for adverse events are often thin or non-existent, there is an even greater difficulty in determining whether a given research protocol is within or exceeds a particular threshold.

The Guidelines for Phase I Clinical Trials published in 2007 by the Association of the British Pharmaceutical Industry (ABPI) include a statement that “the risk of harming the subjects must be minimal”, citing the Royal College 1986 Report for this requirement (34). The ABPI guidelines also include a section identifying “higher-risk” investigational drugs, which are considered to require greater care and expertise in assessment, but which cannot pose more than minimal risk to subjects. One example included in the “higher-risk” list is the first-in-human testing of “any agent that might cause severe disturbance of vital body systems”. As mentioned above, given the imperfect extrapolation of drug toxicity data from animals to humans, it is difficult, if not impossible to accept that, with careful assessment, the first in human testing of such an agent could be considered to pose only a risk of trivial adverse events, or a very remote risk of serious adverse events. Thus the threshold of minimal risk, although theoretically appealing, is unrealistic.

Not surprisingly, a threshold of minimal risk for non-therapeutic research involving healthy subjects has not been endorsed in other reports, guidelines or recommendations. There are a number of reasons for this lack of acceptance, in addition to the difficulties of risk assessment described above. One reason is the belief that competent individuals should be free to accept greater than minimal risk if adequately informed (35). A second reason is concern that such a prohibition might encourage the assessment of all risks as minimal, thereby taking away emphasis from the need to assess, minimize and inform subjects about risk (36). As well, animal toxicity studies do not always predict the behaviour of a new drug in humans (37), so the proposed minimal risk standard will be impossible to meet.
Aside from the Royal College of London’s 1986 Report, the question of whether there should be an upper limit for risk to healthy subjects independent of the knowledge to be gained has received almost no attention. Whether this reflects a broad consensus that there should be no threshold, and that any level of risk is permissible given adequate scientific justification and informed consent, or whether there is a taken for granted presumption of a threshold, is not clear. Emanuel suggests that current regulations are “flawed” for not specifying that the level of risk that can be justified by knowledge rather than therapeutic benefit should not exceed risks that “are comparable to what society can reasonably expect—in other circumstances—a person to undertake for the benefit of others” (38). At this time then, the question of whether there ought to be a limit on the risk allowable for healthy subjects “remains an unsettled issue of research ethics” (6).

3.4 Payment

As Phase I studies in healthy subjects offer no medical benefit, payment is routinely offered as a recruitment incentive. Payments range from less than thirty dollars for a single procedure, to several thousand dollars for several weeks confinement with multiple blood samples or other procedures. Concerns regarding payment have dominated the discussion of the ethics of healthy subjects in phase I drug research. There has been significant discussion about the potential impact of payment on decision-making (39-41). There is also concern that a prospective subject may be tempted to hide medical conditions or otherwise misrepresent him/herself to avoid exclusion from a lucrative trial (42). Finally, because it is expected to selectively attract economically disadvantaged persons, payment of healthy subjects raises concerns about exploitation and justice (43-45). I will consider each of these issues below.

3.4.1 Decision Making

A considerable amount of discussion regarding healthy subjects in phase I drug trials has focused on the concern that the offer of payment may reduce understanding and/or
voluntariness associated with the decision to participate, resulting in a decision that does not meet the requirements for a meaningful informed consent (41). A meaningful informed consent is a requirement for the ethical conduct of research with human subjects, as it is the primary means by which individual autonomy is respected. A higher standard of informed consent for research compared to treatment has been supported by the Canadian legal cases Halushka v University of Saskatchewan (46) and Weiss v Solomon (47). In the latter case, the court held that “The duty to inform in matters relating to purely scientific experimentation is the most exacting possible.” The rationale for this higher standard is that in research, the primary purpose of the intervention is to obtain generalizable knowledge rather than to promote the best interests of the individual subject. For much clinical research with patients, there remains, however, the prospect of individual benefit from the study intervention. It could be argued that non-therapeutic research with healthy subjects, who bear all of the risks but have no prospect of health benefit, can be seen as a more extreme example of placing science before a subject’s best interests, and therefore requiring the highest standard of informed consent. This importance of informed consent in the context of research is one of the reasons for the degree of attention focused on the impact of payment on this process.

3.4.1.1 Understanding
Concern about decision making has particularly focused on the impact of payment on the subject’s understanding and appreciation of the risks associated with participation. Understanding and appreciation are, along with voluntariness, the pillars of meaningful decision making (48). The fear is that the offer of payment may distract subjects from adequately considering the risks, or it may influence assessment of risks, such that the magnitude or probability of the risks may be underestimated (18). This is an ethical concern, because a decision made with incomplete or distorted understanding of the risks associated with participation cannot be considered to be a properly informed one. Psychological studies on risk perception have found that the presence of a perceived benefit may reduce the perception of risk (49,50). Such findings support the suggestion
that the offer of payment as a “benefit”\(^9\) of research participation may reduce a prospective subject’s perception of the research risks. This research, however, was primarily concerned with environmental risks and largely employed hypothetical scenarios to compare perception of different risks rather than use of risk information in decision making. A few studies have specifically attempted to examine the impact of payment on understanding of study related risk. In contrast to the risk perception studies, the limited empirical evidence available from studies on payment and research participation does not support the suggestion that payment reduces understanding of study-related risks (51,52). (It should be noted that these latter studies also used hypothetical scenarios. The details of these empirical studies will be reviewed more thoroughly in Chapter 4.) If this suggestion—that payment does not interfere with understanding or appreciation of risks—is supported by additional empirical evidence, concerns about the impact of payment on this aspect of decision-making are unwarranted. These findings do not address, however, concerns related to the potential impact of payment on the voluntariness of participation, which will be discussed in the section below, titled Voluntariness.

It has been noted that understanding of information is a common concern for all clinical trials, whether or not payment is involved, and that the focus should be on development of ways to improve understanding, rather than elimination of payment (53). Grady (39) suggests that the threshold of understanding for research that does not offer the prospect of benefit should be high and subject understanding should be carefully assessed prior to enrollment. The nature of phase I drug trials, however, poses extra challenges to understanding.

Understanding of the risks of phase I trials may be more difficult, given the often high level of uncertainty regarding the probability and magnitude of individual risks. While uncertainty is inherent in the notion of risk, in later stages of drug research this uncertainty is decreased as there has been some experience in humans. Ensuring adequate

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\(^9\) While payment may be viewed by subjects to be a benefit of participation, as discussed previously, it is generally accepted that payment should not be used as a benefit in risk/benefit calculations by REBs or other regulatory bodies.
subject understanding of the risks is particularly challenging when there is no prior human experience with a new compound. Furthermore, as one of the purposes of phase I drug trials is to determine the acute, dose-related toxicities of new drugs, some subjects may be exposed to doses much higher than will ultimately be used in later efficacy studies. Thus, by their very design, certain phase I studies (such as those designed to establish maximum tolerated dose) must increase the likelihood that a hazard or adverse event (the test substance toxicity) will be experienced. For these studies, the question is not whether a toxicity will be experienced, but how bad the toxic reaction will be. Clinicians can use such findings in the future to choose appropriate dose levels, to warn patients about possible ill effects and also to plan for ways of mitigating such toxic responses. The increased uncertainty of the scope of adverse reactions, and for some studies the increased likelihood of experiencing an adverse event, mean that for phase I drug trials understanding and appreciation of risk information is particularly important and likely to be very challenging.

3.4.1.2 Voluntariness

Even if the risks of participation are understood and appreciated, concern has been raised that payment may induce subjects to accept risks that they otherwise would not. This effect of payment has been called “undue inducement”, and is considered to undermine the voluntariness of informed consent. The Belmont report states that

Undue influence...occurs through an offer of an excessive, unwarranted, inappropriate or improper reward or other overtures in order to obtain compliance. Also, inducements that would ordinarily be acceptable may become undue influence if the subject is especially vulnerable. (22)

The message here is that some amount of payment is acceptable, but that some larger amount is “excessive” and becomes an undue inducement. The concern is that the offer can be so attractive that some individuals might be enticed to take some action, such as accept the risks of participation, that they would not otherwise do (53). The concept of

10 It is important to bear in mind that, as described in Chapter 1, not all phase I trials involve this design. Bioequivalence trials, for example, are designed to collect pharmacokinetic data rather than establish toxicity, and may involve doses that are smaller than routinely taken by patients for therapeutic purposes.
undue inducement has two premises—that there is an acceptable level of payment that does not unduly influence decision making, and that there is a higher, unacceptable level of payment that does unduly influence decision making. If these premises are accepted, the practical challenge is to determine what level of payment would be an undue inducement. As the Belmont Report cautions, the level of reward or payment that crosses the threshold from “acceptable” to “undue” varies with the individual. This need to consider individual variation is made even more challenging, by the fact that it is not known exactly how individuals vary regarding susceptibility to the influence of payment. One common presumption is that someone who is very poor is expected to be swayed by payments much smaller than would influence a wealthy person (39,54). As will be described in detail in Chapter 4, however, the empirical data regarding the impact of payment on the decision about whether or not to participate in research is limited and no consistent patterns of association between influence of payment and income level or other demographic factors have been identified. So, while it is reasonable to assume that there will be variation among individuals regarding the response to a given size of payment, it must be remembered that assumptions about the behaviour of any particular group are, until proven otherwise, only assumptions.

A number of models have been suggested for payment. There is widespread, although not complete agreement that some payment is acceptable, but that the amount should be carefully considered so as not to be an undue inducement (39,55,56). Dickert and Grady suggest payment should be calculated on the basis of time or contribution, at a rate similar to wages for other unskilled work in the relevant community. This “wage payment” model for compensation is suggested to be not so high as to be likely to be a possible undue inducement, while providing a show of respect for a research subject’s time and contribution (55,57). This solution cannot, however, eliminate the possibility that even a modest minimum wage may be highly attractive to some individuals.

The concept of “undue inducement” has been challenged by a number of ethicists, philosophers and researchers. The qualifier “undue” may be “meaningless”, since all inducements act as incentives to get people to do things that they would not otherwise do
Grant and Sugarman (59), suggest a more specific definition of undue inducement. They note that while all incentives “induce someone to do something they might not otherwise do”, an undue inducement is an incentive that “is used to induce someone to do something to which they are averse”. In other words, an undue inducement causes subjects to make choices that go “against their better judgement” (59). A more specific interpretation of undue inducement as leading to a higher acceptance of risk, rather than simply changing behaviour, is suggested by the wording used by the OHRP in their document “Informed Consent Frequently Asked Questions”:

*Paying research subjects in exchange for their participation is a common and, in general, acceptable practice... In no case should remuneration be viewed as a way of offsetting risks; that is, it should not be considered a benefit to be weighed against study risks. The level of remuneration should not be so high as to cause a prospective subject to accept risks that he or she would not accept in the absence of the remuneration* (18).

Accepting greater risk than one normally would, or doing something to which one is normally averse, means going against one’s established values. This interpretation that an inducement becomes undue when it encourages a person to go against his/her established values can be seen as supporting the notion that undue inducement is a threat to autonomy. Others have suggested that even where a choice seems to go against one’s established values, it can nonetheless be an autonomous choice between competing values (58). Even if the more specific definition of “undue inducement” is accepted, the challenges presented by determining what level of payment is due versus undue remain.

Emanuel dismisses undue inducement as irrelevant in most research scenarios, labeling it “nonsense on stilts” (53). Emanuel proposes that the focus on payment is misplaced, and that concerns about undue inducement can only arise where payment may lead to bad judgment with a substantial risk of serious discomfort or harm. Therefore where a research trial has been determined to fulfill the requirements of an “ethical” study, including reasonable risks and adequate provision for informed consent, there is no substantial risk of serious harm and therefore no concerns about undue inducement (38). Others support the notion that, rather than trying to control subjects’ motives for
participation, or protect them from influence by minimizing payment, Research Ethics Boards (REBs) should protect subjects by ensuring that research trials are not too dangerous or too onerous (59,60). Those who reject the notion of undue inducement argue that limitation of payment reduces rather than protects subject autonomy (61). These responses to concerns about undue inducement seem to presume some upper “reasonable” threshold to permissible risk. As discussed above, however, precisely what level of danger or burden is acceptable for research with healthy subjects remains unresolved.

Many of the concerns about the effects of payment on decision making in Phase I studies are based on the assumption that healthy subjects who take part in phase I research are in financially desperate situations, with limited options for employment. This assumption is not necessarily true. For example Zink observes a different population of healthy subjects taking part in his research—persons of middle age and middle class, taking part for extra cash to help pay “extras” such as a vacation, a child’s education or wedding or to pad their nest egg. Zink reports that these subjects thoroughly review the study information and carefully consider participation. They have other options for making money, but choose research participation because they find it more appealing or acceptable than other options (62). Currently information about who takes part in Phase I studies is largely anecdotal. Research is needed to accurately describe who are the healthy volunteers involved, before making assumptions about the context in which they make their decisions.

The philosophical question of whether autonomous decision making is threatened by payment has been debated for several decades “without much apparent motion in the debate”(59). The broad definition of undue inducement as an offer that influences someone to change his or her behaviour is not distinguishable from simple inducement. A more specific definition of undue inducement as an offer that causes a person to violate his or her own values may be stronger. It is difficult, if not impossible, however, to define what level of payment will be fair but not undue for all healthy subjects. Dickert and Grady’s wage payment model appears to be widely accepted as straddling the middle
ground between fair and not undue, and is probably most consistent with current regulations and guidelines. For those who dismiss undue inducement as a concern, this minimum wage model is unnecessarily restrictive and paternalistic. This latter group suggest that promotion of subject autonomy may be better served by ensuring research risks are reasonable and minimized, and by optimizing the informed consent process, than by limiting the amount compensation (19,63-65).

3.4.2 Deception by Subjects
Concern about undue inducement goes beyond decision making, to concerns that payment may tempt some subjects to give false information in order to qualify for a study, or to withhold information about adverse events experienced during participation, which could trigger early discontinuation and loss of payment. Falsifying or withholding information raises concerns about subject safety and scientific integrity (39). Subjects may withhold information about pre-existing medical conditions, recent or current participation in another trial, or noncompliance with restrictions, such as smoking history or alcohol and caffeine consumption. Such deception at best compromises the integrity of the study data, and at worst can lead to subjects experiencing serious adverse reactions from study medication. For example, subjects hiding regular caffeine use may experience withdrawal symptoms such as headache upon confinement in a research facility; headache may wrongly be attributed to the study drug (66). As one of the main objectives of Phase I research is to gather data about safety, the suggestion that adverse events may be unreported is a significant concern. Furthermore, side effects not identified and treated promptly may progress to more serious problems.

Screening methods (e.g. testing for TB, urine drug screens, alcohol breath tests) that do not rely on the subject’s word may help address this issue to some extent, but cannot catch all types of deception. Enhanced monitoring may help to address the withholding of information about adverse events experienced during participation, but would be limited to events that can be observed or measured objectively, such as fever or changes in blood pressure. In the absence of infallible screening tests, researchers and regulators of
research, such as REBs, should assume some level of deception and, as much as possible, incorporate this assumption into the design of phase I trials.

As with voluntariness, concerns about subject deception presume that the temptation to withhold or falsify information will increase with the size of payment. Elimination of payment for participation, or reduction of payment to a minimal amount may remove the motivation for those who would misrepresent themselves in order to qualify. Elimination or extreme reduction of payment would also make it very difficult to recruit healthy subjects into non-therapeutic research, and would not provide fair compensation\(^{11}\) for enduring the burdens of the research. Other strategies, such as providing full payment for those who must discontinue participation due to an adverse event, may improve the integrity of the research data. Empirical evidence regarding the occurrence of subject deception will be reviewed in Chapter 4.

### 3.4.3 Exploitation

The offering of payment is said to be an exploitation of the economically disadvantaged, as this population is assumed to be more likely to be influenced by payment to take on the burdens of research participation (45,67,68). It has been noted, however, that while exploitation in research is a “hot topic”, it is often not clearly defined or analyzed as it applies to various research scenarios (69).

The concept of exploitation has been written about extensively, from a variety of theoretical frameworks (69,70), which will not be revisited here. While there are many different views regarding the specifics of exploitation, there is general agreement that exploitation in a transaction or relationship occurs when one party takes advantage of another party to gain an unfair share of benefit (69). In this general definition, benefit is interpreted very broadly to mean the net good resulting from the transaction or relationship. This broad interpretation also assumes that net benefit is the sum of good minus the harm or losses resulting from a transaction.

\(^{11}\) The question of what is “fair compensation” is itself an issue, which will be considered in the following section on exploitation.
Although it is disputed whether vulnerability of the exploitee is a necessary element of exploitation (70), a state of vulnerability can be seen to facilitate exploitation. In other words, the exploiter takes advantage of the vulnerability to gain an unfair share of benefit. In this conceptualization, vulnerability is again interpreted very broadly, to include either having a need and limited options to meet that need, insufficient knowledge or information to negotiate a fair share of benefits, or lack of freedom or power to negotiate a fair share of benefits (70). These vulnerabilities can put a party at increased risk of being exploited. Thus, for economically disadvantaged healthy subjects, exploitation is viewed as taking advantage of economic vulnerability (financial need and lack of options to earn money) to gain an unfair share of benefit.

While vulnerability can facilitate exploitation, the vulnerability of one party in a transaction is not sufficient to result in exploitation.

If A makes a reasonable proposal that B has no alternative but to accept, given B’s desperate situation, A does not exploit B. If a doctor proposes to perform life-saving surgery for a reasonable fee, the patient is hardly exploited, even though the patient would not have agreed except for the fact that her life was in danger (70).

In other words, “one is not exploited if one is offered what one desperately needs at a fair and reasonable price” (71) in (70).

Thus exploitation requires that one party take advantage of another (possibly vulnerable) party to gain an unfair share of the benefits. Alternatively, this can be rephrased in terms of the exploitee, such that a party is exploited if they are taken advantage of by receiving an unfair share of the benefits (less than what they deserve). Remembering that benefit here is defined as the net of gains and losses or goods and harms, an unfair share of benefits occurs “if B pays too high a price for what she gains, or does not receive enough for what she gives” (70). This begs the question what is “too high a price” for a gain, or “not enough” compensation for something given? Determining what is a fair distribution of benefits is highly problematic, and dependent on the situation. Although there is no one standard for fairness for all transactions, it is possible to examine the benefits
associated with a particular type of transaction, to at least focus the analysis of the question “what is fair?”

The transaction of payment of healthy subjects in exchange for research participation can be framed as a transaction between A, the researcher/study sponsor/society, and B, the subject. Exploitation was defined above as occurring if A takes advantage of B to gain an unfair share of benefit. It was also noted above that exploitation may be facilitated if B is vulnerable.

The economically disadvantaged subject—that is, one who is in financial need and has limited options for earning money—seems to fit the broad definition of vulnerability provided above. Similarly, if undue influence does reduce understanding and voluntariness of consent (insufficient knowledge or freedom), even those subjects who are not financially desperate might be seen as vulnerable. Using this broad definition of vulnerability, it seems likely that some or possibly many of those who participate as healthy subjects are vulnerable to exploitation. As discussed above, however, even if a subject is vulnerable, s/he is not exploited if s/he receives a fair share of benefits in the research transaction. Thus, the question of exploitation seems to rest not with whether or not healthy subjects are vulnerable, but with whether or not they receive a fair share of the benefits.

In phase I drug trials involving healthy subjects, B (the subject) is being compensated for giving something—being a research subject. This can be rephrased as: B is exploited if B is not compensated fairly for what B gives. It is clear that A (researchers/study sponsor/society) benefits from B’s participation as a research subject. It is also clear that B receives benefits (payment and possibly intellectual or psychosocial benefits from the experience) and losses (anxiety, discomforts, drug toxicities, loss of personal time, inconvenience discomfort). Note that the term benefit here is used more broadly as gains to the subject, and not in the way it is traditionally used in research ethics—i.e. therapeutic benefit.
So, for the healthy subject, the benefit of the transaction (participation as a research subject) is the sum of all the benefits minus the losses of research participation. The subject will be exploited if the outcome of this calculation is not fair. Determination of fairness raises a number of challenges. One challenge is how to evaluate what a subject is giving (the losses associated with participation), particularly since many of the losses, such as the risk of adverse drug reactions, are uncertain. A second challenge is how to determine whether the benefits (payment and potentially other benefits) are fair compensation for those losses. Third, given that the losses include risk to health, this fairness calculation also prompts the question of whether it is ethically acceptable to balance this loss with a financial benefit.

Regarding the question of payment as compensation for risk, as discussed previously, it is generally accepted that REBs or other regulators involved in determining the ethical acceptability of a research protocol should not consider payment as a benefit to be weighed against risks of research participation (23). A restriction on the use of payment to balance risk for regulatory bodies considering approval of a research protocol, however, does not necessarily mean that it is similarly inappropriate for research subjects to consider payment as offsetting risk. A number of authors note that there are many types of employment reflecting society’s acceptance of the exchange of financial benefit for assumption of risks, such as firefighting and mining. It is suggested that research participation is not morally different from these other types of employment and that it is appropriate to compensate subjects for increased risk with increased payment. (63,64) In the case of risky jobs, however, those choosing that career are usually aware of the increased risk relative to other types of employment. If increased payment were to be offered as compensation for higher research related risks, this trade off would have to be very clear (72). If it is accepted that payment can compensate for risk, the question of what is fair compensation remains, which will be discussed below.

If it is instead argued that payment should not be increased in proportion to risk, as recommended, for example, by the Royal College of Physicians of London (2), two conclusions are suggested. One conclusion is that, in terms of the individual subject
involved in the research transaction, if risk cannot be balanced by something other than therapeutic benefit, it seems that all healthy subjects are exploited because they can never be fairly compensated for their loss (what they give to society) in terms of risk. Another option is that risk can be balanced for the individual by other, non-financial benefits, such as personal satisfaction, or by the indirect benefits resulting from the benefit to society. It might be argued that although subjects may not benefit directly from the particular medical knowledge arising from the study they participate in, by contributing to the improvement of medical knowledge they increase the probability they will have better health. This type of balancing would be the individual transaction or “market” equivalent to the risk-knowledge calculus that is used to in considering the ethical acceptability of research of no medical benefit. The difference is that in this example, the benefit to society is considered directly in terms of the individual research participant. The question of whether non-financial benefit could be fair compensation for risk requires further consideration. If such a balancing were deemed theoretically possible, we again return to the challenge of determining fair compensation.

There is no simple answer to the question of what is fair compensation for that which research subjects give to researchers/study sponsors/society. To begin to address this question, however, it might be helpful to identify more clearly the nature of the benefits and losses for the research subject. What are the burdens of research participation? What are the risks? How much is known and what is unknown about a test substance? What, if any, is the prior experience of this or similar drugs? How costly is the time lost? How great may be the discomforts and inconveniences associated with participation? The answers to these questions will vary widely from study to study and will also depend on an individual subject’s willingness to assume risk, and his or her subjective perception of the burdens and benefits of research participation. There may be some generalizations that could be made, however. Empirical data are needed to shed some light on the question of benefits and losses, especially from the perspective the research subjects themselves.
Proposals from the research ethics community for addressing concerns about exploitation of healthy subjects include both restrictions on level of payment, as well as lifting restrictions to permit higher payment. Interpretations of the problem of exploitation as grounded in the vulnerability of the economically disadvantaged recommend restriction of payment to avoid creation of offers that will prove irresistible to this population (39,42). This approach assumes that an increase in payment to make it more “fair” will lead to a higher response among the economically disadvantaged, perpetuating the disproportionate representation of the poor among healthy subjects. When examined closely, this interpretation of vulnerability as leading to the exploitative transaction actually reflects the concern of undue influence over decision making, but looking at the impact on a population rather than the individual.

If, as discussed above, vulnerability is seen as not necessarily resulting in exploitation, the focus turns instead to the issue of fair compensation. A number of writers have suggested that concerns about payment be focused on ensuring or facilitating fairness, rather than worrying about undue inducement. Calls to limit payment are seen as paternalistic and, through limiting freedom of choice, result in a reduction as opposed to an enhancement of autonomy.

The worry about overpayment has been framed around the presumption that healthy subjects who take part in drug trials for payment are unskilled, and socially marginal. This presumption is flawed because it is a generalization not based on empirical data (62). Furthermore, the suggestion by ethicists that the presumed low socioeconomic status of healthy subjects warrants limitation on payment may be seen as discriminatory by preventing subjects from being fairly compensated for what they do. “Trial participants, who are contracted labourers, should not be paid according to our perception of their social status, but according to the value of the service they perform.” (62).

Many commentators suggest that fair pay would be at least minimum wage, but with higher payment permissible or even encouraged (62,73,74). Some suggest that payment
should be increased as the study-associated risks increase (63,73). No formal schemes for calculation of fair pay adjusted for risk, however, have been suggested.\(^{12}\)

Lemmens and Elliot (75) propose that, rather than approaching the question of fairness from the position of experts deciding what is best for subjects, the issue should be addressed by giving healthy subjects greater power to negotiate for fair compensation, working conditions and schemes for worker compensation in case of injury. This view of healthy subjects as workers seems a dramatic departure from the traditional research ethics framework, which was founded on the doctor patient relationship, but, according to Lemmens and Elliott (76), is an accurate reflection of the relationship:

*In the world that regulatory bodies have created, healthy subjects take part in studies because of the money, yet researchers have to pretend that subjects are motivated by something other than money. Subjects can’t negotiate payment, since payment is not supposed to be the focus of the transaction. Research Ethics Boards are expected not to determine what is fair, but what is “undue inducement” (p. 52).*

The current regulatory scheme then, may be promoting, rather than preventing exploitation.

### 3.4.4 Justice

As noted at the start of this chapter, the ethical principle of justice requires a fair distribution of benefits and burdens. Although exploitation is a form of injustice, even if a scheme could be devised whereby healthy subjects were fairly compensated for their contribution, this does not necessarily eliminate concerns that the burdens and benefits of phase I participation are being distributed fairly. A separate concern regarding research with healthy subjects is that, even if compensation is fair, it is unlikely that the burdens of participation would be equally distributed across socioeconomic groups. Persons making a relatively high income, for example, are less likely to interrupt their regular work, or

\(^{12}\) A minimum wage model for payment has been accepted by many commentators as a reasonable scheme for compensation. This model, however, does not allow for increased payment with increased risk, and its primary priority is avoid undue inducement, while also being fair. No similar models or formulas for calculating fair pay have been developed where undue inducement has been eliminated from consideration.
forgo their free time, to participate as a healthy subject, unless they are motivated by non-financial reasons such as altruism, just as they are very unlikely to moonlight at a minimum wage job, even if the pay is seen as fair compensation for the work.

Thus, achieving just distribution of the burdens of phase I research across social and economic groups requires more than elimination of exploitation. Research that offers hope of medical benefit is likely to include patients across a broader social spectrum, because it may hold the promise of something that money can’t always buy—access to new treatments that could improve health. Also, there may be a greater sense of contribution participating in research for a condition that one has, and can relate to. Thus, a just distribution of the risks and benefits may be more closely approximated in the case of research that offers potential direct medical benefit, since distribution is determined to a large extent by the occurrence of the disease. On the other hand, research with healthy subjects involves no selection by illness, and so selection is mostly (although not entirely) economic.

An egalitarian approach to justice might suggest that the burden of participation be distributed equally through some system such as conscription. Such a solution, however, would violate the fundamental requirement that research participation be voluntary (77). A more equal distribution might also be achieved if significant enticements were offered for research participation, that were attractive to those of high socioeconomic status. The cost of enticements that would be effective, however, could increase the cost of doing research to the point that conducting the research was no longer feasible. Furthermore, taking people away from other important jobs is not necessarily of benefit to society, particularly if they possess special knowledge or skills that are in short supply (77). Thus, in the case of research involving healthy subjects, society’s interests may not be served by interpreting justice as meaning equal representation of all socioeconomic groups.

Another approach may be to promote justice by making the work more rewarding and empowering through worker self-management. It has been suggested that changing the nature of work in this way changes the moral character of the work—“What was once
harsh, unpleasant and difficult to endure, becomes a source of pride and respect” (77). This approach applies a theory of “complex equality”, which is based on the premises that there will always be difficult work, that equal distribution of this work may not be appropriate, and that the partial solution of giving those who do the hard work more control may be the best compromise to achieve justice. For research subjects, self-management might take the form of community consultation (77). This of course raises the challenge of how to define the community of healthy subjects. Anderson and Weijer suggest the community be represented by “professional subjects” who depend on research participation to make a living, as they have a greater investment in participation than do occasional subjects who might participate only once or twice in a lifetime.

As discussed above, the principle of justice does not necessarily require that all members of society share participation in phase I research evenly, and justice may be achieved in other ways. Detailed examination of this question will not be pursued here. This abbreviated discussion is to distinguish between issues of exploitation and justice, and to call attention to the questions that need to be answered regarding these issues. Without thoughtful examination of what it means to say that research subjects are exploited, or how just distribution of participation in phase I trials would look, there is little hope of resolving these issues.

### 3.5 Ethical Issues Summary

There are a number of ethical concerns regarding the use of healthy subjects in phase I drug trials. The need to set upper limits for risk in non-therapeutic research has been suggested, but not widely discussed, leaving this matter unresolved. The offer of payment raises additional concerns. Various regulations and guidelines require protection of the autonomy of subjects by keeping payment below the threshold of undue inducement. Defining undue inducement, both generally and for each specific research scenario, however, remains a significant challenge. Many commentators suggest that the focus on undue inducement reduces rather than enhances subject autonomy.
Concerns have also been raised that the offer of payment may lead to exploitation of the economically disadvantaged and unjust distribution of the risks and benefits of phase I research. Possible approaches to reduce exploitation and injustice include the promotion of fairness and increased self-management, through consultation with the community of healthy subjects. A better understanding of the experiences, attitudes and behaviours of healthy subjects is needed to inform all of the ethical concerns and help move the various debates forward. The current state of understanding regarding the perspectives of healthy subjects will be considered in the next chapter, which reviews the empirical literature relevant to research involving healthy subjects.
4 Review of Empirical Studies about Healthy Subjects and Participation in Non-therapeutic Research

Despite the ethical concern regarding participation of healthy subjects in phase I drug trials, there have been relatively few empirical studies focusing on this population (13). Of the studies that have been done, most have examined subject motivation, the effect of payment on decision making, and attitudes and experiences about participation. This chapter will describe the empirical findings, how they inform the ethical concerns discussed above, and the limitations and directions for future research. As noted in Chapter 1, my own research in this area attempts, in a modest way, to fill some of the gaps in the literature.

This chapter has been organized into sections addressing motivation, deception by subjects, informed consent, and experiences as a research subject. Of the empirical studies that have been completed to date, most have obtained data relevant to more than one of these categories. In the review below, the data will be considered where it informs a particular category of discussion. Thus, a given study may be discussed two or more times. This may give a false perception of the number of empirical studies that have actually been completed. Given the limited number of studies, this review is not limited to phase I drug trials with healthy subjects and includes other relevant research related to non-therapeutic studies and the issue of payment.

4.1 Motivation

Ethical concerns about payment are founded in the assumption that healthy subjects take part in phase I drug trials because of the money. It is therefore important to check the accuracy of this assumption empirically. Several studies have attempted to address the question of what motivates people to become a subject in non-therapeutic research. These studies have shown that, while money may be an important motivator, other motivations may also be important, or for some people, more important than payment. The studies
also show that attitudes about payment for participation vary among different research populations.

Separate studies using hypothetical scenarios to explore the effect of payment on participation found that willingness to participate increased with increasing payments among pharmacy students (52) and patients with hypertension (51). A clear difference in attitude about participation for payment between populations was observed in a survey of medical students and experienced healthy volunteers (78). Of the medical students surveyed, only 29% had volunteered in a study. Of the 60% who said they would consider participation, only 4.2% would do so solely for the financial reward. Scientific interest alone would be the motivation for 24.7% and scientific interest plus financial reward for 32.2%. In contrast, the financial reward was the primary motivator for 90% of experienced volunteers surveyed, with 6.3% motivated mainly by curiosity. The reason for the difference can only be speculated. There is limited demographic information provided, but of the 80 experienced volunteers in the study, 40 were students and 25 were “professionals”, suggesting a relatively high level of education in experienced subjects and medical students. This suggests that a simple difference in socioeconomic status does not explain the contrasting responses of the two groups. Other possible explanations are that those who had not participated previously did not have enough understanding of what participation involved to know what factors would affect their actual, rather than hypothetical behaviour.

Russell et al (79) surveyed unpaid healthy participants in a vaccine trial about the acceptability of paying research participants. Over half (57%) of respondents disagreed with paying research participants. The generalizability of these results may be limited, however, as these were unpaid volunteers who were mostly health professionals, taking part in a study that had a relatively low burden for participants. The applicability of these findings to healthy subjects in phase I drug trials, with high burdens such as confinement, significant time commitment, and numerous blood samples, is uncertain.
Other studies of healthy subjects who had taken part in various non-therapeutic research found payment to be the most important motivation for the many or most subjects (13,66,80,81). The proportion of subjects citing financial gain as a motivator ranged from 46% (82) to 100% (13) in different studies. Other reasons, such as getting a free medical check-up\(^\text{13}\) and the desire to contribute to science\(^\text{14}\) was more important for 20 to 35% of subjects in various studies (80-82).

It is difficult to compare the percentage of subjects who are motivated by financial gain across studies, as studies varied in how they worded questions about motive. While 80% of subjects in one study indicated that financial gain was highly relevant or relevant, 83% in that same study indicated that helping others was highly relevant or relevant to some extent (80). No information is available regarding the relative weight of these two motivations. In another study, although all subjects indicated money was extremely important or important to at least some extent, 9% said that they would participate without payment and another 52% indicated that they might do so (13). What is clear from these studies is that payment is important to many, if not most, subjects taking part in non-therapeutic research. What is less clear is the relative importance of other factors, such as contributing to science. In studies where subjects noted more than one reason for participation, it is not clear whether each reason on its own would be sufficient to induce participation. More research is needed to get a more thorough understanding of the role of various motivators in the decision to take part in non-therapeutic trials.

Demographic factors may affect motivation to participate in non-therapeutic research, but the findings to date have been variable. A study of healthy subjects in The Netherlands found that for subjects ages 18 to 30, financial reward was the most important motivator, but subjects over 60 years of age were more often motivated by the opportunity to have a

\(^{13}\) Although phase I study interventions do not provide therapeutic benefit, the medical screening procedures performed to assess subject eligibility are viewed by some subjects as a substitute for or supplement to a routine physical examination for the assessment of general health.

\(^{14}\) The actual contribution to science from many or most phase I drug trials has been questioned, with suggestions that they are conducted “simply to fulfill regulatory testing requirements for “me-too” drugs” (76). Thus, healthy subjects may have a “research misperception” about their contribution to science (Hébert, personal communication).
check-up, or by the chance of making a contribution to medical research (80). A more recent study conducted in Portugal, however, found no correlation between age and motivation (13). Whether these different findings reflect changes in attitudes about research participation over the 14-year interval separating the two studies, cultural or economic differences between countries (e.g. access to health care), or differences between the particular group of subjects selected for each study, cannot be determined.

Conflicting findings have also been reported regarding income and motivation to participate in research. Among hypertension patients responding to hypothetical research scenarios, those with higher income were more influenced by payment than those with lower income (51). Another study of healthy subjects participating in various non-therapeutic studies found that payment was most important to those with more education (83). Conversely, Almienda et al (13) found financial reward to be more important to those with lower income and lower education. In a survey of 350 adults who were called for jury duty, 80% believed persons with a low income would be influenced by a $500 payment to participate in a hypothetical hypertension study, while only 65% believed that same amount would influence someone with a higher income. Only 19.7% of respondents believed they would be influenced by the payment (84).

Clearly more data across a range of populations is needed to determine the relationships, if any, between demographic factors and motivation. A better understanding of this relationship would be useful to inform concerns that the offer of payment disproportionately attracts economically disadvantaged individuals.

The empirical research completed to date demonstrates that, while money seems to be a significant motivator, other non-financial benefits such as getting a medical check-up and making a contribution to medical science, are also valued by subjects. This raises the question of whether such non-financial benefits could be maximized to offset the risks associated with research that offers no therapeutic benefit. For example, should the medical screening that precedes phase I participation be considered a benefit? Further consideration is required regarding whether such balancing acts make non-therapeutic
research more ethically acceptable. More research is needed to get a fuller understanding of the relative importance of various motivations and their role in the decision to participate in non-therapeutic research.

4.2 Deception by Subjects

Payment for participation also raises concerns that subjects will lie about their medical history to qualify for or stay in, a lucrative trial. Anecdotal evidence, case reports and empirical research support this concern. For example, healthy subject James Rockwell, recalling his experiences at a hospital research unit, described a study with stringent dietary restrictions where hungry subjects decided to pick the lock on the food closet. Rockwell notes that although the food restrictions were a critical aspect of the study design, “we were just gorging ourselves at 2 a.m. on Cheez Doodles” (68).

A recent news article quoted several subjects as deliberately misrepresenting their medical histories to qualify for phase I research studies. A subject with active TB lied about his health status, exposing study staff and the other subjects with whom he shared living and sleeping quarters. Subjects also admit to ignoring rules prohibiting participation in more than one study at a time, or in quick succession, some going so far as using fake identification to escape detection (85).

Among a sample of healthy volunteers claiming to be non-smokers, 25% tested positive for cotinine in the urine, an indicator of smoking (86). Another study found that of healthy volunteers who had indicated during telephone screening that they did not use drugs or alcohol; 28% were later found to test positive for recreational drug use (87). Published case studies describe incidents of subjects concealing chronic medical conditions, such as a subject who did not disclose a history of arrhythmia which led to adverse events during the screening phase of participation, and a subject with diabetes and dietary restrictions, which resulted in his discontinuation because of inability to tolerate a high fat meal (88). As the subject with a history of arrhythmia was enrolled in the first-in-humans trial of a new drug with the suspected potential to induce arrhythmias,
the concealment might have had serious consequences if the subject’s condition was not detected during screening. The cardiac arrest and death of a young woman who had not revealed having had two previous cardiac arrests (89), and the death of a young man who had concealed having a depot injection of an antipsychotic the day before receiving an investigational drug (90), illustrate the tragic consequences that can result from falsified medical histories. The fact that the woman who had died of cardiac arrest was a nurse, suggests that knowledge of the importance of medical history may not be sufficient to override the motivation (presumably financial—she was to be paid $1300) to participate (88).

In their study of pharmacy student’s attitudes towards various hypothetical research scenarios, Bentley and Thacker found that increasing payment increased subjects’ indication that they would withhold information about restricted activities. This effect of payment on withholding of information was greatest for the low and medium risk research scenarios (52). This may indicate that when the risk is judged as high, subjects become more influenced by concerns about risk than by the payment.

In their survey of 440 healthy research subjects, Hermann et al found that 3% (13/440) of subjects indicated that they had incorrectly answered questions about their medical history: six by mistake, six because they thought this information was irrelevant and one because he didn’t want to be disqualified (66). Survey questions regarding smoking habits and alcohol consumption were left unanswered by 10.5% and 11.4% of subjects, respectively, suggesting a reluctance to disclose this information. Respondents also indicated they had some reluctance reporting the occurrence of an adverse event during research participation. Among those experiencing an adverse event, 14.3% did not report it promptly, and 20.7% first sought advice from fellow subjects (66). The rationale for this reluctance to report adverse events was not explored, but likely indicates a concern about being discontinued from the study and forfeiting some of the study payment.

In addition to the danger to healthy subjects, inaccurate medical histories can affect the integrity of study results. For example, subjects hiding regular nicotine or caffeine use
may experience withdrawal symptoms such as headache upon confinement in a research facility; headache may wrongly be attributed to the study drug (66).

The evidence to date suggests that deception by subjects is a valid concern. Deceptive behaviour also suggests that payment is a primary motivator for participation for at least some subjects, as knowingly threatening the integrity of the study is not consistent with the motivation to make a contribution to science. Limited reliance should be placed on medical history supplied by subjects and enhanced screening mechanisms are required to reduce risk to subjects and to protect the integrity of study data (88). More research to examine the prevalence of subject deception and its occurrence among various subject populations might provide focus for additional scrutiny.

### 4.3 Informed Consent

As discussed in Chapter 1, the informed consent of the subject is a critical requirement for medical research. A few research studies have examined this process in healthy subjects. Fortun et al (91) assessed understanding of study information among 82 healthy subjects taking part in a capsule endoscopy study. Ninety percent of subjects had a university level education, and 60% were medical students. Medical students were significantly better than the other subjects at recall of study procedures and risks. Nonetheless, only 12% of subjects (10 of 82) could name all three study drugs. Only 17% could name 3 or more risks of the study drugs, and 20% could not name any risks. Thirty-seven percent did not correctly identify the main risk of the study procedure. In contrast, 97% recalled the duration of participation and all but one subject accurately recalled the amount of payment they would receive. The authors suggest the use of shorter information sheets with a test and feedback session to try to improve understanding (91). These suggested solutions presume that subjects scored poorly on tests of understanding because the consent form was too difficult. Given the poor performance of even medical students, however, another interpretation might be that recall reflected which study details were most important to subjects.
Other empirical studies have found that when asked, most healthy subjects are satisfied with the amount of information given. Despite concerns that consent forms are getting too lengthy, few healthy subjects surveyed indicated that they have been given too much information (80,81). An examination of the readability of 16 information and consent forms used for phase I studies at a single clinical research unit, found all 16 forms were readable at the high school level, as assessed by four different readability software programs. This was a reasonable fit for the study population, as 84% of subjects at the research unit had at least finished high school. The researchers found that minor adjustments to the form made it readable to all subjects in the study population (92). While encouraging, further research is needed to examine the readability of consent forms and the education level of healthy subjects at other research centres. Furthermore, caution is warranted in the use of readability programs as these rely on formulae such as word and sentence length to determine a rating. Thus, a short sentence that contains words not commonly used, would score as written at a low grade level, yet in reality would be very difficult to understand. In addition, formatting, such as the use of headings or the font of the text, can significantly alter readability of a document, and is not captured by these programs (93). Finally, as suggested above, subjective factors such as the personal relevance of specific information may be more important than readability.

Using a previously developed model of “Vigilant Information Processing”, Rabin and Tabak (11) examined the decision making process of 100 healthy subjects taking part in phase I drug trials, to determine whether they had made a “quality decision”. By these criteria, only 35% of subjects made a quality decision about participation. The criteria required for Vigilant Information Processing include that the decision maker try “very hard to find more information, to tell me whether I am right or wrong about the points for and against each option”, and to think “very carefully about any new information and what experts said” (11). This standard for decision making may be applicable to complex decisions involving choices among a number of different options, but may be unreasonably demanding for healthy subjects deciding to be in a non-therapeutic trial. As healthy subjects are not choosing between research participation and other treatment alternatives, the decision comes down to a choice between participation or no
participation. Current consent forms generally are quite lengthy and contain a substantial amount of information about study drug and procedures, and are typically accompanied by a discussion with research staff (11). Moreover, subjects who have participated in previous phase I studies may be familiar with the study routine or the study drug (for example in the case of a bioequivalence trial comparing a marketed drug with a generic formulation). Thus it is likely that many prospective subjects will not feel the need to “find more information”, nor consider “new information and what experts said”. If it is accepted that healthy subjects can make an informed decision without seeking new information about what experts said, the finding that 65% of subjects failed to make a “quality decision” is misleading if it is quoted without an explanation of the high standard of Vigilant Information Processing.

The empirical data available to date regarding informed consent and understanding among healthy subjects is limited. The two studies that have specifically examined the quality of informed consent have found it to be lacking. More research is needed to relate the findings of these studies to the decision making process used by healthy subjects. Given the ethical concern regarding informed consent for non-therapeutic research, particularly when payment and potentially vulnerable populations are involved, more research is needed to determine what information healthy subjects use to make their decisions, whether they are receiving the information they need in an accessible format, as well as measures of understanding of the information.

4.3.1 Risk Assessment
While the quality of the informed consent process is of concern for all types of research, payment of subjects for non-therapeutic research raises specific concern about the impact of payment on subject risk assessment. As discussed in Chapter 3, there is concern that the influence of a financial reward may reduce understanding of risk, or may cause subjects to accept risks that they normally would not. Several studies have examined these concerns empirically.
Bentley and Thacker used hypothetical scenarios to examine the effect of risk and payment on subject willingness to participate in research. They found that higher payment increased the willingness to participate and the level of risk accepted, but did not decrease awareness of the risk. Pharmacy students were given one of nine different research scenarios, which were designed to have a similar time commitment, but which reflected three different risk levels (non-invasive saliva samples, bioequivalence trial comparing a generic formulation to a brand name marketed drug, and first time in man drug study) and three different payment levels ($350, $800, and $1800). They found that willingness to participate increased with increased payment, across all risk levels. Although the effect of payment was statistically significant, it amounted to a mean change in score of from 4.51 (when willingness to participate was rated on a scale from 1 to 10) for the lowest payment level, to 5.77 for the highest level (52). Thus there seem to be factors other than payment affecting decision making. The risk rating was not affected by payment level (52).

Halpern et al, who examined willingness to participate among patients with hypertension, also asked subjects to rate nine different research scenarios (three different risk levels combined with three different payment levels). They found that in about one third of patients, increased payment increased the willingness to participate. As risk levels increased, the number willing to participate decreased at about the same rate, regardless of the payment level. Thus, increased payment did not appear to affect risk perception (51).

These studies do not support the concern that the offer of payment causes subjects to ignore the risks associated with research participation. A significant limitation is that both studies examined hypothetical decision making, among pharmacy students and among patients with hypertension. It cannot be assumed that the results would be the same for subjects considering participation in an actual phase I research study, nor that the results will be consistent across different populations, such as the repeat subject, or “professional guinea pig”, for whom research participation is a significant source of income.
The actual behavior of subjects may provide clues to the relationship between risk and payment. In their survey of 144 healthy subjects taking part in various non-therapeutic pharmacology trials, Hermann et al (66) presented subjects with a list of potential adverse events and asked whether these would discourage them from participating in a study. While only 1.8% indicated they probably or definitely would not take part in a study if there was a risk of tiredness, the risk of headache, nausea or vomiting would be discouraging to 30.7%, 37.3% and 60.7%, respectively. Since all of these subjects did take part in pharmacology trials, and since headache, nausea and vomiting are potential adverse events common to many drugs, there appears to be a contradiction between subject attitude and behaviour (66). This suggests that the offer of payment influenced risk acceptance, although it cannot be concluded that risk assessment was altered. It should be noted that there is no indication in the report that the study authors specifically examined what types of potential adverse events the subjects in this study consented to, therefore this apparent contradiction must remain at the level of speculation. A follow-up study comparing attitudes and behaviour in more detail would be useful.

Regardless of the possible influence of payment, the overall perception of risk may be low for many subjects. In one study of healthy subjects taking part in phase I drug trials, 48% agreed with the statement “there is little risk in testing drugs like these” (81). It could be speculated that many subjects perceive risk as low because they are blinded by the potential financial reward, thus confirming concerns about the influence of payment. On the other hand, 30% of subjects did not agree that there was “little risk”. Moreover, some subject comments suggest that the offer of payment may call attention to risks—“there’s got to be some risk, or they wouldn’t give you the money” (81).

In another study, only 20% (12 of 60) of subjects raised the issue of risk when asked about “bad aspects of participation”. In that study, 46% of participants said that payment was the “best” aspect of participation, with 33% saying helping others was the best aspect (83). Thus, it seems that not all of the 80% who did not raise the issue of risk were highly motivated by payment. Given this evidence of mixed motivations for participation, the
apparently low concern about risk cannot definitively be explained as being the result of subjects being blinded by the pursuit of financial gain.

Psychology research into risk perception has identified a number of different factors that appear to affect the way people assess the risk associated with a situation. These studies have found that people seem more concerned about risks that affect large numbers of people at once (e.g. airplane crashes) than about risks affecting the same number of people but in small numbers over time (e.g. car accidents). Similarly, risks that have very low probability but great severity (e.g. Mad Cow disease) raise more concern than do risks which have a higher probability but are less severe (94). People are more concerned about risks that are imposed than about risks they choose (e.g. smokers were more afraid of asbestos in the workplace than of smoking). Similarly, people are more concerned about risks that are not under their control (e.g. riding in an airplane) than those under personal control (e.g. driving a car) (95). In addition, perception of benefit appears to reduce the perception of risk (50). These findings raise interesting questions for assessment of research-associated risk. For example are subjects more concerned about a remote risk of death from an investigational drug, or a 50% risk of vomiting? Does the fact that participation in non-therapeutic research is voluntary give subjects a sense of control that reduces their perception of risk? Empirical research is required to determine the applicability of these factors to risk perception among healthy subjects.

Other variables may also have an impact on how risk is perceived and assessed. Studies comparing assessment of research risks among various populations have found significant differences between male and female scientists judging environmental risks (96,97), differences among REB chairs assessing the risk of blood sampling and other common procedures in children (33), and differences between therapists and their patients regarding the risks and benefits of psychiatric research (98).

The way that risk information is presented or “framed” may also affect how risk is perceived. Presenting possible outcomes of decisions in terms of positive versus negative framing of risk information (e.g. 80% chance of survival vs. 20% risk of mortality) has
been shown to affect hypothetical decision making (99,100). Framing risk in terms of loss (e.g. advanced disease without screening) rather than gain (the benefits of acting) has been shown to have a greater impact on behaviour in a variety of situations (101). Similarly, relative risk reduction information regarding treatments or tests had a greater impact on perception than absolute risk reduction information (102). In a series of studies where psychologists and psychiatrists were given another expert’s assessment of a patient’s risk of violence, their response was strongly affected by the framing of the assessment. When the risk of future violence was presented as a relative frequency (“20 out of every 100 patients similar to Mr. Jones are estimated to commit an act of violence”), 41% would refuse to discharge the patient. But when presented with the assessment as a probability (“patients similar to Mr. Jones are estimated to have a 20% chance of committing an act of violence”), only 21% would refuse to discharge the patient (103).

Risk assessment appears to be a complex process, affected by various psychological and social factors. For subjects taking part in non-therapeutic research, the focus has been to examine the impact of payment on risk assessment. The empirical evidence gathered to date neither confirms nor dismisses the concern that the offer of payment causes healthy subjects to underestimate the risk of participation in phase I drug trials. Future studies concerned with risk assessment in healthy subjects should examine the impact not only of payment, but of other factors, such as demographic details and how the risk information is disclosed.

### 4.4 The Experience of Being a Research Subject

Current ethical concerns about healthy subjects are focused on the decision making that occurs prior to participation, and pay little attention to the actual experience of participation. This “up front” emphasis likely reflects the significant involvement of research ethics boards and regulatory agencies in the approval of the research protocol and informed consent process, compared to the lesser involvement in the monitoring of the actual conduct of the research, which is generally limited to ensuring compliance with
the original conditions of approval. This in turn may reflect the focus of guiding principles on the prospective determinations of the risks, benefits, subject selection and the adequacy of the informed consent document. A comprehensive examination of the governance of Canadian research found an “over-reliance on the REB process and informed consent”, which results in an emphasis on the pre-enrollment phase of clinical research (104). While it seems reasonable to suggest greater regulatory attention be paid to the active participation phase of research, an evidence-based approach should be used to inform any proposed changes or additions to ethical oversight. The views of research subjects are one critical source of evidence for identifying areas of oversight that require attention.

For phase I drug trials, empirical evidence about the research experience is limited. Recent reports in the media suggest healthy subjects in phase I drug trials must endure crowded, unclean, unsafe facilities, and unqualified and uncaring investigators and study staff (85). These reports contrast sharply with studies published in the medical literature, which report for the most part an overwhelmingly positive experience among patients taking part in clinical trials (15,105-107). The results from several studies examining the experiences of healthy subjects in non-therapeutic trials also suggest that for most participants the experience is positive. Ninety-seven percent of subjects in one study stated that they were glad that they had participated (83). In two other separate studies 90% (13) and 98% (80) of subjects indicated that they definitely or might participate in future studies.

When asked about the good aspects of participation, subjects mentioned making money, contributing to science, interacting with staff and fellow subjects, and relaxing or “lazing about” (80,83). In two separate studies, meeting new people and interacting with staff was seen as a positive aspect by 57% (83) and 30% (80) of subjects. Interestingly, interactions with staff and subjects could also be perceived as negative, if staff were rude or uncaring, or other subjects were annoying, for example with excessive snoring in the night (66,80,83). As discussed above, concern about risk was seen as a negative aspect of participation by a minority of subjects. Other unpleasant aspects of participation noted by
healthy subjects include physical discomforts such as side effects or repeated blood sampling, monotony, unappealing food, and lack of amenities, such as no cable television and lack of privacy (66,80,83). Although healthy subjects are often required to observe restrictions on use of substances such as alcohol, cigarettes or caffeine, one study that asked about this found that most subjects were not at all or only marginally bothered by these restrictions. Caffeine restriction was the most bothersome, affecting 16% of subjects surveyed (66).

A qualitative examination of the experiences of women testing a new device for breast cancer screening found differences between researchers and research subjects regarding the meaning of “being comfortable”. The study found that researchers were concerned with addressing the physical discomfort that subjects might experience having to stay in awkward positions for up to ten minutes during breast scans. The study authors interpreted this concern of researchers as reflecting their focus on the practical needs of the study—i.e. subjects had to be comfortable enough to be able to sit still for the duration of the scan. Researchers were also aware of the potential for embarrassment, and addressed this by having a female researcher position subjects in the scanning device. Subjects, on the other hand, downplayed issues of physical discomfort, and were more focused on “mental comfort” (feeling relaxed) and “social comfort” (establishing a rapport with researchers). Subjects actively pursued friendly interactions with researchers by making small talk which helped to reduce anxiety and made subjects feel more involved and therefore respected (108). These findings show aspects of research participation that have a significant impact on the experience of healthy subjects but that are less likely to be considered by REB members, regulators, or researchers who place more emphasis on the physical risks of investigational drugs and study procedures. Social interactions appear to be important to subject well-being during research participation and may help subjects feel more like “one of the team” and less like a guinea pig (108).

The above findings are important, since, while only a fraction of subjects will experience any given adverse event, all participants will be subjected to the study environment and study burdens. For phase I drug trials, as the duration of confinement increases, it could
be expected that the impact of the environment will increase. When reviewing research protocols, REBs may consider the burden associated with blood sampling and the loss of personal time associated with long periods of confinement. Based on my personal experience, as well as the lack of discussion of these issues in the literature, REBs appear less likely to consider the other study environment issues. This focus is easily understood, given the potentially serious risks associated with the early testing of new drugs. The principle of respect for persons, however, suggests that issues identified by subjects as important, should not be ignored. Whether oversight of environmental issues would be best addressed by REBs or through some other mechanism of governance, requires further consideration.

### 4.5 Summary

A handful of empirical studies have been published regarding the behaviour, attitudes and experiences of people who have actually participated as healthy subjects in phase I or other non-therapeutic trials. A few other studies investigating issues relevant to phase I drug trials with healthy subjects have involved patients and non-subjects, examining attitudes or response to hypothetical scenarios. Although they do not provide any definitive answers to the various ethical concerns described in Chapter 3, the evidence collected to date both supports and challenges assumptions underlying these concerns and provides direction for future research.

On the question of motivation to participate in non-therapeutic research, the evidence to date suggests that payment is important to most healthy subjects, and is therefore the primary motivator for many. Other motivators, such as contributing to science and helping others also appear important to many subjects, and may be the prime reason for participation for some subjects. It is possible however, that altruism is listed by some subjects as a motivation for participation because it is perceived as a more socially acceptable response. More research is needed to determine the relative importance of various motivators, and to define any psychosocial variables associated with motivation.
There is a growing body of evidence confirming that some subjects will falsify or withhold information in order to qualify or remain enrolled in a study. The prevalence of this problem, which threatens scientific integrity and subject safety, is not known. In addition, it is not clear what factors, such as size of payment or perceived seriousness of risk, might influence the likelihood or nature of deception. A better understanding of this issue is needed to inform approaches to addressing it.

Evidence derived using hypothetical scenarios indicates that, while payment can influence decision making, it does not detract from risk assessments. Research to date on the behaviour of actual healthy subjects suggests that payment can increase risk acceptance, as evidenced by participation. The effect of payment on risk assessment, however, has not been specifically addressed in studies examining actual rather than hypothetical behaviour of healthy subjects. The majority of healthy subjects appear to consider the overall risk of participation in non-therapeutic trials as low\(^\text{15}\). The role of payment or other factors in this assessment is not clear.

Most healthy subjects have found the experience of research participation acceptable and would take part in future studies. An important aspect of the research experience is interactions with other subjects and with staff, which could be positive or negative. The research environment, such as food, furnishings and amenities, also affects the experience. Concerns about risk were of importance to a minority of subjects.

The empirical evidence gathered to date provides only a spotty understanding of research participation—especially participation in phase I trials—from the perspective of the healthy subjects. Most studies have been designed for breadth—surveying attitudes and

\(^{15}\) The “accuracy” of subject risk assessment is difficult to judge, as the empirical studies did not include a comparison between perceived risk and some other gold standard or objective measure. For example if the trial was a bioequivalence study of a topical medication for excema, the assessment of risk as “low” might be considered accurate or reasonable. The assessment of a first in humans study of a new class of immunosuppressant as low risk, however, would likely not be considered accurate by most researchers or ethicists. Consideration of “accuracy” with regard to risk perception is also complicated by the evidence that, as discussed in this chapter, expert risk assessment can be subjective and value-laden.
behaviours on a wide range of topics, rather than in-depth examination of a specific issue. The resulting data suggest interesting trends regarding subject attitudes and behaviours, but support only speculation about the meanings and implications of the findings. Further research is clearly needed to follow-up on the questions raised, before the empirical data will be useful to inform ethical concerns. My research was designed to respond to some of these questions and I will now turn to it in the next four chapters. I will then look at how this research informs current understanding and ethical discussion regarding participation of healthy subjects in phase 1 studies.
5 Methods

5.1 Overview

The previous chapters have provided an introduction to the empirical study component of this thesis. As described in Chapter 3, a number of ethical concerns have been raised regarding the participation of healthy subjects in non-therapeutic research trials that provide payment in exchange for participation. These concerns have been debated for several decades with little forward movement towards a consensus with regard to their appropriateness or how they are to be addressed. One likely reason for the lack of progress in these debates is the lack of input from the subjects themselves. As discussed in Chapter 4, there has been limited research examining the experiences and attitudes specifically of healthy subjects participating in non-therapeutic research, and to my knowledge, no studies specifically examining the experience of healthy subjects in phase I drug trials at commercial research facilities. The empirical study described here and in the next three chapters provides a unique perspective on research participation. In this chapter I will describe the methods that I used to examine the experiences, perceptions and attitudes of healthy subjects in phase I drug trials.

This chapter is organized into the following sections: Relationship Between Empirical and Normative Ethics, Study Design, Study Population, Recruitment, Theoretical Sampling, Interviews, Data Analysis and Role of Published Literature and Ethical Theory. This research was approved by the Health Sciences Research Ethics Board at the University of Toronto.

5.2 Relationship Between Empirical and Normative Ethics

This research is an example of empirical or descriptive ethics. Empirical ethics seeks to address ethical issues by obtaining empirical evidence regarding the behaviours or beliefs of individuals or groups. Empirical ethics examines what is going on in a situation, whereas normative ethics addresses how we ought to act in a situation. A variety of research designs are used to do empirical ethics, such as surveys, interviews, or review of
documentation. In normative ethics, on the other hand, philosophical or theological analysis is used to come to conclusions regarding what is right or ethical in a given situation.

Empirical ethics does not directly generate ethical norms. For example, just because many people hold a particular belief does not mean it is morally justified. Empirical ethics can, however, inform normative ethics. Ethical norms applied to a specific scenario, such as research with healthy subjects, are played out in, and therefore must accommodate, the real life context of that scenario. The normative guidelines prohibiting large payments as undue inducements, for example, are based in part on assumptions that healthy subjects are motivated by payment and that payment is likely to interfere with informed decision making. Whether these assumptions are correct, however, is an empirical question. Similarly, while concerns regarding exploitation and a requirement for fairness in transactions are products of normative ethics, determination of the degree of burden subjects perceive to be associated with research participation requires empirical examination.

In this thesis I used an empirical approach to obtain a better understanding of the context of research participation from the perspective of the healthy subject. The potential implications for normative ethics are considered in Chapter 9.

### 5.3 Study Design

The primary goal of this research study was to develop a better understanding of the experience of being a participant in a phase I drug trial. I used a qualitative approach to answer my research question, since qualitative methods are best suited to understanding subjective experiences such as the experience of being a healthy subject. In addition, in the study of a phenomenon for which there is little existing data, such as the experience of healthy subjects participating in phase I research at commercial research facilities, qualitative methods provide a means to uncover “what is going on” in the situation (109). A qualitative approach allowed the subjects to define what about their experience was
important, rather than collecting data about pre-determined topics such as “informed consent” or “payment”.

I selected a grounded theory approach as the specific method for my research. Grounded theory is a set of “systematic, yet flexible guidelines for collecting and analyzing qualitative\textsuperscript{16} data to construct ‘theories’ grounded in the data themselves” (110). Grounded theory methods are well suited for understanding social phenomena and variations in social behaviour (111,112). Grounded theory methods offer a systematic guide to theory development, directing all aspects of the research, from development of the research question, to data collection, analysis and theory generation. The goal of grounded theory is “to develop a theory that accounts for much of the relevant behaviour” (113) regarding a social area or phenomenon. In my empirical study the area under investigation is phase I research with healthy subjects and the behaviour of interest is that of the subjects with regard to their research participation. Thus grounded theory seemed like an appropriate approach to better understand how healthy subjects experience and view their participation in phase I drug trials.

Since its initial development in 1967 (113), a number of variations on the grounded theory method have emerged. Two main variations are those versions described by the two discoverers of grounded theory, Barney Glaser and Anselm Strauss. A major difference between these two versions is the use of an “axial coding” step (114), which was developed by Strauss and Corbin (109) and opposed by Glaser (115). Axial coding is an intermediate coding step between open coding (see analysis section below) and development of the final theory. Axial coding involves the identification of a core category or categories fairly early in the process of analysis and then systematic development of that category using a “paradigm model”—a set of pre-defined subcategories, such as “conditions”, “context” and “consequences”, which are used to organize concepts around the core category(s) (114). For me, Strauss and Corbin’s method presented a problem because until very late in the analysis I did not feel I could

\textsuperscript{16} Although most commonly used with qualitative data, grounded theory methods can also be used with quantitative data (Glaser & Strauss, 1967).
identify one—or even a few—concept(s) around which to focus axial coding. Glaser’s approach (116) does not involve an axial coding step, and therefore did not present a similar problem for me. In addition, Glaser directs researchers to relate concepts to one another using whichever “theoretical concepts” emerge as necessary to the developing theory, rather than relating concepts according to a pre-defined framework (i.e., the paradigm model) (112,115). In Glaser’s approach, categories from the paradigm model such as “conditions” or “consequences” may emerge as theoretical concepts that become part of the final grounded theory, but they are used only where they “earned their way” into the theory (115,117). This approach to integrating the concepts is consistent with the concept of emergence that is at the very core of grounded theory and for me, felt like a more natural approach to the analysis.  

As the aim of this study was to get a better understanding of participation from the perspective of the healthy subject, and to avoid imposing any of my preconceptions regarding what aspects of participation are most important, my initial research question was very general—“What can we learn about research ethics from healthy subjects taking part in phase I drug trials at commercial research facilities?” As will be described below, the refining of the question began concurrently with the collection and analysis of data, and continued during development of the emerging theory.

5.4 Study Population

Subjects were adult men and women who had taken part in one or more phase I trials at a commercial research facility. Two individuals who had participated as healthy subjects in University and Hospital based trials were also included. Subjects were required to be 18 years of age or older, able to read and communicate verbally in English, and capable of giving informed consent. The demographic characteristics of the subjects are described in detail in Tables 1 to 4, Chapter 6.

17 Given the decades-long debate about the merits of various versions of grounded theory, as a first-time grounded theorist I am in no position to say that one form or another is better. Similarly, I do not feel it is my role in this thesis to justify Glaser’s approach as legitimate. My reflection on the “Glaser versus Strauss” debate is meant only to provide some explanation of why Glaser’s approach was right for me at this time.
5.5 Recruitment

Thirty-one subjects were enrolled over the 14 month recruitment period. Initially, I hoped that subjects might be recruited directly at the phase I research facilities, but in all four facilities I approached, permission was either directly denied, or repeat requests were unanswered. The vice-president of one facility at first expressed interest but subsequently did not respond to my many attempts at further discussion. An executive of a major clinical research organization in the US that routinely conducts phase I drug trials with healthy subjects suggested in a personal communication with me (S DeCherney, Chief Innovation Officer, Quintiles Translational, July 2006) that the facilities may be hesitant to be involved because of concerns that my presence might impose extra burdens on the study staff or interfere with their tight research schedules, or because of fear that the type of research I was proposing might identify problems that need addressing. This in turn, could result in increased burdens for the operation of phase I research. As an example, a finding that subjects felt they were not adequately informed about participation could lead to recommendations for change to the informed consent process, such as disclosure sessions conducted with subjects individually rather than in a group. As the operation of a phase I facility demands compliance with numerous regulatory standards, there is little incentive to support a research project that might result in the promotion of increased requirements.18 I also speculate that the maligning of commercial phase I facilities in various media reports (37,118) has made these organizations distrustful and wary of opening their operations to scrutiny.

Without direct access to subjects, I recruited subjects through advertisements (Appendix A and B) posted on the internet classified ad sites my.utoronto.ca and NOW online (119). By using these sites I was able to target my intended audience, as these sites also feature advertisements recruiting healthy subjects for participation in phase I drug trials. My advertisements included the offer of a $20 stipend for participation, to cover any travel expenses incurred in coming to the interview, and as a show of appreciation for the subjects’ time. Subjects who were interested were invited to respond by email. Further

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18 This informed consent example is purely hypothetical, to illustrate the possible concerns of the research facilities.
communications regarding study details and scheduling of an interview were conducted through email, or telephone, if the respondent supplied their phone number and expressed a wish to be called. Subjects were informed of the purpose and nature of the study, including that the interview would be audiotaped, and if they were still interested an appointment was made to meet.

A few subjects were also recruited using a one-page poster (Appendix C), distributed to fellow healthy subjects by an earlier participant in this study. The posters were distributed to individuals who participated regularly in phase I trials, following my observation that these subjects seemed to provide a particularly rich source of data relevant to the emerging theory about research participation. Such targeted recruitment is part of the grounded theory method as described in the section “Theoretical Sampling” below.

Recruitment through advertising rather than through the research facilities had both advantages and limitations. One practical advantage was that I was not restricted to the scheduling requirements of the study facilities. In addition, as the goal of this study was to better understand the overall experience of being a healthy subject, and not to obtain subject ratings of specific facilities, the interviewing of subjects separated both in time and space from a specific research experience may have promoted reflection on the overall experiences, rather than a single immediate study experience. Furthermore, I was not consciously or subconsciously encumbered by any sense of being obligated to the research facilities for giving me access to “their” subjects. When I had initially anticipated recruiting through the facilities, I had worried that exposing any problems I discovered might seem like a betrayal. Recruiting independently helped me manage that concern.

The major limitation was that this method resulted in my interviewing a self-selected group of subjects who read these online ads, and were comfortable using or had access to email. These selection factors mean that individuals belonging to certain sub-populations, such as those who do not own computers, or who do not read these particular online advertisements, were not likely to be included in my study. In addition, subjects who
could not converse in English were excluded from participation. The result is that certain perspectives may be missing from the final theory developed in this research. For grounded theory, the exclusion of some perspectives results in a loss of richness in the theory. As theories generated by the grounded theory method are always modifiable, however, it will be possible to integrate new data about new perspectives into the theory in the future. Furthermore, the direct distribution of posters to selected regular participants as described above accessed several individuals who did not respond to my advertisements, thus broadening the heterogeneity of the study population.

A second limitation is that by interviewing subjects outside of their research participation, some perspectives or experiences may have been forgotten or altered over time. This limitation is likely not significant, however, as most subjects had participated within the year, and some were actively involved in participation at the time of the interview.

I had also been concerned that the $20 compensation would seem small to those who earned hundreds or thousands of dollars as healthy subjects, and would therefore select for subjects looking for a forum to vent their frustrations about participation. This concern appears to have been unwarranted, as the majority of subjects seemed to be generally content with their experiences in phase I drug trials. (Possible reasons for this will be considered in Chapter 9.)

5.6 Theoretical Sampling

For grounded theory, selection of the study population is based on “theoretical relevance for development of the emerging categories” (113). This approach, called “Theoretical Sampling” requires that, rather than staying with a rigidly defined study population determined prior to the commencement of data collection, data sources change throughout the course of the research, to suit the needs of the developing theory. As concepts emerge, the researcher seeks data that will help the development of the concepts.
In this study, the main inclusion criterion was very broad; namely, anyone who had taken part in at least one phase I trial at a commercial facility. This reflected the general and unspecified nature of the research question at the outset of this study. The intent was to collect a wide variety of experiences to see what similarities and differences emerged. I unintentionally included one subject who had taken part at a commercial facility, but in a trial of allergy medication that might offer some therapeutic benefit\(^{19}\), and purposely enrolled two subjects who had participated as healthy subjects, but at hospitals and universities, rather than commercial facilities. These latter two were intentionally included early in the study to provide possible contrasting experiences or perspectives that might help illuminate aspects of the phase I commercial experience I might otherwise have missed.

As the analysis progressed, the sampling became more focused, to address gaps in the developing theory. For example, the majority of initial respondents were current or recent University of Toronto health sciences students, who seemed to have a high level of understanding about pharmacology and the research process. After ten interviews the decision was made to stop recruitment through the University website, to obtain a more heterogeneous population with a wider variety of experiences and perspectives. As the developing theory began to focus on how subjects cope with the burdens of participation, the decision was made to interview subjects with more experience and not to seek out those who, after their initial experience, chose not to take part in further studies.

For the most part, theoretical sampling was limited to following up on specific aspects of the developing theory by adjusting the interview, rather than by seeking out specific subjects who might be most likely to provide insight into particular concepts. Sampling was significantly affected by practical constraints of recruitment. Recruitment required

\(^{19}\) The inclusion of a subject who had participated only in a potentially therapeutic allergy study, rather than as a true “healthy subject” in a non-therapeutic study, resulted from insufficient screening by me in advance of the interview to determine that she did not meet the main inclusion criterion. As I became aware of the nature of her participation experience only during the interview, I decided to proceed, and use the resulting data to compare and contrast with the data from subjects who had been in strictly non-therapeutic studies.
subjects to self-identify and to take action by responding to an advertisement, making it very difficult to specifically seek out individuals who had for example, had a bad experience, or who had taken part in specific types of phase I drug trials. I did try for several weeks to advertise specifically for subjects who had taken part in more than ten trials, but received a reduced response, comprising only individuals who had done fewer than ten trials. I therefore reduced the request to subjects who had done more than two trials, and accepted subjects who met at least this minimal criterion.

Despite the limitations, the 31 subjects interviewed in this study were sufficiently heterogeneous to include a range of socioeconomic variables, frequency of participation in phase I trials, and attitudes about participation. Recruitment was stopped after the 31st interview, as it was determined that theoretical saturation was reached. This means that further interviews did not seem to bring new insights into the developing theory. More specifically, saturation was identified as the point at which new data did not yield new codes or concepts or add to the description of existing concepts.

5.7 Interviews

The data for this study were interviews with study subjects. The majority of interviews were face-to-face meetings at the University of Toronto Joint Centre for Bioethics. Subjects were given a verbal explanation of the study, and then given time to read the written consent forms (Appendix D and E). All subjects agreed to continue with participation, and were asked to sign the consent form. The first five subjects were given their $20 stipend at the end of the interview. The remaining subjects were given the stipend at the beginning of the interview, as I almost forgot to offer it at the end of two of the interviews. In addition, by presenting the stipend at the beginning, I was able to emphasize to subjects that they were free to end the interview at any time. Interviews lasted between 30 and 90 minutes. Interviews involved a brief demographic questionnaire (Appendix F), followed by an open component. The open part of the interview always began by my asking subjects a very general question, as in this excerpt from an actual interview: “So, we’ll just start in a very general way. Do you want to talk about your experience? Whatever is relevant to you.” Topics raised by the participant were pursued
as they arose, for additional information or for clarification, e.g. “When you say professional, or unprofessional and hokey, and that sort of puts you off, is there a—can you be more specific about HOW it puts you off? Or what you’re concerned about in that case?”

In addition, an “interview map” was used to generate additional discussion once the subject had ceased to raise new issues spontaneously. The map was a simple diagram of concepts representing the state of analysis at the time of each interview. Early interview maps were based on research ethics theory and a cursory review of the literature, and contained concepts such as “informed consent” and “trust”. Later maps were based on the study data and analysis, and contained concepts such as “maintaining control”, “power imbalance” and “burden-pay calculus”. The interview map changed frequently throughout the study, and I used it to help me to make sure that theoretically relevant concepts were covered during the interview. In this way, I was able to seek information to address gaps in the data and to test developing hypotheses about research participation. Interviews were audiotaped and I transcribed them as soon as possible after the interview. In transcribing the first few interviews I attempted to be as close to verbatim as possible, including every “um” and “ah”. After analyzing these interviews, I realized that for the most part, these little habits of speech did not affect my interpretation of the meanings of subject responses. As they added significantly to the burden of transcription, I made the decision not to religiously include such utterances, unless accompanied by long pauses or a grasping for words, suggesting subjects had to put extra thought into their response. For example, I felt the terms “like” and “you know” could be eliminated from the statement “Um, so yah, like, you know, like yah, I don’t have any worries, like, when I’m in there, like, what’s gonna happen and stuff” without altering the meaning, as this subject had the habit of inserting “like” and “you know” frequently in his speech. It was transcribed as “Um, so, yah, I don’t have any worries, when I’m in there, like, what’s gonna happen and stuff”. This “cleaning up” of the language also made it easier to focus on the relevant content during analysis. Support for my decision to edit the interviews in this way comes from the fact that Glaser recommends not tape recording interviews or even taking notes during interviews, and suggests instead that notes should be made after the interview is
complete (117). Although as a novice grounded theorist I did not feel comfortable with forgoing the audiotaping of my interviews (and in fact can see some objections to this approach), Glaser’s approach certainly suggests that verbatim transcripts are not a requirement for doing grounded theory.

5.8 Analysis

Data were analysed according to the grounded theory methods described by Glaser and Strauss (113) and Glaser (116). Analysis was done as the data were collected, so that subsequent interviews could be informed by the analysis that preceded them. HyperResearch™ Qualitative Analysis Tool, Version 2.7 computer software was used to aid in data management and analysis. This program provides a number of tools to facilitate handling of the large amounts of data, including permitting assignment of codes to specified interview text and the generation of summary reports grouping together text according to specific criteria, such as all text which had been assigned the code “motivation”. The summary report feature was particularly useful in the development of concepts, by facilitating comparison of related data.

Analysis proceeded through a process of coding, and constant comparison. In coding, incidents in the data are labelled with a descriptor or code, which raises the incident from the specific empirical instance, to a more general level. (An incident is any bit of the transcript that is assigned a code.) For example, a subject’s describing how they put up with repeated meals of pasta, was labeled “accepting”. Constant comparison means that throughout the coding process, comparisons were made of incidents with incidents, incidents with concepts, and concepts with concepts. So, comparing incidents of “putting up with the lack of privacy” and “tolerating the repeated blood samples”, with the developing concept “accepting”, I decided that these two incidents should also be coded as instances of “accepting”. Although the different types of comparisons occurred throughout analysis, in the earliest stages the comparisons were of incidents to incidents, while later stages focused more on comparison of concepts with one another and the developing theory.
The initial analysis consisted of detailed coding of each incident in the transcript, with multiple codes assigned to incidents where relevant. Initial codes tended to be descriptive rather than conceptual. The codes “not telling others about participation” and “getting a negative reaction from others”, for example, essentially describe the specific actions in the data. This process is commonly called open-coding, and seeks to keep the investigator open to all the possible categories that may emerge from the data. At the early stage of analysis these descriptive codes provided a summary of the empirical data—what was happening in the incident—which facilitated comparison of incidents labeled with the same and different codes. As these early codes were compared I could find similarities and differences and started to develop more abstract or conceptual codes, and transcripts were relabeled with the new codes. So, for example, the descriptive codes “not telling others about participation” and “getting a negative reaction from others” led to the development of the more abstract code of “stigma”, which incorporated both of these descriptions. These new codes became preliminary categories or concepts, which were refined as the analysis progressed. As concepts or categories emerged during the analysis of new transcripts, previous transcripts were re-analysed for data relevant to the new code. As codes became more generalized or abstract, many codes became subsumed by other codes, and the total number of codes was reduced. For example the codes “risk assessment” and “blood sample burden” were subsumed under the code “net burden”.

As the constant comparison continued I further developed the concepts by noting how various codes related to one another. For example, fairly early in the analysis I had developed the concepts of “accepting”, “normalizing”, “buying into study requirements” and “excusing staff” (although some of the labels were different), but had not sorted out where they fit into the overall picture. Through many rounds of constant comparison I was able to get a fuller description of each concept, and see that the latter three were all mechanisms for “accepting”, a higher order concept. “Accepting” in turn was related to the next higher order concept “finding personal control”. Concepts were related to one another until an integrated model or theory about research participation began to emerge.
The theory continued to be re-worked and refined throughout the data collection process and during the writing of the thesis.

Throughout the coding process I wrote memos to record my developing ideas about the emerging concepts and their relationship to one another. Memo writing is a central part of doing grounded theory. Glaser goes as far as saying that if the researcher skips the step of memo writing and goes straight from coding to writing up “he is not doing grounded theory” (original emphasis) (116). Memos are critical because they are not only records of developing ideas about concepts, but are analytical tools. The process of writing memos forced me to think through and crystallize my thoughts, thereby moving the analysis forward. As I accumulated more and more data, memoing became indispensable in retaining and organizing my thinking. During periods of intense focus on a specific concept I wrote detailed memos to capture my thoughts. Without those memos, much of the depth and insight would have been forgotten as I moved my focus to other concepts.

While codes are the generalized abstractions or labels assigned to specific bits of empirical data, memos document the theorizing or thinking about the data. Memos written early in the analysis consider how the data might be interpreted and coded, and raise questions for follow-up with subsequent interviews, as demonstrated by this early memo regarding study restrictions:

Restrictions:
- [subjects] aware of importance to study integrity.
- Variable adherence depending on:
  - chance of getting caught
  - personal burden of adherence (caffeine)
  - perceived (rationalized?) importance to study integrity

Issues to Pursue:
- which restrictions do subjects follow and why
- looking for what context/under what situations they rely on research staff/protocol to protect them vs. their own sense of responsibility for their safety—feeling safe—Do you feel safe? What makes you feel safe?
- maybe bring out themes of trust, responsibility to self and responsibility to study or staff. (Thesis Memo, March 2, 2007)
Later memos, reflecting the outcome of constant comparison of significant amounts of data, operate at a more abstract level, considering more developed concepts and the relationships between concepts, as in this example:

*The other thing I want to write down today is what is to distinguish between conceptualization and description. For example finding a study. That is descriptive, because it doesn’t say anything beyond what is happening in that time and place. “Concepts are abstract of time, place and people, and have enduring grab.” (Glaser, as above) I mean much more by that term, but the words don’t convey it. ...By “grab”, I think Glaser means that when you hear the concept you know what they mean without too much explanation. So “find” or “decide” does not take you beyond the obvious. Does not get you deeper into understanding than describing the situation as someone would the first day looking at the data... Back to tying into the core category, what about Context. Respect, caring and professionalism obviously have a close link. What about stigma—it is one of the things that spurs the need for normalizing. It is a property of normalizing, a cause. Similarly the study burdens are the cause for finding control, as is imbalance of power. Respect and caring, on the other hand, enhance the finding of control. They are properties of control. (Thesis Memo, October 10, 2008)*

Memos thus evolve, reflecting the development of concepts and theory about how they relate to one another. These memos form the basis of the final written Grounded Theory product.

### 5.9 Role of Published Literature and Ethical Theory

A common concern in the conduct of qualitative research is the role of the investigator’s background knowledge and of existing theory regarding the research topic. While a certain amount of background is helpful in developing an initial research question and in interpreting the data, there is concern that beginning a study with too much information can bias the investigator and result in the seeking of data to confirm pre-existing theories. This deductive type of theory verification is the antithesis of Grounded Theory, which seeks instead to inductively develop new theories that explain social processes, based on data derived from the research.

Starting this research project with over 13 years in the field of research ethics, including having reviewed, as an REB member, dozens of phase I drug trials being done at
commercial research facilities, I certainly had some background knowledge of the nature of these trials, and the ethical concerns about their conduct. I was also aware, however, of the lack of information regarding subjects’ views on their participation, and it was my concern regarding this knowledge gap that prompted this thesis research. As an REB member reviewing phase I trials, I had some say in the wording of consent forms, the schedules for subject payment, and to some extent various study conditions, as well as a role in deciding whether or not a study was permitted to go forward and enroll subjects. In performing this REB function I have felt a desire for feedback regarding how my actions affected those subjects whom I was charged to protect.

Thus, in beginning this research project, I was acutely aware that the existing ethical frameworks regarding participation of healthy subjects in phase I trials were based on theoretical concerns and the opinions of experts, and not on empirical data from actual subjects. My knowledge of the existing published data regarding, for example, patient and subject experience with informed consent, had also made me aware that the actual experiences of patients and subjects can depart significantly from theoretical models. I therefore entered this research project humbly aware that I did not know what I was going to discover about how healthy subjects experienced their participation.

During analysis I consulted the literature to stimulate the development of specific concepts as they emerged during the research. For example, the concept of control emerged as important early in the analysis, and persisted throughout the process of constant comparison. I searched the published literature for discussions of control as a concept, and found a framing of control that aligned quite closely with my emerging understanding of control as it related to research participation. Thus the published literature became a source of data that I compared against my existing data to further my analysis.

As mentioned in the section describing interviews, the conceptual analysis of the ethical issues regarding participation of healthy subjects, and the detailed literature review included in Chapters 3 and 4 of this thesis, were not written until after the data analysis
was largely completed. Indeed, throughout the process of data collection and analysis, I tried out numerous outlines for organizing the background chapters of this thesis, and only after my model had taken a shape close to its final form was I able to see how to frame the published literature. My consideration of the existing ethical concerns and the gaps in the empirical literature became much more focused and I believe more meaningful after I could see its relevance to my research results. For example I had in the past not given much thought to the concept of justice, except in terms of selection of study populations. Writing Chapter 1 after listening to the accounts of the subjects in my research, I developed a much deeper understanding of the concept, and how it relates to healthy subjects.

I believe it would be fair to say that my findings shaped my framing of the background information far more than the background information shaped my findings. Conversely, as I examined the ethical issues and existing empirical research in Chapters 3 and 4, the implications of my findings became more apparent to me, and helped shaped my final presentation of the results, as well as my discussion. The entire research process then could be envisioned as a loop beginning with a relatively superficial knowledge of the literature and a desire for more information, the development of a research project to begin to address the knowledge gap, a more reflective review of the existing literature informed by my findings, and refinement of my theory shaped by my consideration of existing ethical theory. The study results are described in Chapter 6, 7 and 8, and the ethical implications are discussed in Chapter 9.
6 Results: Making Participation Work—The Process of Participation

When I rent my healthy body to medical science, I am a temporary employee of a research team, paid as a contractor for each job. I do my bleeding, pissing work in a blurry area between patient and subject.

-Robert Helms, Guinea Pig Zero Anthology (21)

6.1 Overview

This chapter describes a grounded theory of research participation called Making Participation Work. This theory describes how healthy subjects perceive their participation in phase I drug trials at commercial facilities, and explains how various factors affect the experience of participation. Grounded theories identify the main problem or phenomenon of concern for a social group, and account for the variation regarding how the group deals with the problem or concern (116). The main concern for healthy subjects is how to earn income through participation with the least amount of personal burden from participation. The main variations in behaviour are in the type and number of studies subjects take part in, and in the perception of the experience of participation. The theory Making Participation Work defines the problem and accounts for a significant amount of the variation.

The concept of Making Participation Work describes both how healthy subjects frame their phase I research participation and how they cope with it. Subjects frame their participation as work, because they use it as a way to generate income. Although it may differ in important ways from other types of work, the main objective driving research participation is to make money. Subjects also make participation work by finding personal control which reduces the net burden of participation. The degree to which subjects are able to feel personal control over their participation appears to directly affect the degree of burden associated with participation. Thus by finding personal control subjects are able to make research participation a feasible option—they are able to make participation work.
In the next three chapters I will describe the theory of *Making Participation Work* in detail. In this chapter I will describe the study population and explain how subjects frame the process of participation as work. In Chapters 7 and 8 I will describe the factors affecting the participation experience.

### 6.2 Subject Characteristics

As described in the Recruitment and Theoretical Sampling sections of Chapter 5, the study population is a convenience sample, and is also shaped by limited purposeful sampling. It is not meant to be construed as a representative sample. Thus the following characteristics describe this particular study population, and cannot be assumed to represent the population of healthy subjects more generally.

Thirty-one individuals took part in this research. Of these, 30 had participated as healthy subjects in medical research, and one woman had participated in a phase I allergy study that may have had minimal temporary therapeutic benefit. Of the 30 healthy subjects, 28 had participated in phase I drug trials at commercial research facilities; two had participated only in medical research in the University or Hospital setting. Of these two, one was actively seeking participation in a commercial unit, and the other stated he would definitely not participate outside of the University or Hospital setting.

Of the 31 subjects, there were 18 men and 13 women. Ethnicity/race of the study population was: 17 Caucasian, four Asian, three Southeast Asian, three African American, two Hispanic and one Arab. English was a second language for six of the subjects, who, while able to communicate in English, did so with some hesitancy at times (i.e. they were not completely fluent).

Subjects ranged in age from 20 to 63 years of age. The mean age was 34 years. Education level was high. Education level is shown in Table 1 below.
Table 1. Subject Education Level

<table>
<thead>
<tr>
<th>Education</th>
<th>N/30* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High School</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Some College/Degree</td>
<td>10 (33)</td>
</tr>
<tr>
<td>Some University/Degree</td>
<td>18 (60)</td>
</tr>
</tbody>
</table>

* no data for one of the subjects.

Of 18 with at least some University:

5 were in or had completed graduate school or a second degree.
9 had or were working on a life sciences degree

All but two subjects had taken at least some college courses. The other two had completed high school. Twenty-two had completed a college or university degree, or were in at least their third year of university.

Table 2 indicates the number of phase I studies subjects have done at commercial research facilities.

Table 2. Participation Experience at Commercial Research Facilities

<table>
<thead>
<tr>
<th>Number of Studies</th>
<th>N/29* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5 (17)</td>
</tr>
<tr>
<td>2-5</td>
<td>7 (24)</td>
</tr>
<tr>
<td>6-10</td>
<td>7 (24)</td>
</tr>
<tr>
<td>more than 10</td>
<td>10 (34)</td>
</tr>
</tbody>
</table>

* Two subjects had not taken part in studies at commercial facilities.
The category of “more than 10” is a very loose approximation, incorporating a wide range of participation experience—one subject, for example indicated he had taken part in over 90 studies. Another subject indicated that “more than 10” was a very conservative estimate, but declined to reveal the actual extent of his participation, out of concern that such information may be used to limit participation frequency for those who earn a significant portion of their income as subjects. As indicated in Table 2, the sample of subjects interviewed for this study includes a range of research experience, from very little to moderate, to frequent participation.

Table 3 shows approximate income level of subjects at the time of research participation. As described in Chapter 3, ethical concerns about undue inducement presume that healthy subjects are usually poor, with no other options for earning. Although half of the subjects in this study earned less than $20,000 annually, half earned more, with 18% having an annual income of over $41,000. One subject, who indicated he was at this highest income level, earned all of his income from research participation. Others at the highest income level participated to supplement their income.

**Table 3. Income Level**

<table>
<thead>
<tr>
<th>Annual Income($)</th>
<th>N/28(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 20,000</td>
<td>14 (50)</td>
</tr>
<tr>
<td>21 to 40,000</td>
<td>9 (32)</td>
</tr>
<tr>
<td>41 to 55,000</td>
<td>5 (18)</td>
</tr>
</tbody>
</table>

1 Total income, including research participation and other employment. 2 No data for three subjects. 3 For one subject reported income is an average, with annual income ranging from less than $20,000 to $200,000.

Table 4 indicates the importance of study earning relative to total income.
Table 4. Importance of Study Earnings

<table>
<thead>
<tr>
<th>Proportion/Importance of Total Income</th>
<th>N/30 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100%</td>
<td>4 (13)</td>
</tr>
<tr>
<td>About 50%</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Supplement to cover bills</td>
<td>10 (33)</td>
</tr>
<tr>
<td>Supplement but not essential</td>
<td>12 (40)</td>
</tr>
</tbody>
</table>

A number of presumptions have been made about healthy subjects with respect to income. One is that people participate because they are financially desperate and lack other options for earning income. This would suggest that those with the lowest income would be most dependent on research participation as a major source of income. The proportion of income earned from research participation did not correlate with income amount. For example, two of those who earned all of their income from research participation had an annual income of less than $20,000, while the other two earned more. Similarly, subjects who derived 100% of their income from research participation did not necessarily do so because of lack of other options. For example, the subject who earned over $40,000 annually entirely from research participation had a college degree and had done other jobs, but preferred research participation, as described below.

*S: I wish I had started when I was 18 because I had so many crappy, low-paying jobs, that, if I’d started when I was 18 I’d be pretty well off. If I’d, you know, spent the money wisely.  
*I: So how does being a subject compare to some of the jobs you did when you were 18?  
*S: What you mean?  
*I: Like not just by pay, but—
S: No comparison! I don’t have to do anything. They do all the work, right? They’re taking the blood pressure, taking the blood. All we do is just be there. 08-15

Among those who participated because of limited other options, some earned all or most of their income from participation, while for others participation was a supplement to make ends meet. Even for these subjects, participation was not perceived as the only option, but chosen as a lesser evil.

And for new immigrants it’s almost impossible, unless you’re going and training yourself for something highly technical, to get decent job. And I had to, over here, to do the minimum wage jobs, and I just ah, it was stressing me. And it mentally just was killing me. I think to the point where my health became so fragile. So I decided that ah, this physical damage, is not as painful as the mental one. So that’s why I decided to do that [research participation]. 08-26

6.2.1 Demographic Information Summary
As noted at the start of this section, this demographic data is included to provide some information about the subjects included in this empirical study, and should not be extrapolated to healthy subjects generally. The demographic characteristics of the group in this study do challenge assumptions that healthy subjects are poor, with few options for earning an income.

6.3 Making Participation Work: The Process of Participation

6.3.1 Overview
The theory called Making Participation Work describes an integrated theory of why healthy subjects take part in phase I drug trials, how they frame their participation, what factors affect their experience, and how they actively manage their experience to minimize the burdens (Fig.1). The theory will be described in terms of the process of participation, and the factors affecting the participation experience. The process is

20 Where there are two speakers “S” indicates the healthy subject and “I” indicates the interviewer.
described in terms of three main stages that signify important steps in the process of research participation. These stages are *opportunity identification*, *opportunity shopping*, and *getting through participation*. The process is affected by the perceived *net burden* associated with participation, which in turn is affected by the extent to which subjects perceive *personal control* over the research situation, and by the extent to which they *trust* and *feel valued* by study staff and the research system.
Making Participation Work

Figure 1. Making Participation Work.

This diagram illustrates the theory of Making Participation Work. Ovals indicate phases in the Process of Participation. Rectangles indicate factors affecting the participation experience.
The factors affecting the participation experience will be described in Chapters 7 and 8. In this chapter I will describe the process of participation, beginning with a discussion of the concept “work”. Excerpts from interview transcripts will be used where appropriate to support the theory description.

6.3.2 The Concept of “Work”

The responses of subjects in this study paint a picture of research participation as a type of work. If one is able to endure the burden of participation, there is financial compensation at the end. The term “work” is used here to denote something that someone does in exchange for payment—a way to earn money. Some subjects view participation as just another type of job as reflected by the following straightforward statements.

\[ I: \text{Would you say that it seems like a job?} \]
\[ S: \text{It's a job. Actually, not only do I do clinical studies, actually today for example, I'm involved also in focus groups—I'll do that. An hour and I get paid whatever... Yah, I do my research in the papers, I look through see if there's anything going on. Or online or hear things from other people. 08-15} \]

\[ \ldots\text{they were doing a depression study and they were testing some drug... and it was just amazing how people were competing for that job. 07-02} \]

At the same time, it is distinguished from “real” work.

\[ I \text{ tell my friends and family what I've been doing. They're like "why are you doing that?" They think "I thought you went there to get a job". I'm like, “well I fell into these.” 07-01} \]

The interview excerpt below illustrates the difficulty of definitively classifying paid research participation.

\[ I: \text{Would you say—does it feel like a job kind of thing? Would you say it's kind of like your other job? How would you describe what being a subject is like?} \]
\[ S: \text{Um, well I don't think it's like a job. But it's like a—you're getting paid to do something. You're being like a guinea pig, right? So, I wouldn't say it's a job. I don't feel like it's a job... But, I feel like you're getting just paid to—just for someone to use you. So, it's more like, you're doing something [pause] —you're} \]
just following the rules, and what they want you to do, and at the end you get rewarded. So, that's how I look at it. I just do something, I just sleep, and give them blood and just hang out. It's more like—I'm being more passive rather than being proactive I feel.

I: Whereas a job you feel more-
S: More active, right? So that's SO simple, and you get paid to do it. So I wouldn't say it's a job really, no...
I: Yah, I do know some people, that's all they do.
S: Yah. So I don't know if that's like a job. I don't know—maybe, it's probably a job. For me it's just, when something comes up that's available for me, which is what I like, which is what fits my schedule, it's extra income, right? And it's probably like a job for me too, in some ways. Because I'm being paid to do this. Being paid to stay in a research study and giving my blood to them. So it's like a job? Maybe. But it's extra income. 07-13

For this subject, the earning of payment makes participation like other jobs, but the passive nature of participation distinguishes it from more traditional forms of work. Some subjects who more readily identify participation as work, appear to see their compliance with study requirements as the work that is done in exchange for payment.

You know, like, they’re paying YOU money. You’re, basically you’re working. This is your job. Get there on time and do your blood samples on time and don’t cause a fuss. 08-21

Similarly, the quote below shows how this subject, who described his body as his “corporation”, sees his ability to stick with participation and his being in good health as the qualifications he brings to the task of being a regular research subject:

S: In the study game, there’s like—you have like, you’re regulars. And you see a couple new faces that do it and then, they’re out. But, in the whole, like, [names of facilities], this whole situation, you have your regulars. But it’s more of a—it’s not more of a, like a horrible thing or whatever—it’s just like um, it’s just, um, being compensated for your blood.
I: Yah. It’s a reasonable way to—?
S: Yah, for like—to be a healthy person is a good thing. That’s how I see it. 08-20

Clearly, whether or not paid research participation is labeled “work” by subjects or by others depends on the criteria used to define “work”. The label work, however, seems the best fit to convey that subjects see their participation as a way to earn money, and not as a
gift or a donation or a hobby. While participation may differ in many ways from many other types of work, the theory of making participation work is based on that aspect of participation that is common to other types of work, which is, to do something for pay.

6.3.3 The Process of Participation

The question of how the process of research participation is framed by healthy subjects has not received any attention in the published literature. There has been interest in determining the motivation for participation, but this issue is treated as an isolated factor and the impact of motivation on the entire research process has not been examined. The theory that emerged from this research describes the process of research participation as it is framed by healthy subjects. This result is useful both directly, in terms of bringing to light new ways of looking at participation that may not have been considered previously, and indirectly, as it allows a more precise description of where in the process various factors impact participation.

The framing of participation as work emerging from this research can be described in terms of a process with three main stages: (1) opportunity identification, in which subjects identify research participation as an opportunity to earn money, (2) opportunity shopping, the process of seeking and selecting a study for participation, and (3) getting through participation, when subjects do the work of participating. These stages will now be described in detail.

6.3.3.1 Opportunity Identification

The opportunity identification stage includes becoming aware of the possibility of being paid to be a research subject, and deciding to be a subject. At the end of this stage subjects are motivated to earn money by being a healthy subject. This identification of the financial incentive as the motivator for participation is important, as it frames the process of participation as work, and therefore affects subject experience and behaviour. The financial incentive initiates the process of participation, but also sustains participation through to completion, and affects behaviour during participation.
A number of empirical studies have queried subjects regarding the motivation to take part in non-therapeutic research. As described in Chapter 4, the findings of those studies suggest that payment is an important motivator for many subjects, although other factors are also important. In this study, payment was identified as the motivator for all subjects who completed more than one study. Other factors such as interest and contributing to science may make participation more palatable, and for a few subjects curiosity or interest were the motivators for the first participation experience, but all subjects who decided to go on and do a second or more studies, were motivated by the opportunity to earn payment. Thus, opportunity identification is the stage that initiates the research participation process.

The fundamental role of the financial incentive as the motivator for participation is illustrated in direct statements by subjects, and in the fact that subjects had specific financial needs or goals related to participation.

I'd definitely think about going back [to participating], but then it all depends, if I like saw a really nice bike that I wanted to go buy, like twelve hundred bucks, or something then I go do that to get the cash for it ...It's the financial incentive, I don't really need it right now. 07-03

Um, what I did, originally, was I heard it on, I think it was [name of radio station]. They were advertising healthy, postmenopausal women. And I thought, I'll just call and see, because I think our tax bill for the cottage arrived the week before, and I was like "AHH!", you know. How can they ask that much?! ... and I saw this study, and I thought, why not! 07-12

I only started doing these, for the last 4 or 5 months, and I'm doing it out of financial need. And every time I've done it, I've said this will be the only time. But as I'm still looking for work, and I have a family—2 small children—and it's a concern. Money's a concern, and I find myself being on top of what's available. 08-28

I: So was that why you took part, to make some money?
S: Ya. To buy text books. I just got back from a huge trip to Africa and I didn't have a lot of money for textbooks, and I'm like-oh why not...
I: Since you did just the one, why did you not go back and do any others?
S: Well there wasn't a financial need any more, I mean, I graduated and I got the job and there was no need. 07-07

I kind of started off to pay for tuition and books and stuff, and now it's more for, just fancy things [laughs], extras. 08-17

Multiple examples are provided here to support my assertion that the financial incentive is the primary driving force behind participation of healthy subjects in commercial research facilities. This assertion is fundamental to the theory of making participation work. Moreover, as these multiple examples illustrate, although earning payment is a common factor, the significance of the income varies. For some subjects participation provides cash for extras such as a holiday or purchases. For others it helps to pay down bills such as tuition, taxes, or car payments. For still others, research participation is the sole source of income.

Opportunity identification initiates the research participation process, and sustains participation through to completion. Thus, opportunity identification is the step at which participation is framed as employment—opportunity identification makes participation work. The pervasive general impact of the financial incentive throughout participation will be identified as each of the subsequent stages in the participation process are discussed below.

For research participation to be identified as an opportunity, subjects must not only be aware of the opportunity, but decide to take advantage of it. For some subjects, becoming aware and deciding occur simultaneously.

I: Did you look in, like did you do any research about it first, to try to figure out what you were getting in—or did she describe sort of what it was like?
S: Well she did say that it was, like an overnight stay, and that they gave you some kind of medication, and she said it was really easy, and then they pay you,
For others, the decision to pursue research participation is the result of deliberation and overcoming the objections to participation, including concerns about safety and the stigma associated with participation. Stigma refers to the negative perception of research participation as strange, not respectable, or reckless. This negative perception may be held by prospective subjects, or others, such as family members, friends and colleagues. Specifically there is a sense that to participate is foolish or crazy, so that the subject’s judgment is called into question. There is also an attitude among some that to participate for payment is selling one’s body, which draws parallels to prostitution, and may be judged as immoral or at least degrading for the subject.

Prospective subjects may also be concerned about the possible discomfort of multiple blood samples, or being confined at a research facility. These objections are a barrier between becoming aware of participation and deciding to be a subject. Depending on the nature and source of the objections, overcoming them can involve a variety of steps, such as discussion, reflection, and information seeking.

*I: OK, so now I'm just interested in hearing what it was like, and whatever stands out for you.  
S: At first I didn't—I knew that there were risks involved, so I was sort of skeptical about doing that. I was a little concerned, but not as concerned as my wife was—she was, sort of discouraging me from doing it, but eventually I got her to change her mind. 07-11*  

*I did a lot of internet research on it—I just wanted to make sure it was like a reputable company and not some, whatever, weird thing I was getting into. I talked to a few other people who had done it and they mainly had positive experiences. So I figured I wasn't getting myself into too much of a hassle. But I felt kind of wary, because you know, you can never—I didn't really know what I was getting myself into. Like I had no idea really what they were gonna be doing. 07-14*
Once prospective subjects have decided to be a research subject, the next phase in the process is to find a suitable study.

6.3.3.2 Opportunity Shopping

Opportunity shopping is the stage in the participation process where the decision to earn payment through participation is put into action. The objective of opportunity shopping is to be enrolled as a healthy subject in a research study as a means to earn money.

Opportunity shopping is the process of securing participation in a paid research study. The term “shopping” reflects the active looking for or trying to find a study, that meets the subject’s criteria for reasonable burden and payment. Opportunity shopping is characterized by two activities: (1) seeking, the active looking for a research participation opportunity, and (2) selecting, the choosing of certain studies based on various criteria.

6.3.3.2.1 Seeking

Seeking is the active looking for a research participation opportunity. Seeking contrasts with the traditional view of research participation\(^{21}\), where a prospective subject is presented with a specific study and invited to consider participation. In the traditional view, the prospective subject considers participation only after being presented with the details of a specific study. The decision to be a research subject is synonymous with the decision to consent to a given study. In other words, the decision is to be a subject in a specific study. Outside of participation in that specific study, the individual is not considered a subject.

With seeking, however, the decision to be a subject has already occurred, or there is intent to be a subject, with a final decision pending further information, before the subject considers the details of a specific study. Although there has been no informed consent to a specific study at this point, through seeking a suitable study, subjects have made a

\(^{21}\) The term “traditional view” is used here very broadly to describe the common framing of research participation and informed consent to research. This view is the taken for granted assumption reflected in most commentary about research ethics, rather than being articulated in any particular document.
decision to be a research subject, thus the informed consent process can be seen as having been started. The objective is to be a subject, rather than do a particular study:

I: Hmm. And you were saying you were trying to get into the study. So was this—you heard about one—like did you pick, I'm gonna do a blood pressure study? How did you decide which study?

S: No, I just called them, and I asked them what they had available, and that's what they told. They had some other longer studies, but that wouldn't suit me, cause I had to go back to school. So I was like, what's the shortest that you have. This was the shortest available at that time, so I just picked it. Picked one, whatever was available, not choosing it. 07-09

Seeking reflects the financial motivation for participation. Subjects seek participation as an opportunity to earn money. In the framing of participation as work, seeking can be seen as the act of looking for a job. This economic view of seeking as job-hunting is emphasized by the perception of competition to “get into” studies that offer significant compensation.

Oh yeah, people with huge credit card debts, or mortgages, like you know, behind in their mortgage payments, they were desperate to get this work and um, that's what caught my eye and said wow, the competition, and obviously people were lying about their backgrounds...But at the same time the moment they publish the numbers—if it's high, you're going to get a lot of people compete. 07-02

Subjects who derive a significant portion of their income from participation become very active seekers, always on the lookout for new participation opportunities. This may involve searching research facility websites, looking for advertisements, calling the facilities, or communicating with a network of fellow subjects.

You have all different types of people. A huge range of personalities thrown together. And you'll have some people that do it for a living. And they travel to the states, they travel all over the country to do these. 07-12

I: So, when you look at, when you are finding studies—first of all, how do you find out about—do you go online?
S: No. I think what happens—like when you start doing studies, you get a little network of people. So, we have a little circle. So, somebody calls—hey, there’s a study, blah, blah blah. And I call my friends, and then I’ll just try to get in. 08-20

Research facilities also maintain databases and will seek subjects directly.

*I think these companies, um, like, since I’ve done this study, I’ve done the whole thing. I think once they see that as a loyal kind of thing, so if another big study will come up, they call me...They call to say OK, we have a study, you know, are you interested? That’s how I get it. 08-20*

The sense of competition for “good” studies also illustrates that subjects do not have an unlimited choice of possible studies, and are often restricted by practical considerations, such as being able to get to the research facility, or scheduling conflicts. Subjects with full time school or employment, for example, are only able to participate on weekends. Many subjects are also limited by the inclusion and exclusion criteria associated with phase I drug trials.

*I: That's interesting. OK. So last summer was the most recent one. Is there, have you not done one since because you've sworn off them, or you were busy, or—?*
*S: You know, it's scheduling and it's being qualified. I think it's easier for men, because they don't have the fluctuating—*
*I: Yah, yah.*
*S: But for women it's always this, this, this. You have this, you don't have this, you don't qualify.*
*I: Yah.*
*S: But you do go through a screening. You know, whatever it is, they say no.*
*I: OK. But you're open to doing more?*
*S: Absolutely. 08-23*

*S: I want to, actually, before I did one at [name of facility], I actually went in for a couple more...but I didn’t get in because my weight was not equal to my height. It wasn’t the right proportion. So that was the only thing that didn’t get me in.*
*I: That was before you actually did some of these studies?*
*S: That was before I did... the one I recently did. I tried to get in a couple more, but didn’t because of the BMI. -07-11*

Thus seeking a study resembles looking for temporary work, where having certain qualifications—in the case of healthy subjects the qualifications are physical—increases
the potential opportunities. Some subjects who participate regularly take specific actions to increase their chances of qualifying for participation such as taking iron supplements or eating an iron-rich diet to ensure hemoglobin levels are above the threshold required for enrollment.

_I actually found out that there is different even standards. At [facility name] for male subjects, it [hemoglobin level] has to be 135, no less. Even 134, you won’t make it. [another facility name] has the standard of 128 for male subjects. Which is pretty much normal for me. Cause my blood is 127-128, um and with the supplements, makes it 135... Like for example I am athletic actually, and ... My pulse, like normal pulse, can be easily 42-45—my trouble is always make it 50, because 50 is the lowest range. And I know now, myself... and I tense my muscles or breathe [hyperventilates] and it goes to 50. 08-22_

The use of strategies such as taking iron supplements to qualify for participation appears to be common among subjects who ignore the required 30 to 60 day interval between studies or participate in more than one study simultaneously. For these subjects, qualifying becomes a skill that one can develop.

Subjects also take supplements to protect their health against the physical risks and burdens of participation. This aspect of subject behaviour will be described more thoroughly in Chapter 7. As prospective subjects are seeking potential studies they are also applying criteria to rule out or focus on particular types of studies in the process of selecting.

### 6.3.3.2.2 Selecting

Selecting describes both the processes of focussing on a subset of potential studies as well as deciding about a particular study, using particular criteria. In selecting, subjects are both looking for studies that broadly fit their individual criteria and more carefully comparing specific studies against their personal criteria. The process of selecting seems to involve the application of the same selection criteria at two different levels of specificity. At the first level, subjects narrow the field, by applying their personal selection criteria to focus in on or rule out specific types of studies, without considering any particular study in depth. The outcome of this first level of selecting is a subset of potential studies to consider for participation. From this subset, subjects will consider
specific studies more carefully, using a burden-pay calculus to determine the acceptability of a given study. These two concepts will be discussed in detail in the next sections.

6.3.3.2.2.1 Narrowing the Field

So, I try to keep abreast of what all the testing places are offering, just in case I need the money. And, I do have screening, certain screening, my own personalized screening. First of all, there’s certain drugs I will not do. Without a doubt, wouldn’t even consider doing. The first one, and they’re always trying to get people to do, drugs for mental illness—schizophrenia, depression. Schizophrenia—they’re always trying to get people for that. And I’m not gonna take that. There’s no way I’m gonna take that. No way ever. The other one is organ rejection medication, which doesn’t pay as much as you think it should. And that always causes, real bad side effects. And the last one I won’t do is HIV drugs. So, right off the bat I ask them when I call, “what drugs are you going to study?”

All subjects approach selection by narrowing the field using general rules, before considering a specific study in detail, although the specific criteria and the degree of strictness with which the criteria are applied will vary among individuals. Two main strategies, burden threshold or maximizing payment, are used to narrow the field of potential studies for participation. The burden threshold approach selects first for studies that are below an individual subjective burden level, for example studies that are no more than two nights confinement, or only bioequivalence studies involving marketed drugs, or some combination of criteria. This strategy first rules out all studies that are above the burden threshold, before payment is brought into consideration. The maximizing payment approach selects first for studies with large compensation amounts. With this strategy, the studies identified as high paying are then considered in terms of the burden associated with payment.

Most subjects in this study appear to use a burden-threshold approach, and the weighing of burdens takes priority over payment. That is, perceived burdens have to be below a certain, individually determined threshold for a study to be even considered for
participation. Where burdens exceed this threshold, the study is ruled out, regardless of the compensation. The compensation, however, has to be sufficient to be “worth it”.

I: So as far as, choosing which studies you go in—you talked about choosing just which ones are available on the weekend and you talked about not doing a first in humans study. When you come to talk about a study how do you decide whether your gonna go in it or not. What do you think about?
S: I’m pretty scared—first of all…I look at the risks sometimes. Like at the back of the sheet they say you might have internal bleeding, plus, plus, plus—those one's I'm totally scared about. I wouldn't do those. For certain risk factors I'm like, oh I don't think I want to do that. I'll get pretty freaked out—I wouldn't do it...But, if it's available and if it's OK—according to my knowledge, if it's safe enough, then I'll do it....
I: What about other things like um, how much it pays versus how many visits, or stuff like that?
S: Yah. That too. Like if um, I know some people do a conversion, like they look at how many times you go for returns, cause they say returns pay a lot, something like that. So how much returns you go for versus how much they pay. I just look at, if I can afford to go for the returns I'm like—OK, then I'll do it. I'm not really the type who would sit there and try to calculate—Like I feel OK. If I'm available I'll go.
I: So you don't necessarily just look for the most pay—it's just—
S: Oh for good paying ones, but, if I'm available I'll do it, but if I'm not available then I wouldn't inconvenience myself pretty much to go and do something that's high paying. 07-06

Subjects who participate frequently and derive most of their income from research participation are more likely to use the maximizing payment strategy to narrow the field of potential studies. For these subjects the amount of compensation is virtually the only factor in selecting a study, and will for the most part outweigh any other considerations.

S: It’s the amount of money. That’s what I—to me that’s the bottom line. I mean, that’s what I look at first. When I call, it’s, what is your biggest study?
I: And then?
S: After that? [long pause] Hmm, you mean, what’s my next factor?
I: Yah.
S: [pause]

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22 “Returns” are short study visits for blood draws at scheduled times (e.g. 24, 36 and 72 hours) after the end of each confinement period. Some subjects refer to these as “call-backs”.

89
I: Or is that pretty much it? Did you ever turn down a study ‘cause of risk?
S: No. 07-15

You know some people go by the medication, like phase I’s or phase II’s.23 I’ve done them all. I go by the money. And the time spent at the place, the duration. And some people go by how much blood they take out of you, too. But I go by the money and the time spent. That’s how I do it. 08-18

Like seeking, the first level of selecting contrasts with the traditional view of research participation. In the traditional view the decision about participation is “Should I do this study?”, whereas for healthy subjects narrowing the field, the question about participation is “Which studies should I consider?”

One impact of this differential selection of studies by subjects is a non-random distribution of participation among the pool of healthy subjects. The choice by many subjects to limit participation to studies with relatively low risk and short confinement, means that the longer, riskier studies are likely populated from a smaller pool of “hard-core”, professional subjects. As payment “maximizers”, these subjects are also more likely to ignore restrictions, such as washout periods between studies, thereby further increasing the risk of the already higher risk studies. (See “Getting Through Participation” below.) The selection for studies that maximize pay or minimize burden may also mean that the studies that offer the worst deal may be left to those who have less choice, either because of practical limitations, such as ability to get to various research facilities, or because they qualify for fewer studies, because of age, gender, lifestyle (e.g. smoking), weight, or other factors.

6.3.3.2.2.2 Burden-Pay Calculus

The second level of selecting is deciding about a specific study from the subset that fit the initial selection criteria. Selecting is based on perceived risk, time commitment, number

23 Although all of the studies done by these subjects technically fit the definition of phase I clinical trials (see Chapter 2), subjects commonly used the terms “phase I” or “investigational” to refer specifically to trials that were first-in-humans or very early testing of a new drug.
and timing of blood draws, location of the research (both in terms of the geographical location of the facility and the actual facility) weighed against the payment for a particular study. Although risk is an important part of the decision making for most subjects, the other factors have a much more important role than is assumed by the traditional view of informed consent to research participation. These various factors are considered in terms of an overall net burden, which is weighed against the financial compensation for a given study. Subjects choose a study based on a burden-pay calculus, rather than a risk-benefit calculus that is traditionally viewed to guide decisions about research participation. A burden-pay calculus is used to determine whether a study offers a reasonable deal. The weight of each component that goes into that calculation varies among individual subjects. Calculating the burden-pay ratio becomes more routine with experience, and many subjects develop loose standards for reasonable compensation.

Well, um, I have a friend that—what he does is, if it’s like a 3-day—I don’t know how he calculates it, but, a lot of studies are like 1300, 1400, like that, right? And, it has to do with the blood. If it’s over, like 300 or 400, some people say that’s way too much blood, you know, the compensation should be in the 2500 range. 08-20

Subjects will participate in a given study if they judge the burden-pay ratio to be favourable. An exception to this is the subject who feels the payment is not adequate compensation for the burdens to be endured, but who participates nonetheless, out of financial desperation and perceived lack of other options. These reluctant subjects will be discussed in more detail later in this chapter. Even among reluctant subjects, however, the burden-pay calculus is used to choose a study that, in their judgment, is the least objectionable.

The next section will review the various burdens that healthy subjects use in the decision about participation. The focus will be on how burdens are used in the burden-pay calculus. In Chapter 5 I will describe how the study burdens affect the participation experience, and how subjects cope with these burdens.
6.3.3.2.2.1 Study Burdens

The burdens associated with research participation have an impact both on selection of studies and on the participation experience. The burdens most important to selecting a study include risk, time commitment and blood draws. In the following section I will describe those burdens that subjects indicate have an impact on their decision making about participation in a given study, and how these burdens are weighed against payment.

6.3.3.2.2.1.1 Risk

One of the concerns about offering payment for research participation is that prospective subjects will fail to consider the risks associated with participation. The term risk here is used to mean possible adverse effects of the study drug(s) or study procedures. This refers to possible harm, as opposed to the anticipated discomforts associated, for example, with blood sampling.

The healthy subjects in this study did consider risk, although perceptions about risk, and the degree to which risk factored into decision making varied among subjects, and even within individual subjects over time.

The degree to which subjects reflected on the specific risk associated with participation ranged from very little to great concern about risk. Where there is less concern about study specific risks, subjects seem to have made a generalized assessment that the risks associated with research participation are reasonable, and therefore put less emphasis on individual risk assessment.

I: Are there other—Some people won’t do certain kinds of studies, like drugs for depression—like anything that affects the brain. Did you have any rules for yourself that way?
S: No, no. But, nothing concerning ever came up. At all. Like not even close.
I: So you never saw a consent form and read about the risks and said ah, forget about it?
S: No, but then again, I wasn’t paying a lot of attention. But, I mean they went through—they went over everything word by word, whether you read it or not. So, if there was some word out there that’s gonna jump out of the page and strangle ya, ah, I mean yah, they got your attention. But no, never, never had anything that was risky whatsoever. Not at all.
I: In that way you always felt safe when you went for these?
S: Oh yah. Oh yah. That was never a concern. 08-27

Yah, so it was just um, I just went in, signed some papers, and um—sometimes—most of the time though, when they’re giving me those papers to read, and telling me about the medication, and the side effects, and all of that—going through all of those—telling me about you know, about this research—I don’t really, I’m not really aware. Well, or maybe I don’t really pay attention to those things, those little things. Like about what the medication is about, what the side effects are about. All those little details. Because I’m just more interested in the pay [laughs] and also about the kind of meals that they would serve, so. Because, also, I’m sort of unfamiliar, too, when they tell me about, you know, there’s some terminology—medical terminology—that’s involved, that I’m not aware of. So that’s why, I don’t know half of the time what they’re talking about before I’m going into the study. What kind of medication they’re talking about, or for what kind of purpose it’s supposed to be serving. What kind of medication it’s supposed to be—07-13

The latter set of comments illustrates an extreme example of basing decision making on general rather than study-specific assessment of risks, which are considered “little details”. Factors contributing to a lack of focus on study-specific risks include perceiving the study procedures as routine and similar from study to study, and seeing individual risks as minor and temporary. There is also a high level of trust that subject safety will be protected through the expertise of the staff and the ability of screening tests to identify subjects if they are at increased risk, leading to a high reliance on trust rather than personal risk assessment. The subject perspective on risk and trust will be described in detail in Chapters 7 and 8.

More commonly, however, subjects do make a subjective determination about the risks for a given study before deciding to participate. Risk assessment involves considering the number, nature and frequency of reported risks associated with the study drug, as well as the drug’s mechanism of action (body system affected) or the drug indication. Drugs that are used to treat “serious” diseases (e.g. cancer, HIV) or that affect mental functioning, are viewed as more serious than drugs to treat minor ailments, such as allergies or indigestion. The seriousness of individual side effects depends on the severity, probability and duration of adverse effects. Drugs are also seen as more risky if there is
not much previous human experience with the drug. Bioequivalence studies, which compare a marketed drug to a generic version, are preferred by the majority of subjects interviewed.

Risk assessment is a subjective process, with individual variation on the perceived risks associated with a given study, and the determined reasonableness of those risks. For most subjects interviewed, the risk assessment is applied to a personal risk threshold, such that studies which exceed that threshold are ruled out, regardless of other factors, such as payment. For two subjects in this study, higher risk served as a trigger for more deliberation and information seeking.

S: I’ve tried—I’ve done one’s where it says investigational drug, first time tested on humans—I’ve done 2 of those, and I had nothing to complain about. Nothing happened, as far as right away.
I: So, were those the one’s that caused you the most concern or whatever?
S: Yes. They were. Cause the first one was at [facility name], and I got onto it, got the study, and then I read this stuff again, like the informed consent, and I actually called and backed out of it.
I: Ya really? Oh.
S: Then gave it a few more days, and I kind of said “aahh, I’m gonna try this”. And I called and I ended up doing the study. But I was, that was the very, ’cause it was investigational. It wasn’t even a name, it was like N A slash slash...And when you talk to other people at clinical trials—lab rats—whatever you want to call ’em, um, they all, like some of them say I’m never gonna do this—I’ll never do investigational, I’ll never do that. And so it kind of got me thinking, but then I said, well, they’re gonna test it on somebody. You know. I’ll take a chance. 07-01

Where the risk was not rejected outright as exceeding a personal threshold, this increased deliberation seemed to reflect more of a coming to accept the risk, rather than further assessment, as the two subjects who described getting to this stage ultimately went ahead with the study.24

24 This coming to accept, or rationalizing the higher risk associated with certain studies seems to differ more in degree than kind, from the participation in “lower-risk” studies. In all cases subjects make a decision to accept the level of perceived risk and go ahead with participation. The process of rationalizing risk, and how it shapes the experience of research participation, will be described in Chapter 7.
6.3.3.2.2.1.2 Time Commitment

Participation in phase I trials often involves confinement at the research facility for one to many days, as well as one or many return trips for timed blood samples. The burdens of time commitment are considered during selecting in terms of practical challenges, such as scheduling and travelling to the research facility, time lost from other things, such as family, hobbies and personal responsibilities, and enduring confinement, which is the difficulty subjects experience during participation.

6.3.3.2.2.1.2.1 Practical Challenges

The practical challenges to participating in phase I drug trials at commercial research facilities can be a significant obstacle for many prospective subjects. For those who participate in addition to working, going to school or caring for family members, the time commitment is a significant practical obstacle, and subjects are limited to studies that fit their personal schedule. Studies that can be completed over one or several weekends are generally the most feasible. Studies may have a number of short return visits in addition to the period of confinement. Whether these are seen as an advantage or disadvantage depends on individual schedules and factors such as a subject’s proximity to the research facility, or availability of transportation.

I: So what do you look for when you choose?
S: Ah, once the drug—like an allergy one or something—once—like I don’t want to have 500 returns. One I think I applied for and got it, but—I think it was [facility name], but you had to come back like 7 times, and I thought, you know what, I have to rent a car to go, and so, OK, it sounds like a lot of money, but break it down and OH, RIGHT. OK. You know there are some that, if they have a lot of returns, they—yah, it’s just not— 08-24

In this example the subject found the study drug to be acceptable, but the burden of getting to the facility for return visits did not balance favourably with the payment offered, and the study was declined. This example demonstrates the process of narrowing the field in terms of the type of drug (allergy) to identify potential studies, and the application of a burden-pay calculus to decide about a specific study.
6.3.3.2.2.1.2.2 Time Lost

Time lost refers to all of the activities that a subject gives up when he or she is in confinement, such as contact with or caring for loved ones, doing productive work outside or within the home, or engaging in stimulating or pleasurable activities. When selecting studies for participation, subjects also weigh the time lost from their personal lives while in confinement.

Like for every night that I'm not able to access the outside world and do my normal things, then yah, I'd like to see it commensurate in the compensation...07-03

Subjects noted, however, that the ratio of time lost to payment can be more favourable than for some other work options.

So you get a cheque for 3 thousand dollars. So you know I'm looking for work? Um, essentially, what I'd be earning a week—pretty much 750 a week, right? So I'd have to be away from my kids 9 to 5 at a regular job. This way I'll be with my kids Monday, part of Tuesday, and part of Friday, and the weekends. So I took it. 08-28

But it means that I—I mean I have my current job in an office. I've got to go in for 2 full days and just work at the office, and that's it. And it means that I don't have a job necessarily where I have to be in every single day. It [research participation] gives me time off. 08-17

Time lost becomes more of an issue when confinement periods are longer, and many subjects select for a shorter confinement.

S: I don't think I could, I don't think I would sign up for a say 2 week study or say even 30 days—I just can't believe anyone could do that. I mean, drop out of sight for 30 days?
I: Yah. I can think from my perspective what I would hate about that, but for you, having been there, what about that makes you—?
S: Um, I think just family connections and worrying about what happens while you're not there. And, just different things that could go on. If there's an emergency, you know, that sort of thing.
I: Not so much that it would be so horrendous in there, or that part too?
6.3.3.2.2.1.2.3 Enduring Confinement

Beyond the impact on the “outside” life of each subject, the time commitment associated with research participation is perceived as a direct burden because of the difficulty of enduring confinement. Many subjects limit their participation to studies with a maximum of three days and two nights confinement. This limitation reflects the experience that enduring confinement becomes less tolerable after two or three days.

You know I think it's because—that's why I don't do those, um, long studies. There are those, you know, long studies. And well paid. But I can't—I just know myself—stay longer than 3 days. I need to have my fresh air. They don't—the ventilation's terrible. And even if they're working, but I need to see the sky. I need to see, to have, fresh air. And psychologically somehow, after 3 days being inside, I start fighting with everybody. You know I'm a nice person, I get along with people easily. But after 3 days, being in a cell—or like a closed environment. After that, another me comes out of me, you know.

This burden of confinement has a significant impact on Getting through Participation, which will be described in detail in Chapter 5.

The time commitment requirements to be a healthy subject in phase I drug trials pose various burdens that are considered during study selection. These burdens lead most subjects to select studies of shorter duration, leaving a smaller population of subjects able or willing to take part in studies with confinement periods of a week or longer.

6.3.3.2.2.1.3 Blood Draws

Multiple, frequent blood draws are typically required in phase I drug trials. The importance of the number and frequency of blood draws to decision making varies with the degree to of burden subjects associated with this procedure. The most commonly expressed burden associated with blood draws was the discomfort of the needles and the
anxiety of being poked. The discomfort and anxiety were made worse at the hands of research staff who appeared to lack skill or compassion. Most subjects had at least one story about a bad experience with blood sampling.

Um, sometimes I don’t trust the people with the needles. Like, I don’t think they know what they are doing, cause some people kind of, they call it, fishing around in your veins? That’s really painful and they don’t seem to know how painful that is. So they get on with their schedule. They’re like fishing to get your veins, and you’re—that hurts! And they’re like “yah, I know”, but they’re still fishing. OK. Yah, thanks a lot. So, that part, I’ll say, it’s pissing me off sometimes, cause I’m like, what are you doing? What are you trying to do there? Why are you fishing around in my veins? If you can’t get that one try the next one. Call me back later—something. Don’t be fishing around my veins for about 5 minutes. I hate it. 07-06

Some subjects were concerned about the long-term risks of repeated blood sampling, such as generation of blood clots or permanent damage to the vein.

BUT, they all admit that, every time when they puncture the veins, it causes the scar tissue forms inside—forms the scar tissue, and eventually it causes collapsing of the vein. And when I was doing research on the internet about the collapsing of the veins, it said it’s just inevitable process of puncturing. So, whenever the vein is collapsing, longer term side effects are the numbness of the—very bad side effects. They—it’s like a step by step—that’s logical. It doesn’t say in the contract that, by default, every time they’re puncturing you, it causes the collapsing of the veins, and blood flow changing, and has to find a new way to get to the arm, let’s say... So eventually it causes the other problems in the future. So I was asking them if he would put that in the contract, that the very procedure causes permanent damage. 08-26

Less common was the psychological discomfort of having needle marks in the arm, which made subjects feel violated.

Yah. And it’s so much that the poking really hurts, it doesn’t. But it’s just the idea of—you can, you know, showering you see it. You see where they poked you 20 times. Mentally it, it bothers me, you know? Yah. 08-17
The degree of burden associated with blood sampling varies among subjects from it being not an issue to being something difficult to endure.

_I: More than enduring the pain of it?_
_S: There’s no pain.
_I: The blood samples aren’t a big issue for you?_
_S: For me, yah, cause I have good veins. For people that don’t have good veins—they’ll suffer every time. That’s why, usually, they’ll get a catheter. 07-15

_I: So you don’t um, what about the number of blood samples or stuff like that? Do you think about that kind of stuff?_
_S: Oh, well, um—no, that doesn’t really bother me. I mean I’ll give as much blood as they want [laughs]. 07-13

Subjects who did not find blood sampling to be a burden, did not consider the number of blood draws in a study as part of their decision making. These subjects seem to view blood sampling as just part of the job. Blood sampling is not considered a big deal, and so the number of blood samples is not considered as a specific factor to be balanced against pay.

Those who do find blood sampling a burden, however, include the number of blood draws in their decision making, and weigh it against payment. There seem to be two different ways of balancing number of blood samples against payment. Most commonly, the calculation seems to be based on a general assessment—a large number of blood samples in a study are perceived as a burden, pushing the decision away from participation. The payment then must be seen as sufficient to balance the burden and push the decision to participation. The payment has to be large enough to offset the aversion to the blood samples.

_The next thing is compensation. No, sorry, the next thing is the amount of blood draws because to sit in a weekend and do 40 blood draws is insane...But I'd rather not do a lot of blood draws. The third thing I ask is, compensation. You know you do 18 blood draws and 15 hundred dollars, you say OK. But if you're gonna do 50 blood draws and get a thousand dollars, you don't want to do it. 08-28_
For a few subjects, there is a sense of wanting compensation for the blood itself, in addition to the discomfort of the blood sampling procedure.

So—and the amount of blood that they take too, I look at that, to see, how much you should pay you versus how much they shouldn't—Cause I'm like, if I'm gonna give all that blood I should get more money for that, that kind of thing, you know. So yah, I look at that too. 07-06

S: It's interesting. The first one I was in, there were a large number of black women. And I was asking, is it weird for you? And a couple of the black women gave the same response. So I don't know if it's a cultural thing, or ?? thing, but they said that, you know what? I feel my blood is very precious. So they should pay me for it. Which was very interesting. I had never heard of that.
I: That's interesting.
S: Yah. 08-24

These subjects seem to be thinking not only—“Is the money worth the discomfort of the needle sticks or catheter?” but, “Am I being fairly compensated for what they are taking from me?”

6.3.3.2.3 Decision Outcome
It must be remembered that the primary objective for subjects is to participate in a study to earn a payment. The selection process is to some degree a decision of which study, rather than whether to participate at all, although if no studies can be find that are within a subject’s personal threshold, they will not participate. Subjects who are strongly motivated may lower their threshold to participate. This overriding objective to find a study to take part in means that the decision making processes described above are used to select the best deal among the available choices. In some cases this may mean selecting the least objectionable study. The term shopping is not meant to suggest that

25 The use of “???” in a transcript excerpt indicates that when transcribing, I could not understand what was said on the interview tape.
26 This distinction is tentative. As this interpretation arose late in my analysis, I was not able to pursue the issue during the interviews, and therefore do not have sufficiently rich data to flesh out the concepts. Future research is needed to better understand how subjects conceptualize blood sampling and the possible affects of various social or other factors.
subjects have unlimited choice and are picking and choosing amongst a vast array of possible studies. In reality, for most subjects choice is limited by factors described above. Where choice is limited, subjects are using the above decision making process to select the most acceptable study.

For a given study, if the subject qualifies, his/her shopping has two possible outcomes—participate or do not participate. In selecting, a burden-pay calculus will be used to choose between studies or to decide whether a given study is acceptable. If acceptable, subjects will participate. If not, subjects will not participate and may continue to shop for studies, or may decide against further participation. In some cases a subject may conclude from the burden-payment calculus that the payment offered is not reasonable, but may nonetheless participate due to feelings of financial desperation. In other words they participate because they feel they have to, but feel they are being unfairly compensated for what is being asked of them. These reluctant subjects perceive the study burdens to be high, and have a negative participation experience.

6.3.3.2.4 Opportunity Shopping: Summary

Opportunity shopping describes the process of finding a suitable study for participation. The two main elements of shopping are seeking and selection. Subjects actively seek participation and select studies that meet their individual criteria. Although all repeat subjects are motivated by payment, most subjects select first to minimize burden, with a minority selecting for maximum payment.

6.3.3.3 Getting through participation

Once a decision has been made to participate in a given study, the subject must get through participation. Getting through participation is marked at the beginning by the first study visit (usually entering confinement) and at the end by completion of study participation. This means that subjects must fulfill the study requirements, and endure the study-associated burdens. The driving force to get through participation is to earn the full
payment by completing the entire study. This financial incentive causes subjects to stay in the study, and to develop strategies to reduce the burdens, thereby making it easier to get through participation.

Getting through participation may at times involve resisting the desire to leave the study before completion or avoiding early dismissal by the study staff. Subjects may feel the desire to leave the study early if they find participation particularly burdensome. The financial incentive is the motivation to resist this urge.

...the staff were quite friendly. I really appreciated that. I’ve never had problems donating blood before. I think probably just cause it was so many my veins were, I don’t know, not collapsing, but getting smaller or something [laughs]. They weren’t too happy about it, so it got progressively more difficult as the day went on...I was sort of toying with the idea of leaving. I was thinking I’ve been here this long—I’m not gonna leave now and only get, you know, 100 bucks or something, for whatever I’d been through. 07-14

I: When you call about what the drug is do you do any research yourself, like google it or anything?
S: No, that would—the more research you do, you’re probably less likely to do it. ??? dissociate yourself from it—you’re in there, and you’re just trying to think, of other things. They’re taking blood, you’re not feeling good, you’re tired, you’re not being fed, there’s crazy people about. So what I do is, I brought my car, my son’s little toy car. When they were gouging my arm for the blood I would think about him. You can try talking to other people. That can take your mind off of things... And ah, anyway, that’s pretty much how I get through it. Don’t think about it just try to get past it. 08-28

Subjects are also concerned about being dismissed early from the study by research staff, as a result of inability to comply with requirements, such as consuming a meal or experiencing and adverse event.

S: Um, I’ve seen—I saw—you know some studies they tell you what time you can start and what time you can’t. And one guy started too early, and—
I: Started what, eating, you mean?
S: Yah, and he got kicked out of the study. And another girl who—and this is what kills me—standard meal! There was this one girl who was TINY. And she was trying to eat all the food. And she was—she threw up because, and you know, they kicked her out of the study. 08-24
First or second hand accounts of hiding adverse events to remain enrolled were common in the interviews.

*S:* You know if I’m going into a study and they send me home early with a hundred dollars, I’m not gonna be honest about an adverse reaction. Um, but if you have an adverse reaction, you should still, be paid, I think. Because you’ve injured the person, right?
*I:* Paid the full amount, you mean?
*S:* Or something close to the full amount. What you could do is make it a prerequisite that they stay there the whole time, so at least they’re not using it as a way to get out early... I was in a study, desperate financial need, and my chest hurt, terribly. Terribly. I thought I was having a heart attack. And even afterwards. Even now it hurts, OK? And, ah, I didn’t report it, because, we needed the money. And, I wonder if I was damaged from the drug. And now I not only wonder that, I wonder if someone else is gonna take it if it goes on the market and someone else is gonna be damaged. But I needed the money. There’s no incentive for me to look out for the greater good. They’re not looking out for my good. 08-28

This subject clearly felt both worry and guilt about concealing his chest pain, but the motivation to earn the full payment won out over his concerns. Subjects also noted that many adverse events associated with study participation more likely reflected the normal response to study requirements or conditions, such as fasting or lack of sleep, than a reaction to the study drug. This reasoning may have helped subjects justify withholding information about adverse experiences. It should be noted that not all subjects hide adverse events from research staff. The subject quoted below for example, places a greater emphasis on safety than on completing the study,

They [other subjects] wouldn’t say if they didn’t feel well. They wouldn’t say if they’re puking or something. So, it’s their income and they don’t want to lose it. But I would. Personally I would say if there’s a problem and I would say “I don’t feel good” or “I want to go home” or whatever...I don’t want to be sick, I don’t want to have any complications. I don’t want to feel like, I take the thing and something happens to me. I want to know, if it’s going to have any side effects I want to know. 07-06
6.3.3.4 The Process of Participation: Summary

The framing of research participation as work shapes the process of participation as healthy subjects experience it in phase I drug trials. The main stages of participation—opportunity identification, opportunity shopping and getting through participation, reflect the primary motivation of participation to earn money. The stigma associated with participation, the active seeking and selection of research studies, and the staying with participation sometimes even in the face of negative health experiences, contrast with the traditional view of research participation involving patients in clinical trials with a prospect of direct therapeutic benefit.

The potential impact of the study burdens are considered during the shopping phase of the process of participation, but it is in getting through participation that the burdens are experienced. This chapter considered getting through participation as it relates to the motivation to earn money and make participation work. In Chapters 7 and 8 I will describe getting through participation with regard to subject experience, and the main factors affecting that experience.
7 Results: Factors Affecting the Experience of Participation

_Hamlet_: What have you, my good friends, deserv'd at the hands of Fortune, that she sends you to prison hither?
_Guildenstern_: Prison, my lord?
_Hamlet_: Denmark's a prison.
_Rosencrantz_: Then is the world one.
_Hamlet_: A goodly one, in which there are many confines, wards, and dungeons, Denmark being one o' th' worst.
_Rosencrantz_: We think not so, my lord.
_Hamlet_: Why then 'tis none to you; for there is nothing either good or bad, but thinking makes it so. To me it is a prison.

- _Hamlet_. Act 2, Scene 2

_For the most part, I can honestly say it's an easy way to make money._

- _Healthy Subject 07-01_

_I hate it. It’s miserable. It’s awful._

- _Healthy Subject 08-24_

7.1 Overview

In Chapter 6 I described the process of participation, which shows how the financial incentive makes participation work. Chapter 6 also described how framing participation as work shapes the process of participation. In this chapter I will describe the experience of participation, focusing on the factors affecting that experience. Among the subjects interviewed for this study, the overall impression of the experience of participation ranged from very negative to very positive. At the very negative end of the spectrum were subjects who rejected further participation after trying it once, followed by reluctant participants, who took part out of financial desperation, but found it a very disturbing experience. At the positive extreme were subjects who took part regularly and found it to be “easy money”. These characterizations of participation seemed to vary among
subjects, rather than among different facilities for a given subject. Even where subjects described specific negative or positive experiences occurring at one facility or another, subjects also formed an overall opinion about participation as very easy, very difficult, or somewhere in between.

As described in Chapter 6, healthy subjects vary in age, educational background and employment status. Although the motivation for all subjects who did more than one study was to earn money, the income level, and financial purpose of participants ranged from being entirely dependent on research participation, to paying off a few bills, to participating to purchase luxury items. Subjects also varied with respect to the number and type of studies done, and in willingness to accept research related risk. None of these variations, however, seemed to be associated with a particular outcome regarding research experience. Those who participated more frequently tended to see the participation experience as positive, but there were exceptions to this.

The primary factors that account for the difference in attitude about whether participation is easy or difficult seem to be the perceived net burden associated with participation, and the extent to which subjects are able to find personal control over participation. The perceived net burden determines whether participation will be an easy or difficult experience. The perceived net burden in turn is affected by the amount of personal control subjects feel they have over their participation experience. Where the perception of personal control is high, the net burden is reduced. These factors relate to the theory of making participation work, because they account for the variation among subjects in how they experience the stage of getting through participation. Net burden and personal control also affect the initial process of decision making, as conditions of the burden-pay calculus. Finally, by finding personal control, subjects are able to make participation work, using “work” here in the sense that participation is made a feasible or effective

27 A couple of facilities did seem to be most often associated with negative experiences, such that those who participated mostly at these “less desirable” facilities were more likely to have a negative experience, compared to those who participated at some of the “better” places. There was a great deal of variation, however, with some subjects favouring those places labeled as the worst by others. Thus, no one facility was uniformly viewed as negative or positive by all subjects.
mechanism for earning an income. Where there is a high perception of personal control, participation works as a way to make money. Finding personal control is enhanced when subjects feel valued by and have trust in, the researchers and study staff. In this chapter I will describe the concepts of net burden, and finding personal control, and how these relate to the theory of making participation work. Feeling valued and trust will be considered in Chapter 8.

7.2 Net Burden

Chapter 6 described how subjects consider various study associated burdens when selecting a study for participation. In this section, I will describe what the subjects in this study perceive to be the important burdens affecting the participation experience.

The perception of participation as very easy, very difficult, or somewhere in between, reflects the overall net burden associated with participation. This net burden in turn reflects the accumulated impact of various specific burdens. The burdens that most affect the participation experience are stigma, risk, physical discomfort and deprivation of control. The importance of each of these burdens varies among subjects, so that individual subjects are more or less concerned about a particular burden. The following is a description of these individual burdens and how they affect the participation experience. Following the description of study burdens is a detailed account of how subjects cope with these burdens through finding personal control.

7.2.1 Stigma

The concept of stigma was introduced in Chapter 6, as affecting opportunity identification. For some subjects, stigma is never an issue, or is overcome at that first stage in the participation process. For a few subjects, however, stigma lingers as a negative shadow over participation. As described in Chapter 6, the stigma associated with being a healthy subject is that this behaviour is unwise or unsavory, suggesting that those who do participate are deficient in their ability to make reasonable decisions, and perhaps are lacking autonomy or self-respect. The stigma associated with participating as a paid healthy subject therefore leads to assumptions about a person’s character or self. By
promoting certain assumptions about a person, stigma takes away some of a subject’s control over his or her own image. This effect on image may be in relation to a subject’s own self-image, as well as the image the subject presents to others.

I: Do you, do you talk to anybody about your participation, like friends or family?
S: Family, yes. Like I told my mom and one of my sisters that I’ve done them…But my friends no, I would never bring it up.
I: And why's that?
S: Um, embarrassment.
I: Yah?
S: Yah. Honestly, like, I'd just be embarrassed to let them know…I think they'd think less of me for it. I either won't call them during those days, or I usually go—travel to [city] for work, so, I'll tell them I have to go to [city] for 2 days, you know, say that.
I: So you have a sense that people look down on it in some way?
S: I know I do. No, I do. I mean, not that I look down on it. But, I mean, doing something that, that I do a lot of them. I think I would have less shame in myself if I was only doing one or two. But I do a lot of them, I think, in my mind. And so, I just—I don't share with people. 08-17

The stigma leads many subjects to hide their participation from others. For some, as the subject above, this may reflect a sense of shame in being a healthy subject. For others, participation is hidden to avoid being judged by others who don’t understand the nature of phase I research.

S: I have a—if you've ever watch "Bewitched"—the old—we have Gladys Kravitz living down the street from us. And this year, she went to my husband—why is [subject’s name] going out every day at 7 o'clock? And I said to [husband’s name]"oh God!" [laughs]
I: That's very funny! Do you talk to people about your participation?
S: No I don't. I talk to family—immediate family because I once said—a girl I worked with...was off in the summer and there was no work available. And she said something like "oh my God, what am I gonna do for money?" And I said—I didn't say I did it, but I said I'd heard of drug studies, and she said, "oh right, I want to grow antennas." And I thought, “fine, find yourself another job.” [laughs] So I haven't really. 07-12
For these subjects, stigma adds to the burden of participation because of the extra effort to maintain secrecy. It may also cause psychological angst when subjects feel they are doing something that is socially devalued.

### 7.2.2 Risk

As described in Chapter 6, concerns about health risks play an important role in the selection of studies for participation, and/or in weighing the burdens and payments. For a minority of subjects in this study, concerns about risk persist during the participation experience, causing anxiety about participating. In some cases concern about long-term health risks remain even after participation is completed.

*I thought I was having a heart attack. And even afterwards. Even now it hurts, OK? And, ah, I didn’t report it, because, we needed the money. And, I wonder if I was damaged from the drug. And now I not only wonder that, I wonder if someone else is gonna take it if it goes on the market and someone else is gonna be damaged.* 08-28

For most subjects, however, it seems that once a decision has been made to participate in a given study, concerns about risk are set aside, and do not play a noticeable role in the actual participation. This apparent lack of focus on risk during participation suggests that during the phase of getting through participation, subjects turn their focus to the actual experiences of participation, rather than the theoretical—i.e. what the risks might be. This attention to the actual rather than the theoretical is reinforced through experience, as most subjects did not experience what they would consider adverse events. Subjects also seem to employ a variety of psychological and behavioural strategies to deal with risk concerns. These will be described in detail later in this chapter (see section 7.3).

### 7.2.3 Physical Discomfort

Physical discomfort refers to the experience of physical unease resulting from study procedures or environment. The most common is the discomfort of multiple needle sticks, which varies in degree between subjects and also with the skill and caring displayed by the technicians obtaining the blood sample. The varying degree to which
blood sampling is a burden was described in Chapter 6. Discomforts also arise from other study requirements, such as having to fast, or to sit upright in an uncomfortable chair for four hours after dosing, as required by some studies.

You sit there, like sometimes people, the first 4 hours after drug administration they need you, they make you sit in an upright position and you sit...they just put the chairs together, and people were sitting like this [arms tucked against sides, knees straight] for 4 hours. And you're privacy-you feel like the elbows, everything-it's quite stressing. I didn't like it. 08-26

For the subject quoted above, the physical discomfort was exacerbated by the psychological discomfort caused by having to sit elbow to elbow with the person next to him. The deprivation of privacy will be described in more detail in another section below.

The perception of burden associated with physical discomfort varies among subjects, and for individual subjects over time. The perception of physical burden resulting from the physical discomfort of blood sampling is generally greatest for the first research participation experience. Although subjects have all experienced blood sampling previously in a health care context, the experience of multiple blood samples over a short period of time required for PK analysis in phase I studies is almost universally surprising, and most often distressing during the first study. Some subjects noted that they were either not informed or did not pay attention to the fact that there would be so many samples.

I: And that fit what—your expectations based on the descriptions were what your actual experience was?  
S: Yeah, I think for the most—the first one, the very first time at [facility name], I didn't understand it completely, what was gonna go on, and I didn't get the blood draw thing. I went, I did the informed consent—I just heard fourteen hundred dollars for two weekends. That's what I heard. Right? And I did the study and while I was in there, they did blood draws like every half hour, and I'd never done anything like that before and I thought, oh my god, this is ridiculous. But once I did the first one, I knew what to expect when I went back. 07-01

Others noted being informed about the numbers, but were surprised by the actual experience.
The reality of a blood draw every fifteen minutes is somewhat different from when you see it on paper. 07-03

These quotes demonstrate that, while information is important, actual experience leads to a more complete understanding. Knowing what to expect gives subjects the opportunity to psychologically prepare for the blood draws, which changes the experience from difficult to tolerable.

As with its role in decision making, the importance of the physical discomfort to the experience of getting through participation varies among subjects. These two phases in the process of participation are of course directly related, as decision making takes into account those issues that have an impact—positive or negative—on an individual.

Among those interviewed in this study, physical discomfort did not appear to be much of an issue for most subjects, especially in second or later studies. Further research with different populations would be needed to get a true idea of the range of perspectives regarding physical discomfort. Perceptions about discomfort would also be expected to increase with studies involving invasive procedures other than blood sampling.

The experience of physical discomfort is also affected by the perception of staff attitude toward subjects. When staff are perceived to be sensitive to a subject’s discomfort and try to attend to or minimize it, the burden is lessened. The impact of staff behaviour on the burden of participation will be described in detail in Chapter 8. The findings in this study suggest that psychological and social factors have a significant influence on the perception of physical discomfort in healthy subjects.

7.2.4 Deprivation of Control

_S: The worst part is probably, I mean, I’m—being in a controlled environment is hard. If you’re like me and you’re kind of spazzy all the time. I cannot sit still. I can’t—I mean I like people, but to sleep in the same environment with a whole bunch of people is really annoying. I don’t know, you just have to—being in a controlled environment is tough. If you smoke—I do smoke—I: But you can’t._
As with risk, the time commitment required for participation plays an important role in the decision making process about participation. The time commitment includes both the confinement period, and return visits. In Chapter 6 the time commitment was considered in terms of its predominant role in the burden-pay calculus. In this calculus, subjects consider the overall duration of the study, the duration of the confinement period and the number of return visits. Once the decision has been made to participate, the aspect of time commitment that has the greatest impact on the experience of getting through participation is the deprivation of control that is an inevitable condition of being a research subject in confinement. It is the reaction to the deprivation of control that is one of the key determinants of whether participation will be easy or hard.

As described in Chapter 2, healthy subjects in phase I drug trials at commercial research facilities are often required to be confined to the research facilities for some time ranging from overnight to many days. During this time, in addition to the carrying out of study procedures, there is tight control on most aspects of daily living, including meals, sleeping, washroom use and leisure time.

Deprivation of control reflects the feeling by subjects that they are being denied or deprived of the usual control that they have over their actions or situation. Control here refers to the ability to influence or manage a situation. Although this deprivation of control is entered into voluntarily, subjects nonetheless feel its impact on their well-being. The following sections will describe how subjects experience deprivation of control while getting through participation. From the descriptions of the healthy subjects in this study, I have described three main types deprivation of control—deprivation of choice, deprivation of privacy, and imbalance of power. These will be considered in detail in sections 7.2.4.2 to 7.2.4.4. Section 7.2.4.1 below will describe an aspect of control where most subjects do not experience deprivation, namely, voluntariness in the decision to be a research subject. In section 7.2.4.5 I will examine some of the general
factors that affect all types of deprivation of control. A relatively large portion of this chapter is devoted to the description of deprivation of control; this reflects the predominance of this issue in the interviews in this study, and its apparent importance in getting through participation.

7.2.4.1 Voluntariness

For most subjects, deprivation of control is not experienced in the choice of whether to enroll in and stay in the study (The exceptions to this will be described later in this section.) All subjects are aware that they are free to walk out of the study at any time.

I: But if you did want to go, do you feel that it would be OK or do you think they would want you…?
S: I think that’s OK. They told the participants all the time that everyone can withdraw at any time. 07-05

I: Did you always feel like you could leave if you wanted to?
S: Yah, they gave me the option of leaving if I wanted to, I was reminded of that. But, I really wouldn’t want to start something and next thing leave halfway through. 07-11

Although subjects realize they have the right to leave, the desire to earn the full payment, usually motivates them to remain and complete the study.

S: They say you have an option if you want to go—you want to stay—it’s up to you. If you feel uncomfortable at any point in time you can always leave. So that’s pretty—that’s an option if you—you know, it’s up to you.
I: And you feel like they mean it? You feel you would be comfortable leaving if you wanted to?
S: Um, yah.
I: You don’t feel pressure to stick with the study and finish it out?
S: Sometimes. Sometimes. I guess depends, if you want the money I guess. You feel pressure to stay.
I: That’s your own pressure, for the money?
S: Yah. Not their pressure. I guess your pressure because you want the money—oh I better stay because I want—but other than that, you know, you can leave if you want to leave. 07-06

This decision, however, is not perceived as a deprivation of control, but rather the same type of autonomous choosing that leads them to enroll in the initial study.
Where deprivation of control is experienced is in the activities and conditions of life in the research facility. The types of deprivation of control relevant to the experience of healthy subjects are deprivation of *choice*, the opportunity or freedom to choose a preferred thing or action, deprivation of *privacy*, the freedom from unwanted intrusion of others, and deprivation of *power*, which prevents subjects from asserting themselves or exercising their rights. These three types of deprivation of control will be considered below.

### 7.2.4.2 Deprivation of Choice
The term choice here refers to the opportunity or freedom to choose a preferred thing or action. Confinement in phase I facilities results in a significant limitation in the numerous choices a person normally makes throughout each day, such as when, what and how much to eat, when to sleep, or what to watch on television. The consequences of deprivation of choice are *boredom* and *feeling uncomfortable*.

#### 7.2.4.2.1 Boredom
Boredom specifically was cited as the worst aspect of participation by a number of subjects:

> I could never do these things where people go in like 2 weeks at a time. For one thing I'd be beating my head against the wall if it was for 2 weeks, because it is so boring... I just go for 2 days, and that drives you crazy, the monotony. Just the monotony, that's it. Because you're confined and, you just SIT there. You feel like a lump sitting there, watching movies; which is fine—I like to watch movies—but 8 or 9 movies a day! ...I can imagine being in prison how, you literally would just want to jump out of a window if you were there for any certain amount of time—2 months even...It's the monotony. Boring. Nothing going on. 08-21

The contribution of constraint to perceptions of boredom has long been recognized by psychologists (120-123). Fenichel described boredom as arising “when we must not do what we want to do, or must do what we do not want to do.” (122). Healthy subjects in confinement are routinely constrained from doing what they want to do such as leaving the facility, watching a particular movie, or socializing with their friends, and are required to do things they do not want to do, such as remaining seated for several hours
after dosing, living in an institutional setting, or sharing leisure time with people they do not like.

The provision by research facilities of amenities such as pool tables and internet access were important in helping subjects relieve their boredom. Similarly, facility policies that gave subjects more freedom, such as reduced restrictions on the use of laptops, allowed them to address their boredom.

For example, at [facility name]...they accommodate...So, they need as much as possible [to]...compromise for people’s convenience...For example they allow us to use laptop...Some places they ban cell phone, they ban laptops. There’s not much left. You sit there...You can watch TV or walk. So again, you sit there. 08-26

It is worth noting that although boredom is not typically an issue that arouses the concern of research ethicists, it is of sufficient importance to subjects that it can be a limiting factor in study selection, highlighting the different priorities of subjects and “experts”.

7.2.4.2.2 Feeling Uncomfortable
Earlier in this chapter I described the physical discomfort directly related to study procedures. This section considers comfort in a broader sense as the state of feeling at ease or relaxed. Constraints on choice can result in subjects feeling uncomfortable or not at ease, by preventing them from taking actions a person would normally take to make themselves feel comfortable or create a sense of well-being.

They have those push things that you can't control hot or cold water. But you know, you don't want to brush your teeth with hot water. I mean that's another—it would be nice if you could control. 08-24

Two subjects described the frustrations of not being able to take the simple action of getting an extra blanket when they were cold.

So there's a lot of attitude. And, really, you know, unless you know who to ask if you need an extra blanket, I mean it's really—I think prison would be ???, honestly. I don't really know but it's just—yah, it's uncomfortable. 08-24
S: You can’t get an extra blanket, you have to negotiate for things. Yah, it’s freezing, and you’re locked in there for a couple day....  
I: So have you tried to, ask for things and had problems like—?  
S: Blankets.  
I: And you had—you were given grief about it?  
S: Yah. Grief about it. About blankets...It’s a real, it’s a whole us against them type of attitude. And, you know, I understand they want to control everything they can, and make sure people aren’t either taking things they shouldn’t, that may affect the study, but I think it’s, more confrontational than cooperative. And I think that kind of, breeds this kind of, um, situation. 08-28

This loss of control, which might be seen as relatively minor, had a significant impact on the experience of these subjects. The relative triviality of the specific matter where control was denied suggests that it is the feelings of frustration or powerlessness resulting from the lack of control that are the real problem for subjects. The latter quote above, regarding “having to negotiate for things”, suggests a feeling of being at the mercy of staff. The triviality of matters over which subjects lack control, may in fact serve to increase a subject’s feeling of vulnerability, when an independent adult finds him/herself infantilized by having someone else decide whether they can have a blanket or not.

It should be noted that not all subjects felt equally deprived of control.

S: I was OK. People are always like-it's cold![whiny voice] Put on a sweater! [laughs] So you need to bundle up, right? So.  
I: So you didn't—I know people who have said oh it's cold, but they didn't want to give me a blanket. Like they sort of feel like they're at the mercy of the staff. You know what I mean?  
S: Oh yah. I mean you can be.  
I: Do you feel like that, or do you feel like you can kind of—?  
S: Yah, if I want something I'll go ask for it.  
I: And are they pretty good about giving it to you?  
S: Usually they're OK. I mean, I don't know. It depends on how much they have to put up with. How fussy the other people are. But usually it's OK. I mean, I'm, I'm just not—that's not me. I don't—it's 24 hours, 48 hours. I don't care. 08-23

This difference likely reflects both differing practices at different facilities or by different research staff, as well as differences among subjects regarding how they interpret the lack
of choice (i.e. as a threat to their dignity versus just the way these studies are run), and their actual or perceived personal control. The inter-subject differences will be considered in detail below in the section entitled finding personal control.

7.2.4.3 Deprivation of Privacy

_Besides the loss of freedom, besides the forced labour, there is another torture in prison life, almost more terrible than any other—that is compulsory life in common._

_I could never have imagined, for instance, how terrible and agonizing it would be never once for a single minute to be alone for the ten years of my imprisonment. At work to be always with a guard, at home with two hundred fellow prisoners; not once, not once alone!_

-Fyodor Dostoyevsky, _The House of the Dead_, as quoted in (125, p229)

A second type of deprivation of control is deprivation of privacy. Privacy refers a person’s control of access to themselves by others. "To breach privacy is to violate participants space or to intrude where one is not welcome or not trusted" (124).

Although differing in degree and duration from prison life as captured by Dostoevsky, deprivation of privacy during confinement at phase I drug facilities had a negative impact on subject experience.

_And each room where they've got you sitting after you've been dosed, is supposed to have a phone. But they don't. You know the big thing for me was when I started was, you know what, I just want to have a 5 feet square area where there's not another person, where I can feel like I have privacy. You know, make a call—but there’s NO privacy. So even that first time where they allowed cell phones—even then it was just REALLY frustrating, because you just haven't any, you just—I don't know, it wasn't as frustrating as it is now, but they don't care, you know._ 08-24

Many facilities now forbid bringing cellular phones into the research facilities. As most newer cell phones include cameras, this requirement likely reflects an effort to protect the
confidentiality of the facility operations as well as the privacy of other subjects. Ironically, while subjects may have the privacy of their images protected, they experience reduced privacy during telephone conversations.

Deprivation of privacy was experienced for specific activities, such as making a phone call or using the washroom, but also in a general sense as the inability to get away from people.

S: Ah, the smallest ones I’ve ever done were overnight.
i: For the long one’s what’s the worst part about that, when you’re stuck in there?
S: Ah, just being confined, with no privacy. Nowhere to get away. At [name of facility], one of their facilities, on [street name], it’s way too small for a study that long with people that you don’t know. And there’s no way to blow off steam. Cause it doesn’t matter who you are as a person, I’m just not used to being confined for that long, and it got too much.
i: So you’re never alone I guess?
S: You’re never alone. There’s not a room, there’s no privacy to get away. Absolutely impossible. The best you can do is put earplugs on. 07-01

Two types of deprivation of privacy that were described with regard to prison life (125) namely, forced exposure and forced spectatorship, seem relevant to the experience of healthy subjects. Forced exposure refers to being compelled to expose to others that which we would wish to keep to ourselves, such as our body, our conversations or our thoughts. Forced spectatorship refers to the inability to get away from the exposure of others, including being forced into the company of persons with whom we would not normally wish to associate (125).

In the context of research participation, subjects are not strip searched or paraded in the nude in front of others, but some subtle and not so subtle forms of forced exposure occur. Several female subjects were uncomfortable in facilities that lacked individual shower stalls and tried to shower in the middle of the night or opted not to shower. Another female subject was bothered that the main door to the bathroom stalls was wedged open all the time. (Her little triumph over this situation will be described in the section “finding personal control” below.)
Upon entering the research facility subjects routinely have their bags searched and are subject to a “pat down”. Subjects are also subject to urine tests, to screen for prior drug use, as well as to detect possible health problems. The finding that some subjects were using urine samples from others to hide their drug use led one facility to require male subjects to be observed while filling the sample bottle. Only one subject, who found it extremely bothersome, raised this issue.

S: A lot of people have been getting caught, so they change their ways now. Which bothers—It's OK, but it bothers me. Now, what they do is they watch you urinate. Which is embarrassing.
I: Yah!
S: It's the only place. Like, they did that to me the last time, and I was embarrassed. The guy stands right beside you while you're peeing in a cup. It's like, it was embarrassing. I felt—you know—you know the feeling.
I: Of course! Yah.
S: I mean, I know they have to do it. People have been sneaking the pee in and lost the privilege of going in on your own, but there's got to be a better way...These people, the staff, are doing what they're told from upper management. It is frustrating though and it bothers me, but what can I say, what can I do, right? If I don’t like it, don’t come there...It just bugs me. It's embarrassing! It is!

The strong reaction from this subject contrasts with his generally positive appraisal of research participation, emphasizing the degree to which he was burdened by this invasion of his privacy.

Even more difficult for many subjects, however, is the burden of forced spectatorship.

That study was particularly bad because they had some street people who weren’t of sound mind. And, you know, at that clinic, to share a room, it was like, 50 beds in a room—25 bunks. To share a room with somebody who’s unstable, you don’t sleep very well. 08-28

S: Or you know women...They are like-tak-a-tak-a-tak-a-tak-a-tak-a-tak-a-tak-a-tak-a-tak. Oh! [makes sounds and gestures of being highly annoyed] ...you know

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28 I believe that this practice is relatively new, and may at the moment be limited to one facility in the Toronto area that specifically recruits recreational drug users for many of its studies. This may explain why only one subject mentioned the requirement for supervision for urine samples.
get a book, read or something. Or at least take a break once in a while --tak-a-tak-a-tak-a-tak-a-tak-a-tak-a-tak-a-tak-a-tak—a-non-stop! And if you listen to them, it’s about nothing. Woyy. Take a break! Do a favour for me. And if I stay longer than 3 days, they will be my first target [laughs]...

I: But is there somewhere to go or are you sort of stuck there sometimes?
S: Um, sometimes when you’re like, ah, for the first, like 4 to 6 hours usually, or maybe sometimes even longer, you are in the same room, because of the blood draws. You can’t really avoid, you can’t leave. 08-22

Most if not all subjects, including those who have few other complaints about participation, experience deprivation of privacy as a burden. Unlike the situation with deprivation of choice, the burden associated with deprivation of privacy seems to result from the actual consequence—loss of privacy—rather than the feeling of vulnerability associated with loss of control. This impact of the consequence rather than the implications or interpretation may explain why even those who are not troubled by most other burdens feel the burden of loss of privacy.

7.2.4.4 Deprivation of Power
The third type of deprivation of control is deprivation of power. Subjects are aware that ultimately the research facility and staff call the shots, and so they weigh their behaviour against the possible actions by those with the power. This imbalance of power sometimes prevents subjects from asserting themselves or exercising their rights, and leads to incidents that subjects judge as “small injustices”. There is a range of how far subjects will dare to go with asserting themselves where they perceive an injustice. Some subjects claim they will not put up with anything that bothers them, or that they think is unjust. Others seem to pick and choose. No subjects I interviewed felt they would never speak their mind, although some seemed quite close to this. Subjects show awareness that they are the more vulnerable players in the research relationship.

*Every subject has to experience turbulence of some kind—say you get called for a blood draw. You get called. They call you once—they don’t see you. The manager starts screaming at the subject. Subjects just take it—they want to*
Enduring these small injustices is experienced as a loss of control and accompanied by feelings of frustration or stress.

Awareness of the imbalance of power can also result in a constraint on subjects’ expression of their autonomy. This occurs where there is concern that certain actions may threaten the opportunity to finish a study, or to be accepted for future participation. Constrained autonomy occurs when subjects feel that they have to direct their behaviour to the goal of not losing the opportunity to participate. This may relate to not getting withdrawn from the current study they are in, or making sure they are not blacklisted from future studies. Constrained autonomy is manifested as a restraint of some type, holding back on acting in accordance with one’s preferences, such as not complaining about a study situation that is an issue, walking away from problems with other subjects, or ignoring “bad attitude” from study staff. One subject expressed a concern about the impact of decisions about participation on future access to studies.

*S:* The thing is that—let's say if you have ah, you have denied a study more than one time or something like that—they have a rule whereby they can, you know deny you from getting in or whatever. Let's say you haven't been—you've ah—you say you want to join but then after you kinda dropped out, you didn't feel like staying any more. You know their gonna weigh that with giving it to somebody who hasn't done that—whose always been excited about the study.
*I:* Yah. But that's more like if you've said yes and then later changed your mind?
*S:* Yah. Or even if you have called and cancelled I guess. Like even before the study started you just like—you find out about it and you're like "OK, I'll take a medical or whatever" then you just kind of cancel. They kind of—I'm not sure if they have those recorded—how many studies you called and cancelled, called and cancelled—versus go, then cancel. I'm not sure if they have that recorded but it makes you feel bad sometimes like "Oh I wonder if they're gonna say I did it again" kind of thing. I makes you think about it, like—“oh, no, I wonder if I get in based on what I did the first time”, you know? So you actually do think about that. 07-06

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29 This subject was interviewed by telephone and the interview was recorded with hand-written notes. I attempted to capture the conversation as faithfully as possible, but the transcript, and therefore the “quote” is not verbatim.
Consideration of the impact of behaviour on future opportunities might be viewed as either an act of control, or a manifestation of lack of control. While the subject is consciously altering his or her behaviour for a certain outcome, which would suggest an act of control, the behaviour is contrary to immediate personal desires and values. In other words, subjects are acting against what they want to do, thus constraining their autonomy.

### 7.2.4.5 Factors Affecting the Degree of Burden Associated with Deprivation of Control

A number of factors or conditions seem to increase the impact of deprivation of control. These are *lack of information*, perceived *arbitrary deprivation of control*, and *reluctant participation*.

#### 7.2.4.5.1 Lack of Information

Deprivation of control is increased when subjects are not adequately informed about various study procedures or the research environment. Insufficient or incorrect information can result in uninformed decision making, or can deny subjects the opportunity to prepare for a given situation, either psychologically or through action. This deprives subjects not only of control over the situation, but over their own response to it, thus magnifying the loss of control.

*I: Do you feel that they explained, like the whole setup well enough?*

*S: I think they could have—I think they minimized the sleeping arrangements, so they don’t get everyone going “are you kidding?” And, I don’t think they say enough about that, that you’re going to be in very cramped, uncomfortable sleeping conditions, and that you really should bring extra blankets, because they really can’t provide the number of blankets that are sometimes required…and they have group showers. You’ll have one shower and you could have three people showering together. I frankly don’t shower—no, I don’t think so.*

*I: With the open—not the stalls?*

*S: Mm hmm. That’s bizarre. 07-12*

#### 7.2.4.5.2 Arbitrary Deprivation of Control
The negative impact of deprivation of control is made worse when subjects feel control is being deprived arbitrarily, and is not necessary to maintain the integrity of the study.

*Also the security they have increases stress.*

*Most of the time the rules are enforced for the sake of putting you under control.*

*But 35% of the time, staff are just making up the rules.*

*S: I’m bothered how he treated—like, very strict, like a drill sergeant, you know. I mean like I asked for a simple favour like finishing watching this show on TV for 15 more minutes and he said no. Like get up right now, you’re out of here, you know.*

*I: Was that unusual?*

*S: That is unusual. It’s not the norm.*

*I: Is it more like, would you say one person, or the place?*

*S: Yah, like certain individuals. They really take their authority, like, you know, they think they’re God or something.*

The lack of a good reason or purpose to the deprivation of control causes subjects to resent their suffering as wasteful and disregarding their needs. It is disrespectful and uncaring because it does not minimize subject burden, but adds to it unnecessarily. The arbitrary imposing of control may also emphasize the power imbalance between subject and research staff, increasing the feelings of frustration and vulnerability described above.

### 7.2.4.5.3 Reluctant Participation

As mentioned at the start of this section, although most subjects seems to feel that participation in phase I research is a freely made choice, three of the subjects interviewed for this study participated reluctantly. These subjects felt financially desperate and participated as healthy subjects because they felt they had no other current options for addressing their financial need. While this type of reduced control regarding decision making is caused by factors external to the actual research participation, it is included as part of the concept of deprivation of control, as the condition of reluctant participation seems to exacerbate the experience of deprivation of control during participation. Subjects who participate reluctantly appear to be more negatively affected by deprivation
of control during participation.

*I mean the whole thing that I'm doing this it's not because I want to. I mean I hate it, it's miserable, it's awful. It—it could be worse. But I mean it's really, really a stress for me. I'm really unhappy doing them. Maybe if it was at the point where I was doing it for bonus money, or to buy a vehicle, or to go on vacation, it would be a different perspective. But because it's out of need...You know I don't enjoy it.*

08-24

If, as hypothesized here, the burden associated with deprivation of control is, to a large extent, related to the feeling of vulnerability it causes, the enhanced burden experienced by reluctant subjects might be explained by their already feeling deprived of control and therefore powerless upon entering the study.

Two distinctions are important to note regarding reluctant participation. The first is that it is the *reluctance* and not *financial need* per se that is associated with increased experience of deprivation of control. The second is that not all subjects who participate out of financial need do so reluctantly.

### 7.2.4.6 Deprivation of Control Summary

Choice, privacy and the power to assert ourselves are taken-for-granted freedoms that we normally enjoy without thinking as we go about our daily lives. Subjects’ experiences of deprivation of control highlight the numerous minor and not so minor instances of control that we may take for granted each day. With regard to choice, the specific instances of control may not always be important—it is *having* control that seems to matter. In the case of deprivation of privacy, on the other hand, the associated burden is directly attributed to the actual loss of privacy, rather than a more symbolic loss of control. Only in its absence does the full importance of control become apparent. In being deprived of control, subjects are not moved to a neutral state, but become controlled.\(^{30}\)

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30 I think that the negative impact of deprivation of control transcends the specific context of the research facility. Since identifying this concept in my data, I have become aware of many little instances of deprivation of control in my own life, and the feelings of stress or frustration aroused by such situations. While the specific issues may have been very minor, where I was deprived of control I felt a momentary reduction in my autonomy.
Being deprived of control over these taken-for-granted little things leaves subjects stressed and sometimes irritable. As one subject pointed out, in addition to having a negative impact on subject experience, this stress may cause physiological changes that could wrongly be attributed to the study drug. As with other burdens, the degree to which subjects are bothered by deprivation of control varies among subjects. Nonetheless, for most subjects, deprivation of control is the limiting factor regarding the duration of confinement subjects are willing to endure. Depending on the subject, the impact of deprivation of control on duration of participation may be in reaction to the general lack of control, or to some specific consequence, such as boredom or lack of privacy. The remainder of this chapter will describe how subjects cope with and reduce the net burden associated with getting through participation, by *finding personal control*.

### 7.3 Finding Personal Control

#### 7.3.1 Overview

The first part of this chapter described the main burdens affecting the experience of getting through participation. This section will describe how subjects mitigate these burdens by finding personal control. The degree of burden associated with participation appears to be directly related to the perception of personal control over the participation experience. Subjects who perceive greater personal control view participation as a relatively easy way to make money, whereas those who seem to feel a low level of control view participation as very difficult. The concept of personal control is important to the theory of making participation work, because it, along with net burden, explains much of the variation in how subjects experience research participation. In addition, by finding personal control, subjects are able to play an active role in making participation reasonable, or making it work.

As described in Chapter 6, healthy subjects are motivated to participate to earn money, and they try to minimize the burden associated with the work of participation through selecting studies that meet their personal criteria. This selection is a passive minimizing of burdens, as subjects are merely choosing among available options. Where subjects find
personal control over participation, they can actively reduce the perceived burden
associated with being a healthy subject. Thus, through finding personal control subjects
can actively alter the burden-pay ratio associated with research participation.

Personal control is enhanced by specific subject behaviours, and by positive interactions
with research staff. In general, the success at finding personal control seems to increase
with increased experience as a research subject. Those who participate frequently
generally seem to have a higher perception of personal control than those who participate
infrequently, and most subjects seem to have an increased sense of control as they gain
experience as participants.

This association between control and experience may reflect both the opportunity to
know the system and therefore how to find control, as well as the necessity to find control
if the stressful research situation is encountered more frequently. As the theory predicts,
the majority of frequent participants, who are those more likely to find personal control,
also have a positive attitude about participation. Thus, it may also be that those who are
successful at finding control, because they have a relatively more positive experience, are
more likely to opt for repeat participation. In other words, increased repeat participation
may reflect a selection for those who have a positive experience, which in turn is the
outcome of ability to find control. According to this theory, those who perceive their
personal control over participation as low are likely to have a bad experience, and avoid
further participation, or participate reluctantly.

The concept of control is a complex one, about which much has been written, particularly
in the field of psychology (126). There are many meanings associated with control. The
term is used here to reflect the ability or power to manage or exert some influence over a
situation. The qualifier “personal” is used to reflect that the control subjects have is over
their own actions and their psychological or emotional responses to the research situation,
such as the meanings they assign to a situation. In some cases subjects may consciously
exert this control, and in other cases, it may be done unconsciously. No attempt will be
made to distinguish between these modes of control. What I will do here is describe how
healthy subjects find personal control and how this impacts the experience of research participation. The remainder of this chapter will address what behaviours are associated with finding personal control during research participation and how finding control affects the participation experience.

7.3.1.1 How Subjects Finding Personal Control
Subjects seem to find personal control in a number of different ways, which I have conceptualized as accepting, rationalizing risk, emphasizing autonomy and managing the burdens. The impact of these behaviours can be found at all stages of the process of participation described in Chapter 6. For example by normalizing (a mechanism for accepting), subjects are able to overcome the stigma associated with research participation to allow opportunity identification. As the degree to which subjects find personal control affects the perception of burdens, finding personal control will have an impact on study selection. Rationalizing risk also plays a critical role in the selection of studies. But the greatest impact of personal control is in getting through participation, where subjects endure the burdens of participation, especially deprivation of control. The following sections will describe in detail the behaviours associated with personal control, and how they affect the participation experience.

7.3.2 Accepting
7.3.2.1 Accepting Overview
Accepting refers to tolerating the study burdens without regret or resentment. Accepting is feeling that the study conditions are reasonable or acceptable. This is different from simply agreeing to participate, as one can agree while nonetheless being unhappy with the situation. One may consent to participation, being informed about what will happen, and agreeing to that thing happening, but may still not accept the situation as “OK”. Consent refers to the agreement to comply with the study requirements. Accepting is a psychological process that affects the perception or interpretation of study burdens. Although it may seem a passive action, and a sign of lack of control, accepting is considered here as a type of personal control because of its apparent effect of increasing the perception of control. In their examination of the various types of personal control,
Cornelius and Averil describe “cognitive control” as ‘the way an event is interpreted, appraised, or incorporated into a cognitive “set”’ (127). Accepting is a type of cognitive control because subjects who are accepting interpret study conditions in a positive way that can be incorporated into a framework of participation as reasonable work. Accepting requires defining the extent and limitations of one’s own control and actively deciding to tolerate it.

_Yah, I mean you are in lack of control. I mean you’re in a place where there’s, on average, say, 50-100 people, each time—Even though I’ve been in smaller ones—but you are in lack of control. If the wake up time is 6 o’clock you have to be up at 6. Dosing’s at this time. Right? So, you have to know that going in to the study. You have to be flexible. Yeah there is a lack of control. But I mean, what do you want to do about it? I don’t know what you can. Cause if they tell you the clinic rules and regulations before you come in, and they’re done because they have to, cause they themselves as a company, that’s what the sponsor tells them. 07-01_

There is a range in the degree of acceptance among subjects. Accepting helps subjects find control because it reduces or eliminates an internal struggle between what one has consented to (the research) and how one feels about it. This struggle is apparent in subjects who take part but are not very accepting.

...they had 100 people so they had to get 1 a minute. So, a lot of these people, are new to Canada. English skills are terrible. Very poor English. All they do is take a couple week course on how to take blood, and for them it’s just a way—it’s just a job. So, and they were very very conscious about the time, and about themselves. And they will do things to you, that are nasty, to get the blood. I mean, I was black and blue on my arms....Also, they will squeeze it out of your arms to get it out, and that’s very painful. I’d rather have 100 blood draws if no one squeezes the blood out of my arm. And plus, when they put a catheter in, for example, they don’t know what they’re doing. Some of these people are absolutely terrible. Some of them, you gotta wonder if it was intentional. Maybe they don’t like the job, they don’t like being rushed. But [facility name] is terrible. And then when you add that into it—the poor compensation, the poor food, the risk to yourself. You wonder if it is worth a thousand dollars, but you do it because you’re desperate...I never thought, in a million years, that I’d be doing this. But I also, have a family, and I’m in financial need, and my options are limited. And, I’m not the kind of person that’s going to go out and rob a bank or something. And also I like to pay my bills. So, I’m doing this, but I’m doing this reluctantly. 08-28
Accepting reduces the perception of study burden. Subjects with a high level of accepting see participation as easy, while subjects with a low level of accepting see it as very difficult. The impact of accepting on experience is illustrated in the following two quotes from subjects who found participation easy, or difficult, respectively.

*It’s just for, you know, I make some extra money. I bought myself a couch—a free couch. It’s nothing. It’s a free couch. I went in for a couple weekends. I would have just been—I would have been sitting here writing and probably going out and spending money. Instead I’m there writing and getting paid money. So yah, I got a great couch.* 08-21

*S: Yah. And it’s not so much that the poking really hurts, it doesn’t. But it’s just the idea of—you can, you know, showering you see it. You see where they poked you 20 times. Mentally it, it bothers me, you know? Yah.*
*I: So that’s the main thing when you say a hard one is that, not so much the drug thing. Would you say most of the studies you would call hard, or not hard? S: I mean I guess they’re all hard.* 08-17

In some cases, accepting appears to be a deliberate strategy—a conscious effort to deal with the situation.

*S: You have to really have a mindset for it, and just think “well it’s only 2 days”. Ignore any problems. Don’t get involved with anyone’s problems, or if they sidle up to you, and just sort of keep an open mind. Just go in it, and just do it—you know, what they want. You know, it’s not gonna be a lifetime. And once you’re out of there, you’re out of there. So it’s sort of a mindset.*
*I: And the mindset for dealing with the other people, or the environment—? S: Everything. For the environment, for the people, for the blood draws, for the constant blood pressure checks—everything.* 07-12

In other cases accepting may simply be the result of the way certain things are perceived—if they are not a problem in the first place, they are easy to accept. What is clear, however, is that a high degree of accepting is associated with a positive perception of research participation, and for some subjects may be the primary if not the only way of finding personal control.
7.3.2.2 Mechanisms for Accepting
Accepting is the end result of a number of specific behaviours, which I have grouped into three main categories, labeled buying into study requirement, normalizing, and excusing staff. These mechanisms for accepting will be described in detail below.

7.3.2.2.1 Buying into Study Requirements
Buying into study requirements refers to seeing the requirements as reasonable. This means that the requirements make sense to the subject, in light of the research purpose.

S: Um, I feel sort of from my perspective, like from being in school and being in science. I understand the importance of replication and control in doing studies, like I understand that’s why this is a priority...Um, ya, I guess maybe that’s something that’s underemphasized, in a lot of consent forms and like a lot of the protocol designs.
I: Is the need they strictly adhere to ...?
S: They need to impress upon the subjects a little better the reason that everything is done so stringently and by the numbers is because like this is, like the experiment was designed to be run in a specific way, and any time things fall outside of the norm, um if that happens too much it can invalidate the results and as a result, this is everybody’s time and everybody’s money is gone down the drain, you know, because, things, like if you didn’t want to get your blood drawn, at seven nineteen, you wanted to stick around and wait till seven twenty... if there was like a little blurb in the consent that was like “The reason we’re so anal about how we do everything”, you could say “because we need to be, you know that’s how it works.” 07-03

Where subjects understand and accept the rationale for burdensome requirements, accepting these requirements becomes a natural consequence of consenting to be in the research. Subjects do not feel ill-used because they see the need for the requirement. There must be understanding of the rationale for a requirement if it is to be seen as necessary. Subjects most often gain understanding through being informed about not only the requirements, but their relation to the study, although in some cases the requirements are seen as a matter of common sense.

In contrast, when the purpose or necessity of burdensome study requirements were not clear to subjects—that is they seem arbitrary—subjects are less likely to buy into the
requirements. When subjects do not see the requirements as reasonable, yet must go along with them or be removed from the study, they suffer a loss of control.

Um, for example, when you have your food, in other companies, someone stands right with a watch clock, and you wait for the last second, before you start eating. Then you have to um, then you eat and you have to report and then they come then and they watch you and then you have to exactly, eat to the last crumb. Even if something falls on the tray. It doesn’t make sense. Cause again, stupidity. 08-26

7.3.2.2.2 Normalizing
A second way that subjects come to accept the participation experience is through normalizing. Normalizing is the change in perspective regarding research participation, from seeing it as crazy, risky, or weird, to seeing it as “normal”, and sharing commonalities with other jobs or health care experiences. Normalizing is a rejection of the stigma associated with being a “human guinea pig”. The degree to which subjects see participation as abnormal before becoming a research subject varies, but after their first participation experience, subjects who choose repeat participation tend to shift their view away from “weird” and towards normal, every day life. For example, the study environment might be compared to a dorm, and participation likened to other jobs, where the employee must accept the conditions of employment. Normalizing increases accepting. In finding normalcy within the research experience, participation becomes more reasonable and easier to accept.

The first time I was really scared. I thought this is crazy, I don’t know if I can do this…but after the first couple of times I’m like, it’s not as bad as it seemed... I really found that at [facility] especially—they’re pretty good. I like the environment, it’s—makes me at home. 07-06

Where subjects focus more on the ways that research participation differs from every day life, there also is less accepting and more complaints and participation remains more difficult.
I'm like, what the hell did I do? Why did I come here? And I'm not scared, but it was a strange feeling, strange environment. I thought that I'm a rat. Like something like that. And I'm like Oh my God, people actually walking around with those white uniforms. You feel like you're really in a prison. And they don't let you go out. All the doors are locked. And it gives you a feeling like, oh my god, what's going on? What are they gonna do to you? 07-09

7.3.2.2.3 Excusing Staff

The third mechanism for accepting identified in this study is excusing staff. Excusing staff refers to providing explanations for staff behaviour that is bothersome or potentially offensive. Often when mentioning some complaint about staff behaviour, subjects spontaneously added a comment explaining that behaviour as understandable in light of the situation.

I mean, you gotta understand, people are people and some of the clinics I've been in, like I've been to [facility name], and they've got 4 studies and the study I was in alone had a hundred people in it, so you're not gonna get, you know—they're don't treat you mean, but they're treating you like "we've got a lot to do". I mean, I'd still go back there. 07-01

This excusing seems to help accept the negative behaviour, because the behaviour is seen as a product of the busy environment, and therefore both understandable, and not to be taken personally. This helps subjects to see the behaviour as reasonable and therefore more acceptable. Excusing staff also seems at times to be used to help a subject redirect potentially negative feelings from the staff to "other subjects".

S: Um, the people who are, like, the supervisors—they're always anal. “OK you have to come over here now! NOW! And you have to be done NOW!” You know, they're very—to the minute, to the second. They repeat things over and over. Like you really must be stupid.
I: They treat you like you're—?
S: They really treat you like you're—oh yah, yah. I mean they—of course you know what, some of the subjects we get—I mean, you know. Some people you just HAVE to talk to 'em like that. And some people, they just don't get it. It's like—honest to god, people don't get basic instructions.
I: So they end up just treating everybody like that?
S: I could see why. Otherwise, you know. 08-23
This redirection allows subjects to preserve their perception of a positive relationship between themselves and staff, and perhaps to maintain a positive perception of themselves as participants. This in turn may make subjects feel more autonomous, because it would be harder to say you are making an independent and reasonable decision if you also had to say you are accepting being treated poorly. By excusing and redirecting negative comments, subjects change their perception of a potentially negative situation and make it acceptable. It is also possible that excusing staff reflects a view of the staff as “fellow workers”, reinforcing the notion that research participation is a type of work.

S: I know this has happened to me one time whereby you go in for the study and the study was cancelled. Then I came back again—it’s cancelled. They said come back again. I’m like “what’s happening”? ...
I: And did you say anything? Did you complain to them or anything?
S: Ah well, most of the subjects were complaining. They were rowdy. There were riots going on [laughs]. It was kind of—we were like really mad. I was mad too. I wasn’t really saying anything much. But other people were voicing their opinions. Yelling at the people at the desk. And it wasn’t their fault cause they don’t know what’s happening. They’re just working. We’re just working. But they were just, like, really upset. 07-06

Seeing staff and subjects as partners in getting the study completed may also make participation feel more honourable and consequently more palatable. In their interviews with subjects taking part in non-therapeutic testing of a new breast imaging device, Morris and Balmer (108) found that subjects framed their relationship with researchers as collaborative as a way to become active participants rather than passive subjects, and make a potentially awkward research scenario more socially comfortable (108).

7.3.2.3 Accepting Summary
Accepting involves a variety of cognitive strategies that help healthy subjects see research participation as reasonable. By framing the experience of participation in a positive way, accepting increases the perception of control during participation. The degree to which subjects accept the conditions of participation has a significant impact on the experience of participation. The data from this study suggest that accepting may be a minimal requirement for a positive participation experience—all subjects who appeared
to have a positive experience were generally accepting of study requirements, while subjects who were not accepting had a difficult experience.

### 7.3.3 Rationalizing Risk

A second way that subjects seem to find personal control during research participation is through rationalizing risk. Rationalizing risk describes coming to conclude that participation, as the subject constructs it, is relatively safe. It is similar to accepting, in that there is an accepting of risk. However, rationalizing risk goes beyond accepting, to justifying risk exposure, positioning the risk as relatively low, and taking steps to limit or reduce exposure to risk.

The term rationalizing is used because subjects are able to provide reasons for their feeling that they are not taking on unreasonable risk, rather than simply ignoring risk. The term is not meant to be pejorative, or judgmental as to the “objective” reasonableness of the reasoning. Some reasoning, however, does seem to be based on an imperfect understanding of pharmacology and physiology.

The negative connotation of the term “rationalization” comes from its use by Freud as a label for one of the psychological defense mechanisms he described. In Freud’s conceptualization, “rationalization occurs when you unconsciously give yourself a false explanation of your own behaviour”; that is, one lies to oneself about the reasons for one’s behaviour to provide an explanation that is more personally or socially acceptable than the real reason (128). As will be described in detail below, rationalization as used in this research to describe the behaviour of healthy subjects is similar, but not identical to the rationalization described by Freud, since subjects are not necessarily providing false explanations for how they come to accept a certain level of risk. While rationalizing risk does appear to reflect a positive bias rendering risk more acceptable (i.e. a focus on reasons for reducing rather than increasing risk perception), the reasons themselves are not necessarily false.
The dictionary definitions of rationalize include “to bring into accord with reason or cause something to seem reasonable”, as well as “to create an excuse or more attractive explanation for” (129). This range of meaning (i.e. both explanation and excuse) is incorporated in the concept “rationalizing risk” as it is used in this study, as subjects, through rationalizing risk, are making their participation rational, logical, or consistent with their values, and justifying the risk of participation, either to themselves or the outside world.

Three main mechanisms for rationalizing risk were identified in this study—health beliefs, reducing exposure, and being philosophical. Each of these will be described below.

7.3.3.1 Health Beliefs
Health beliefs are various notions subjects maintain regarding pharmacology and physiology to explain why they are not particularly concerned about the risks from the study drugs in the trials they do. Health beliefs can be grouped into three main categories: washout of study drug effects, differential susceptibility to risks, and the ability of various protective behaviours to reduce personal risk.

7.3.3.1.1 Washout of Drug Effects
A relatively common health belief is that drug effects are temporary and will wash out of the body in a matter of days.

*I'm actually putting into my body some kind of medication which might be toxic to my system. But that’s, but um, I guess—they say that there’s always like a washout, so after 30 days or so it’s going to be out of your system. So that’s OK I guess.* 07-13

Rather than state a belief in the “washout principle” directly, some subjects displayed this assumption about the temporary nature of drug effects in their descriptions of side effects as something to get through or endure.
I: Have you had some side effects?
S: Oh, of course. Well mostly like, something that I can handle. Stomach ache, or, you know, diarrhea, or headache, or, you know, drowsiness. 07-15

A related notion expressed by one subject was that in the case of an acute toxic reaction, an oral medication could be eliminated from the body to reduce any side effects, imparting control over the risks.

_They had it intravenously, so maybe, first in humans intravenously I'd probably never do. I have my—maybe that is my cut-off. Cause I have no control over getting it out of the body—if something goes wrong, right? At least with the pill, if you feel sick you could throw up. Or you could get your stomach pumped, you know._ 07-15

### 7.3.3.1.2 Differential Susceptibility
Differential susceptibility refers to the belief that people vary in their susceptibility to adverse drug reactions generally. Some subjects attributed their lack of adverse experiences to their having a low susceptibility to such reactions.

_Um, as an individual I've actually found that I usually don't suffer from the side effects. I don't know, maybe I've just been lucky, so I ??? think about that, so even if—sometimes like, almost every drug has, like a hundred different side effects, so I know that usually I won't suffer from any of those. So, um, I'm OK with that._ 07-04

A variation on the belief of differential susceptibility is to attribute adverse events experienced by other subjects to their using other investigational or recreational drugs while in the study.

_Like I said, some of these guys go from one to the other to the other. They might be in a study, and they're in this study and then they have another study, so. Yah, we had one a few months ago and it was nothing. It was like, one pill that you take and this was a pill, again that 80 year old women take like three of these pills a day for weeks. And you take one little thing, but this guy across from me, his eyes were rolling back and he was shaking. So they kicked him out of the study actually. But like I was saying, they do three studies at a time._ 08-21
7.3.3.1.3 Protective Behaviours

A third health belief that helps subjects rationalize risks is belief in the ability of various behaviours to decrease their personal risk of adverse events. Subjects rely on a variety of actions to help safe-guard their health specifically in light of research participation. Some will seek reassurance from a family physician, in the form of a check-up or advice about the safety of participation. Many subjects use herbal or mineral supplements to keep the body in good condition or to speed recovery from the possible negative effects of participation, such as iron supplements to replenish hemoglobin.

*S: Well since I'm active, I think that my body works very well, and I'm pretty sure you know, especially with the green tea, it flushes away very easily and pretty fast, so.*

*I: Do you do anything special because of the studies, like do you take um—you said about the meat, maybe you have to start eating meat, but um, what about iron supplements? Do you do any of that?*

*S: Yah. That's what I started taking, because I need—it's probably even better for my body, you know, since my body is not as young any more. I probably should have it to recover. Because I take the iron supplements now.* 08-22

Subjects who participate more frequently than recommended may use supplements to help ensure that they pass the screening tests for each study. “Regular” subjects may also share information among one another about the use of supplements.

*They share information about how to fake your way into another study. Like one guy told me—he does back to back studies—you buy vitamin E, and you rub it over your wounds, where they've taken the blood out of your arms, so that way they won't know that you've done a study. Or think you're a drug addict. Or, when you go in, offer the other arm for the blood test. Wear long sleeves. Drink lots of water. If they're taking a lot of blood, drink lots of orange juice and eat hamburger before you go in to get your iron up. People do that. People say about times they were caught, times they weren't caught. How they do it.* 08-28

While the specific protective behaviours used by different subjects vary, they have in common a belief in one’s own role in staying healthy for, or in spite of, research
participation. In this way, subjects find personal control over the risks associated with research participation.

**7.3.3.2 Reducing Exposure to Risk**

Another mechanism for rationalizing risk is reducing exposure to risk. Subjects generally feel safe because they select studies that they believe reduce their exposure to risk. Exposure to risk is reduced by choosing safe studies, and by limiting participation in terms of the frequency or duration of participation. The actual behaviour considered “safe” varied among individuals—what was common was the belief that a relatively safe level of participation could be established.

**7.3.3.2.1 Choosing Safe Studies**

Applying criteria to select low risk studies was commonly mentioned as a response to why subjects felt safe about participation. While the criteria and/or risk thresholds varied among individuals, each individual felt that they were making safe choices.

_I’ve heard stories where you go in, they give you a drug, and they just kind of watch you. And if you’re OK they give you—you start off with 30mg and if you’re OK they give you 40 mg and they watch you and they give you 50 mg and they give you 100mg and then you start barfing and throwing up, and that’s when they like oh, OK, so that’s when—I don’t do those. I do the ones where—like you say, bioequivalence, what they give, you know, little old ladies for their bones, you know 3 pills a day, for 30 days, and I take 1 pill. That’s fine. It doesn’t do anything. 08-21_

Criteria include indication, previous experience with the study drug, and seriousness of side effects listed in the consent form. The most common indication to be avoided is psychiatric or psychological disorders such as depression or schizophrenia. Some subjects avoided drugs for “serious” conditions, such as HIV infection or cancer, or drugs that affected vital body systems, such as the cardiovascular system. Many subjects considered the extent to which the drug had been already tested in humans, with bioequivalence studies (comparing a marketed drug to a generic formulation, often requiring only a single dose of each test drug) seen as least risky.
7.3.3.2 Limiting Participation

Subjects often noted that they limited their frequency or duration of participation. Limiting the duration of participation includes selecting shorter studies, as well as planning not to participate for too many years. Limiting the frequency of participation is seen as a way to reduce the exposure to investigational medication, and to let the body recover from possible drug effects as well as from multiple blood draws. Selecting studies of shorter duration usually means fewer blood samples and possibly fewer doses of study medication.

I: So um, as far as, that issue of the safety and the drugs, do you think—so you said you’re not particularly worried about the um, like, when you ingest that pill, you’re not thinking—waiting for something to happen?
S: No. No, no. Because it’s such a low dose. It’s only like one or two doses. So it’s not like, oh my God, I’m taking this stuff for Alzheimer’s or something’s gonna happen to me. It doesn’t feel that way, because I feel only 1 dose will really not—it doesn’t—because when I read the literature and hear everyone else and talk with people, it’s in the, in the blood level that they’re looking at, really it doesn’t affect any of the major organs right away and stuff. So I’m not worried THAT way. I’m just worried about, you know, being poked all the time, you know, going into these places and just—taking pills, not taking pills, taking pills, not taking pills, taking pills, not—it’s up and down, up and down, you know what I mean? So, I’m sure like over a long period of time MAYBE it might not have like, good health benefits for you, MAYBE it doesn’t matter. I just don’t want to take that chance. 08-25

The plan to quit or reduce participation at some point in the future suggests that subjects are making certain assumptions about health and risk. One assumption is that negative health affects accumulate over time, so that fewer total participations will result in less accumulated harm. This assumption of accumulating long-term effects seems to contradict the notion of washout. More research into this issue is required to sort out more clearly how subjects think about risk. A second assumption suggested by the limiting of participation is that there is a safe level of participation. By identifying a category of “excessive” participation, subjects can stay below that level and feel that they are participating safely.

Subjects defined safe and unsafe categories of participation by constrasting their prudent behaviour with the risky behaviour of other subjects, who did not limit participation.
S: But um, yah, people do talk about what's happening at the other places and, some people do double up as well...You're not supposed to do that. It's really dangerous.
I: So you wouldn't normally do that?
S: That doubling thing? No. I think it's dangerous because you need to recuperate first off cause they're taking so much blood—get yourself—You know what I mean? But I think there are people who depend on the income who do double a lot. Double and triple. That's crazy. 07-06

By identifying unsafe participation, and differentiating their behaviour from that, subjects can put their own participation in a category of “safe” or at least “safer”. By making these safer choices, subjects enhance their feeling of control over research risk. Downward comparisons have previously been identified as coping mechanisms in a variety of situations including aging, breast cancer and HIV infection (130-134).

7.3.3.3 Becoming Philosophical
Subjects also rationalized risk by becoming philosophical about it. Adverse events are seen as something to be expected regardless of research participation.

I: What kind of thing would you look at then, when you were thinking about it?
S: The percentage of people that reacted. Down to 0.1% had a blood clot, or had a seizure, and you're thinking, well, that would have probably happened anyways. So I think, a lot of drugs, you've got a lot of people that are taking them, they could be at risk for anything. 07-12

Comparisons are made to other everyday risks, or other substances people might consume.

I do think about it and think well, some people drink 10 beers a day, or smoke 4 packs of cigarettes. I take a medication twice in every 30 days or something like that, if I’m doing these studies regularly. 07-01

These comparisons to everyday life help to normalize the risk of research participation as not substantially different from other routine behaviours. Some subjects demonstrated their awareness of the uncertainty inherent in the concept of risk, and their lack of control over drug-related risk. They reacted to this lack of control by setting concerns about risk aside.
I: And what kinds of things will you look at then in choosing?
S: Well because, I mean, I know that the symptoms are usually listed in the consent form, but you don't really know what will happen. I can't control that, the symptoms. I may get sick, I may not. And so what I mainly look at are how many blood draws and how frequently they're spaced out.
I: So that's part of the reason you don't think about the risks as much, cause—
S: No, I still read over the risks, and sometimes you won't do a study because you know, they'll be tons of symptoms and you just kind of turn off. But I think the blood draws are what I focus on most. 08-17

7.3.3.4 Rationalizing Risk Summary
Rationalizing risk is accomplished through a collection of behaviours that help subjects accept, justify, and reduce their risk associated with participation. It is not a complete denial of risk, but a way to see participation as relatively safe, and the risks as reasonable and consistent with their values. Rationalizing risk results in an increased sense of personal control over participation. Like accepting, the degree to which different subjects rationalized risk varied.

7.3.4 Emphasizing Autonomy
Emphasizing autonomy refers to the way that subjects define themselves as autonomous agents who are making a free choice to participate. This helps justify participation as reasonable, and helps to refute the stigma associated with participation, because it says “I am not a sucker. No one is taking advantage of me. I am making good decisions.”
Overall, the image projected is that of an autonomous, reasoning and reasonable decision maker, and not someone who is vulnerable, exploited or a victim. Emphasizing is done through straightforward statements—“this is my choice”—as in the example below.

I: Yah, like do you think it’s wrong? Like I remember this one woman, she just did it once for the first time and she hated everything.
S: It’s not for everybody.
I: She said “How can they treat humans like this?”
S: OK
I: You don’t feel like that—degraded if its not clean or anything like that?
S: Were all adult—I’m an adult. I make up my own mind. They’re not brainwashing me or anything like that.
I: So you’ve chosen—
S: I’ve chosen. This is the thing. 07-15
A number of psychology studies have found that people are less concerned about risks that they have voluntarily chosen than about risks that are imposed (e.g. smokers were more afraid of asbestos in the workplace than of smoking) (95). By focusing on their autonomy regarding the decision to participate, subjects may also feel a reduced sense of risk.

Comparisons with other subjects include both differentiating from and identifying with them. Subjects who are more selective about which studies they participate in differentiate themselves from those who do “crazy” things like dose-escalation studies, or participate in multiple studies in a short space of time. By making this distinction subjects emphasize that they are using their reasoning and free choice to distinguish between safe and risky participation, and through exercising their autonomy, are able to participate in a safe and reasonable way. For some subjects this differentiating demonstrates a devaluing of participation as a career choice, not just out of safety, but as a poor use of time/life. Participation is seen as OK if done up to a certain level, but socially unacceptable beyond a certain point.

*S: One guy was talking about [facility name], and how he'd rank [facility name] better than [another facility name] and which is better than [another facility name], and I just said "Wow, you do this for a living?" And he just said "I been doing it for he last four years and I bounce around because you have to wait thirty days till the next time you start, cause it cleans the system, so I keep bouncing around from place to place." Wow, I told the guy "you're wasting your life. I mean you should only do this maybe once or twice a year".

I: So why would you say that?
S: Ah, because the guy was in his mid forties, late forties and it just seemed he got a thrill out of it. He got a thrill out of making $780, tax free, instead of bettering himself through a real career. 07-02

Subjects also differentiate themselves from others who consent without really understanding the study details. Concern is expressed that some subjects don’t seem to speak English well, or seem “out of it”, or don’t seem to pay attention during the informed consent process, and therefore must not really know what they are getting themselves into. These statements may reflect genuine concern for those less-informed and therefore more vulnerable subjects. The comparisons also show, by contrast, that the subjects making them are informed and not vulnerable.
Some subjects differentiate themselves from what they see as unreasonable, attention-seeking complainers. These “complainers” are found to complain about every little thing, even though they know what they are getting into.

_Some people think that they’re, that this is like a vacation for them, that they’re paying to be here and they want, they want things. And ah, it drives me crazy to listen to these people. You know, like, they’re paying YOU money. You’re, basically you’re working. This is your job. Get there on time and do your blood samples on time and don’t cause a fuss. And, you know, if you don’t like your breakfast that they give you then, who cares? It’s one breakfast. You’re making two thousand bucks to sit here and do nothing, so just shut up. Do your thing and shut up. Everybody complains constantly, about just anything. Like I said, they think that they’re on vacation._

08-21

By commenting on the inappropriateness of this behaviour, subjects are showing that they, in contrast, are reasonable. They have made an informed decision, know what they got themselves into, and are sticking up to their end of the bargain in exchange for payment. They tend to be highly accepting of study conditions, and see this as a job. There is an “if you can’t stand the heat get out of the kitchen” feeling.

Similarly, some subjects identified with fellow “regulars” or “professional guinea pigs”. This was only observed in some male interviewees who identified themselves as belonging to a network of subjects who trade information about various facilities, good study opportunities, information on what restrictions they ignore (“we drink coffee all the time”), health tips specific to study participation (e.g. what supplements to take) and stories about extreme participation (“I heard of a guy who got paid $10,000 to have his heart stopped”).

By identifying with other professionals, subjects elevate their status to more of an expert subject. They know what to do and how to get the job done and are willing to do what it takes. Being part of a group may makes subjects feel more empowered, and participation is made more reasonable.
7.3.4.1 Emphasizing Autonomy Summary
By emphasizing their autonomy, subjects reassure themselves and the outside world that their participation is reasonable and they are in control. Autonomy is emphasized through statements about voluntariness, through downward comparisons with others who seem less autonomous, and through identification with fellow “regulars”. Subjects’ emphasizing of their autonomy suggests that, in addition to the moral importance of respecting autonomy, awareness of being autonomous or exercising one’s autonomy may provide an important psychological benefit during research participation, and perhaps in other scenarios where autonomy might be threatened or questioned.

7.3.5 Managing the Burdens
Accepting, rationalizing risk and emphasizing autonomy are social or psychological processes that healthy subjects engage in to find personal control within the context of phase I research. Managing the burdens refers to a group of behaviours subjects use to find control by directly influencing the situation to diminish the burdens. Burdens are managed in a variety of ways, such as knowing which staff members to talk to with a complaint, choosing the technician most skilled at blood sampling, bringing in activities to reduce the boredom, bringing in earplugs or a sleeping mask to cope with crowded sleeping conditions, and selective compliance with study requirements or restrictions. Repeat participation allows subjects to get to know the system, which increases their ability to manage the burdens.

While the burdens managed may be minor, the sense of control gained from managing them can have a significant impact on a subject’s actual experience, and the resulting sense of personal control.

S: I started—one time I came in and the bathroom door was closed ... and I thought you know, I’d just like to poop in peace. It makes such a big difference! You don’t hear the guy walking by in the hall and, you know?
I: So the main door’s open?
S: Yah. Always.
I: You can close the stall door, but not the—?
S: Right ... I thought, that’s a good idea, I’m gonna do that. I just thought, OK...
And I just closed it and I thought, OK, good. It’s making a huge difference in my experience.

I: The knowledge that you could shut that door?
S: Privacy when I pee all the time—it’s great. 08-24

Selective compliance refers to subjects consciously ignoring various study rules. Selective compliance allows subjects to avoid certain burdens, such as having to do without caffeine, herbal supplements, or even recreational drugs. In some cases, the benefit of selective compliance is purely symbolic, an act of defiance that gives the subject a sense of control.

I mean smuggled my cell phone in. But the thing is you can’t talk on it anyway. I never turned it on, but just KNOWING, yes! I mean it’s ridiculous, right? 08-24

In other cases, selective compliance is used to reduce the study burdens. By continuing to take multivitamins, the subject quoted below feels she is reducing the physical cost of participation, thus finding personal control over the burden of participation.

You know you’re not supposed to take vitamins for the study. Sorry, but you know I’m not gonna give ’em up for my system to get down. Am I gonna tell you that I stopped taking vitamins? Yes...You know I don’t do the coffee, I won’t do the grapefruit, but I’ll have my multivitamins. I’ll have things so I’m not feeling I will really compromise my health, which I already feel like I am by going to these studies. 08-24

Several subjects shared stories of selective compliance not only during the washout period between study visits, but while in confinement.

S: Um, [thinks]—well it’s good to know probably, that some people—women, no offence—women manage to bring all their pills with them. And they take their pills.
I: You mean, other medication?
S: Other medications, they are constantly on. You know like—it’s funny, my, just recently I made a friend who is in some kind of studies with me, pretty much the same, and she told me you know what, if you have a headache, they’ll give you TYLENOL. If you have like a muscle spasm, they will give you a relaxant or whatever. They have everything—whatever you need...What kind of results those women, do? That’s probably what I would like to mention. Because, I don’t think men do that. No. Men are too simple. [laughs]. Women are more, you know, tricky. 08-24

There were reports of subjects smoking in the facility washrooms during trials where smoking was prohibited, and instances of the smuggling in and use of recreational drugs.
The account below describes an extreme example of non-compliance. It should be noted that this experience took place some years before the interview, and may not reflect the current state of oversight at research facilities.

*S:* I mean if you had an unhealthy lifestyle and you tried to lie about certain things they were asking you prescreening, they would catch you in the physical. But um, some of the stuff was off, because I remember from that lengthy study, number one, every one in the study is supposed to be non-smoking, OK? Um, every evening, a group of us would be in the men’s bathroom, playing cards and smoking cigarettes. And we were in there smoking cigarettes like all night long.

*I:* Oh wow! I’ve heard stuff but not a group of people—

*S:* Oh yah. There would be some days, you know, on the day’s we’d draw—have to be taking blood, and one girl might say, oh listen, you didn’t wash your hands, you can smell cigarettes on you. They were telling you to wash your hands, brush your teeth, the whole thing because, when you’re in a non-smoking facility, totally non-smoking, and there taking blood and stuff, you go puff on a cigarette and you STINK. Like they gotta-

*I:* But she knew and she’s part of the cover-up.

*S:* Yes, and um I can even say that we um, on that study we had one of the guys—a little clique of us formed, and we got together and we ah, we actually had a guy’s girlfriend bring us a 10g chunk of hash. And we were smoking hash in the bathroom playing cards.

*I:* And that smells too.

*S:* Oh yah. 08-27

These subjects were able to manage the situation quite extremely, apparently with the cooperation of some of the staff. Subjects generally justify their selective compliance, with the specific justification depending on the nature of the breach. Justifications related to the integrity of the study and following the rules, and to possible health consequences of non-compliance.

Some subjects took compliance seriously, out of concern both for their own health and for the integrity of the study. Others try to be mostly compliant—their need to justify their behaviour suggesting a sense of guilt at breaking the rules. These subjects justified the non-compliance as compensating for some lack of fairness in the study situation, such as the subject who will abstain from coffee but will not stop taking multivitamins. This self-preservation is justified as reasonable, to make up for the physical demands of participation. Similarly, hiding adverse events is justified by the perceived unfairness of
payment policies that do not provide full payment to subjects who are unable to complete the study.

With other subjects, the justification was focused more on the safety of non-compliance, specifically in terms of ignoring wash-out intervals between studies. These subjects see their ability to pass the pre-study medical screening as the true indicator that they personally are fit to participate, regardless of what the rules might say. Although not explicitly discussed, these subjects may also feel that they are not threatening the integrity of the research, if they are judged as suitable by the various screening tests.

In the case of subjects who very brazenly broke the rules during confinement, there was likely little concern about study integrity, and subjects appear to be limited only by what they can get away with. For these subjects, selective compliance reduced the burdens associated with participation, by eliminating some of the restrictions. It also seems very likely that this blatant defying of the rules gives subjects a strong sense of control over their participation, although there is insufficient data from this study to specifically support this speculation. A similar conclusion was drawn regarding the deliberate sabotaging of research studies observed among a group of healthy volunteers in the Philadelphia area, which was interpreted to reflect an attempt to “recover their sense of humanity and agency” (12).

7.3.6 Finding Control Summary
The perception of net burden associated with participation in phase I drug trials is significantly affected by the degree to which subjects are able to find personal control. The main ways that subjects find control are accepting, rationalizing risk, emphasizing autonomy and managing the burdens. Finding personal control can affect how a subject interprets a situation, which in turn can affect how a subject feels about the situation or about him/herself, leading to a decreased perception of burden. Finding personal control can also directly reduce the net burden. Subjects vary in the degree to which they are able to find personal control, and in the type of control that they find. As perception of control increases, the net burden decreases and participation becomes easier.
7.4 Factors Affecting Participation Summary

The experience of getting through participation as a healthy subject varied among subjects from being very easy to very difficult. The variation in experience does not appear to be accounted for by any particular demographic factor or pattern of research participation (e.g. type of studies), but by how individual subjects think about or perceive participation. The main factor affecting the participation experience is perceived net burden, which in turn is affected by finding personal control. In this chapter I identified the specific burdens that had the greatest impact on participation. Deprivation of control emerged as the most significant burden during participation and a key reason for most subjects to limit participation to studies that have a duration of confinement of no more than a few days. I also described how subjects cope with study burdens by finding personal control, and examined the various mechanisms used to find control in the context of research participation.

This chapter has focused mainly on how subjects’ reaction to and interaction with the research environment affects their experience. In Chapter 8, I will describe how interaction between healthy subjects and research staff affects the experience, by affecting whether subjects feel valued and have trust in the research enterprise.
8 Results: The Impact of Feeling Valued and Trust on Making Participation Work

Chapter 7 described how perceived net burden and finding personal control affect the experience of participation for healthy subjects in phase I drug trials. This chapter will describe how feeling valued and trust affect the perception of net burden and personal control. I will begin with a brief overview of how subjects’ feeling valued and trust in the research enterprise fit into the theory of making participation work. I will then examine each of these concepts in detail, in terms of their meanings for healthy subjects in the context of research participation. I will end this chapter with a consideration of how trust affects the way that healthy subjects frame research participation.

8.1 Feeling Valued and Trust Overview

Reaction to and interaction with research staff and the research setting—including the actual research facility, the study sponsors, and regulators—have a significant impact on the experience of being a healthy subject. In this study, reaction to and interaction with the staff and setting determined whether subjects felt valued and the degree of trust they had in the staff and the research enterprise. Feeling valued and trust in turn affected the research experience, by affecting the perception of net burden and finding personal control. As illustrated in Figure 1, feeling valued and trust enhance finding personal control and reduce net burden. Conversely, where subjects do not feel valued or where there is a lack of trust, the perception of net burden is increased.

This relates to the core concept of making participation work, because through their impact on the participation experience, feeling valued and trust make participation more or less reasonable, thereby facilitating or hindering the process of making participation work. In addition, as will be described below, through feeling valued and trust subjects define their relationship with the research, which modifies how healthy subjects frame the process of participation.
8.2 Feeling Valued

*What we obtain too cheap, we esteem too lightly; it is dearness only that gives everything its value.*

-Thomas Paine (1776)

Feeling valued refers to subjects feeling that the research staff or the research facility see them as individuals, worthy of having their specific interests being heard and attended to. Staff behaviours or research conditions are interpreted by subjects as indicating they are valued or not valued. Feeling valued enhances subject’s feeling of control. Feeling unvalued decreases the perception of control and increases the perception of study burden. Subjects feel valued when they perceive the research setting or the behaviour of research staff as showing *caring* and *respect*. Caring and respect are distinct concepts that overlap to some degree. These concepts have been examined in detail in a variety of contexts, including nursing and patient care (135,136). In the following sections I will describe the meaning of care and respect for healthy subjects in phase I drug trials, and how they relate to making participation work.

8.2.1 Caring

Subjects feel cared for when they are treated like an individual, and staff show concern for their personal well-being, including health/safety and physical and emotional comfort. Feeling cared for means not being treated just as a means to an end. Lack of caring was associated with a view of subjects as disposable.

*Well, they get so many people, right? It doesn’t really matter if they throw me out or kick me [out]. For them it’s immaterial. 07-10*

Caring is also demonstrated through giving subjects options regarding their comfort—letting them make choices about what is best for them. In this way, subject welfare is put first, or at least optimized to the degree possible. By giving subjects choices, their perception of personal control is increased.
The staff in general was pretty comforting. They’re like—“if you have anything to worry about, if you have any problems, just say what it is and they’ll try to help you out.” 07-05

I think [name of place] was a little more compassionate, because they gave me more options, as far as the blood draws. They asked me if I wanted to continue in the same arm or use a different arm, so, that made me more comfortable. 07-11

When subjects were given some control over their own comfort, they felt cared about. Caring was also perceived when staff showed empathy, listening to subjects, and trying to respond to their needs. Staff showed empathy by demonstrating awareness of discomforts or burdens, and trying to reduce them.

They will try to make you feel comfortable—try their best to not make it as painful as possible. 07-06

I think one of my biggest things is that in some places they understand the stress of what you’re going through, I think. They’re more...they understand the situation you’re in and they accommodate you. Whereas at others, like maybe [facility] or [facility], they don’t really take that into consideration. 08-17

When staff were seen as uncaring, there was the feeling that they were insensitive to subject discomfort, or that they put the study before subject comfort and well-being.

...cause some people kind of, they call it, fishing around in your veins? That’s really painful and they don’t seem to know how painful that is. So they get on with their schedule...you’re—“that hurts!”, and they’re like “yah, I know”, but they’re still fishing. 07-06

Uncaring staff did not listen to subjects, or give them options, as described by one subject, who contrasted his experience as a subject with how he, as a researcher, treats other subjects.

When they say they are in high discomfort we stop and ask them what’s going on and what they feel and if we do it in a different way would they be OK? And I’ll try to give you a five minute break. Do you want to drink some water? They don’t ask any of those things. They just do, do, do, do. 07-10
In the absence of caring, subjects may feel increased physical discomfort from a procedure as well as emotional or psychological discomfort from anxiety about what is being done or what might be done. There may be worry that well-being is threatened and a feeling of lack of control over the situation. Where staff are caring, subjects retain a sense of control over the situation, and also are able to relax and relinquish control to the staff where necessary. There is confidence that staff will promote subjects well-being.

8.2.2 Respect
Subjects also feel valued when they perceive that they are being treated with respect. The meaning and significance of respect has been considered extensively, as a primary human value, and as it applies to specific situations (137,138). Central to all of the various conceptualizations of respect is the recognition of the inherent worth and uniqueness of each person (137). The concept of respect as a theoretical construct will not be examined here. This section will describe the nature and meaning of respect, specifically as it is experienced by healthy subjects in phase I drug trials.

Caring and respect share some conceptual overlap as both actions involve seeing/treating individuals as unique and worthy, with the common outcome of making subjects feel valued. In the situation of health care or medical research, respect is often tied closely with caring (136,139), sometimes making it difficult to classify a specific incident as an instance of respect or of caring. Nonetheless, some distinctions can be made between the two as they were experienced by the healthy subjects interviewed in this study. While caring relates to being looked after, respect here refers to how one is regarded (looked at) and therefore treated.

Respect, or the lack of it, is an important part of interaction with study staff. In some cases staff behaviour is seen as reflecting the attitude of the individual staff member, while in other cases it is interpreted as a product of the attitude of the research facility toward healthy subjects. When the facilities are uncomfortable, and don’t seem to consider the needs of the subject, for example by having crowded conditions or no
windows, this is seen as a reflection of the research company’s attitude about the subjects—that they as individuals do not matter, that the bottom line is the most important issue, and that subjects are just a means to an end. When subjects describe facilities that seem not to respect subjects, they often perceive staff behaviour as also disrespectful. In four separate interviews subjects spontaneously chose the term “cattle” to describe how they were treated when describing a particular facility.

The idea that the culture within a facility determines or at least strongly influences staff behaviour was suggested explicitly by one subject, who noted that one staff member he had found to be not respectful became more respectful after the staff member moved to a “better” facility.

> So then what happens, I was told that [facility name] pays [staff] better. So, apparently—again, everything comes from the management. I guess how everything is organized, and so you see the same employees at [facility name] behaving differently at [different facility]. Again, because there is no pressure, maybe, that much. Again, they probably treat us more as clients as opposed to rabbits. So that's the difference. 08-26

Thus, there appear to be organizational factors that can contribute to subjects feeling respected or not.

As noted above, there has been much consideration about the concept of respect. In research ethics, respect for persons is usually considered in terms of informed consent for participation (140). Others have suggested that respect for research subjects means promoting certain rights such as protection of confidentiality, permitting withdrawal of participation and maintaining welfare in terms of subject health (23). While these modes of respect are important, in this study subjects seem most concerned with the way that staff interacted with them during participation. The interviews from this study suggest that subjects feel respected when staff or the research facility treat subjects as individuals, recognize their capability, reduce unnecessary constraints, and compensate fairly. Each of these conditions of respect will be considered in below.
8.2.2.1 Treating Subjects as Individuals

The importance of being treated like an individual came through most clearly in descriptions of instances where subjects were not treated this way.

*And the way they treat you they don’t allow you to like, step aside. I mean like, not step aside, but you always have to be, handled like a crowd. Something like you are cattle.* 08-26

*One of the staff they were saying treated them like goats, like herding goats or something like that.* 07-15

The repeated references to animals illustrates the dehumanizing effect of this treatment on subjects. Some respondents found the common practice of referring to subjects by a number rather than their name was also dehumanizing, although others did not.

*And I got in and got a bed and a number—forget about my identity. I was number 12. And I'm like "wow"! That was the first thing. I was like OK, I lost my identity in 2 seconds, right.* 07-09

*S: There are probably practical reasons for this, but everyone is issued, a number. But [facility name] issues a t-shirt with a number on it. And as far as they’re concerned, you’re just number 75. I: Do you find that a lot different, the actual t-shirt thing versus just, like even though you know you’re issued a number at [different facility] as well—it’s a different feeling? S: Right. It’s like one step down. It’s a little more dehumanizing. You’re number 75. Um, there um, you know, I mean, I understand it, it’s just, it just ah, all taken all together the whole experience is dehumanizing. You’re treated like cattle. They don’t care about you. All they care about is you taking a pill. You giving the blood. And you making as little noise as possible.* 08-28

*I: Was it an issue for you, being called by a number? S: No, no. Not at all…They’re terribly nice. They’re really nice. I didn’t mind. I thought the number system was good. I really did.* 07-12

Personal interactions with staff, in contrast, made subjects feel respected and valued as individuals.

*There’s one woman, she was more like a, not a coordinator, but I think she’s like a, supervisor. Like a nurse/technician. And one time she said [in a whisper] “I like her”—about ME—and I said why? She said, because, you have your own mind… I thought OK, it’s nice to hear that from someone whose actually there.*
So, again, I like the older ones because they know I’m not some sort of—yah.” 08-24

Some subjects make a point of interacting with staff to personalize the experience. In some cases interaction may reflect subjects’ normal behaviour in a social situation.

I have experience, they like me, they’ve known me for a long time. I go there, they say “Hi [subject name], how you doing?”. As soon as I walk in there they know me. They respect me and I respect them. So I try to get along and I talk. I talk to people like that...So it’s mutual respect. 08-18

Subjects may also use social interaction more deliberately as a strategy to remind staff that they are individual persons with feelings and not merely bodies.

S: And then a lot of the guys won’t even look at you and I’ll be like “HI!”
I: You mean they don’t look at you when they’re taking you’re blood?
S: Right. And I’ll be like “hi!” Cause I’m like, remember, I’m a person you’re attacking with a needle here.
I: Really? Wow!
S: Yah, so I’ll make a point of saying HI. 08-24

8.2.2.2 Recognizing Subjects as Capable

Closely related to the concept of individuality is the importance to subjects of being recognized as a capable adult. Again, the importance of this issue is illustrated most clearly by incidents where subjects are treated as incapable. A relatively common complaint was being scolded or talked down to—being treated like a child.

…and you know when they just TREAT you—basically when I first read the sheet that they gave you before you come in, basically they treat you like misbehaving grade sixes. So how do you—when you set it up like this, how do you expect people to respond in a positive way? 08-24

Staff also failed to recognize subject capability when they ignored subject suggestions or requests regarding their blood sampling.

S: But it was painful…I just tell ’em "shallow veins, don’t go in deep”. When they go in deep it hurts.
I: Do they listen to you when you say that?
S: You know, it's like, funny. Some of them do and some of them don't. They think you're telling them something. And I'm just trying to help so I don't feel pain. Some of them think "Ah, you're telling ME? This is my job." They get like big nosed. So it depends on the individual. 08-18

On the other hand, subjects appreciated when their opinions or suggestions were taken into consideration.

Well they have a, just like a, a suggestion box. So you, like, I think the main problem was the food. That was the main thing. And the suggestions that we did, they followed up on them. And if you have a complaint with, like a staff member or whatever, it's OK, to say this was this and that. You're not trying to, you know, get somebody fired or anything, you're just making a suggestion. But, they really catered to the subjects. 08-20

Recognizing subjects as capable means acknowledging that they have more to offer than their physical body. This form of respect is important on a psycho-social level, but also has practical benefit. By recognizing, for example, subject expertise regarding their own bodies and taking into account their feedback, staff can alter their practice to reduce the burdens of participation.

8.2.2.3 Reducing Unnecessary Constraints
In an examination of respect as it relates to palliative care, Woods (141) has argued that respect included reduction of constraints to allow patients to make their own determinations of what is in their best interests. In this study, healthy subjects associated respect with a reduction in unnecessary constraints. Reduction in unnecessary constraints means that the restrictions and requirements placed on subjects are minimized to the extent required by the study. Constraints experienced by healthy subjects during participation are often necessitated by the study requirements. In some cases, however, subjects felt that they were unnecessarily constrained by research staff. In these situations, individual staff members were seen as abusing their power, by arbitrarily imposing unnecessary restrictions or by enforcing rules too stringently. Subjects interpreted seemingly unnecessary strictness as unjustified and felt such treatment was
disrespectful. Facilities or staff members who permitted some liberties, on the other hand, were seen as more respectful.

But with [facility name], it is probably the most liberal...so I think they develop a, like room for a—I felt like I was respected and I didn’t feel that, pressure, um...They don’t have uniforms. They don’t, close ah, clinic. Because some other places...Frequently they close the bunk room, where you keep your stuff, like you need to brush your teeth or something. And they keep people all concentrated in one small area of the lounge. And then you have to go find them, and beg them sometimes to open the bunk room and get your things. So, this is like a small things but they get ah, not only annoying—I don’t know if that is the right word, but they get unnecessary. And, sometimes it shows derogatory. 08-26

It is easy to see the inconvenience or burden created by excessive strictness. Restrictions come between a person and what they want. Why subjects find excessive strictness disrespectful or derogatory, however, requires more interpretation. The reference above to having to “beg” for access to one’s belongings emphasizes the power imbalance and that subjects are at the mercy of or under the control of the research staff. When this is required by the protocol, it is not seen as disrespectful, because it is not personal—the purpose is to fulfill an objective scientific requirement. When restrictions are imposed unnecessarily, they are experienced as personal. At best unnecessary restrictions suggest to subjects that they are not valued enough to have their interests taken into account where possible, and at worst they seem to have the object of deliberately keeping the subject down as an end in itself.

8.2.2.4 Fair Compensation
Although fairness is conceptualized in ethics as part of justice, for healthy subjects the concept of fairness also seems to be related to respect. The issue of fairness arises for subjects who feel that the payment for study participation is not a reasonable exchange for their contribution as a participant. Fairness is linked to respect, because unfair compensation is seen as just one more way that the research company undervalues research subjects.

cause you know I—you could offer 10 thousand dollars a study, you’re still not going to get any Bay St. professional people who are going to do it. Because you
know they’re gonna say, well it’s attractive money, but I’m not gonna risk my health. These people who are doing it now, all they have is their bodies, essentially. So ah, they will offer themselves up very cheaply, and it’s heartbreaking, and the testing companies, I think, use it to their advantage. I don’t think they pay as well as they could. You know they treat us—when you go to a place and they treat you badly, I mean the tone, the attitude, the atmosphere, it’s very clear, you know. 08-28

Because you know what—it’s a compromise and a sacrifice as far as I’m concerned. And so I would like to be fiscally rewarded in a way that feels fair. Would I feel as resentful of the treatment if I’m being paid more?—I don’t know. Maybe, because you’re still gonna feel like a number, but maybe not so much, cause for five thousand dollars you want to give me attitude and not enough blankets? OK! 08-24

For these subjects the perceived low pay is just one more manifestation of lack of respect for their worth.

Lack of respect increases the burden of participation for healthy subjects. In the absence of respect they feel dehumanized, oppressed and unappreciated. The imbalance of power and deprivation of control inherent in the research situation are emphasized. Finding personal control through accepting, rationalizing risk and emphasizing autonomy become more difficult where subjects feel disrespected, and the stigma associated with participation is increased.

S: So it’s just ah, yah. I think I feel like, you’re the, you know, the unwanted stepchild. You know you’ve got the crappy equipment, the crappy food. It’s cold. They don’t care. They’re more put into to keeping things from you. Like blankets—than actually making sure that—you know what? You’re a guest. “Without you here we wouldn’t have a job. Let’s try to make it a little more comfortable.”
I: Yah. So it’s more like you’re a nuisance than—?
S: Exactly! They just want to get your blood and then after that—you know. 08-24

8.2.3 Impact of Feeling Valued on Participation
Healthy subjects feel valued when they are cared for and respected. Feeling valued decreases the burden of participation by helping subjects feel at ease in the research
environment. Feeling valued means that individual needs are given consideration. Feeling valued also enhances finding personal control, as subjects are given opportunities to promote their best interests directly. Moreover when subjects feel valued, finding control through cognitive mechanisms is facilitated.

You know, they cater so much to the subjects, cause, you know—other places it’s like, ‘we need THEM’ kind of situation. But, this one at [facility name], it’s like “we need YOU”, so they makes the subjects, like, I guess empowered or something. 08-20

S: They acknowledge that, hey, I know it’s cold in here. Here’s a blanket. So you can sit in a chair and have a blanket. You know. Do you want some more water? Are you OK? How do you feel? Here comes lunch! And lunch is some great big, you know, like really good food. Wraps, with chicken and stuff like that.
I: Yah. It seems to be quite a range from different places.
S: Yah. Wholesome meals. Um, You know I found the people to be very friendly! You know, not like—do this, do that. They talk to you like you’re a human being. You’re not an animal. You know, and that sort of thing. So yah, I feel that they look after you that way.
I: Yah. And, this is maybe, kind of hard to think about, but—how does that, does it make you feel—?
S: It makes me feel important. It does. It makes me feel like I’m of VALUE to them. Yah. That’s what it makes me feel like.
I: And does that affect in any way how you feel about your safety while you’re in there, or anything like that?
S: It makes me feel more confident. That everything’s going fine. It does. Cause that goes hand in hand with everything else, you know. Um, so yah, like, you know, like yah, I don’t have any worries, like, when I’m in there, like what’s gonna happen and stuff. Because they’re, they’re, they talk to you like you’re a person. And they acknowledge like, you know, just the little things, like you’re cold. Yah, you know. So I think when they acknowledge little things like you’re cold, well they acknowledge and they KNOW, about the bigger picture, the bigger things. 08-25

8.3 Trust

In this study trust was seen to have a significant effect on the experience of participation as a healthy subject. As the degree of trust increases, participation becomes easier. Subjects expressed varying degrees of trust. Most subjects expressed general trust in the research enterprise, but were wary or distrustful of specific facilities. A few subjects were less trusting or even untrusting; they participated reluctantly. For two subjects, their
distrust in the commercial research enterprise resulted in their declining participation. For one subject this was based on a bad first experience, and for another subject this was based on assumptions about commercial research facilities. This section will describe the nature of trust for healthy subjects in phase I drug trials, the basis of that trust, and the impact of trust or distrust on the research participation experience.

8.3.1 The Nature of Trust for Healthy Subjects

While there are many definitions for the concept of trust, it is generally accepted that trust involves “positive expectations and the willingness to become vulnerable” (142). In this study, trust was expressed regarding personal safety. Subjects trusted that they would not be exposed to unreasonable or excessive risks because some other entity (the researchers/the facility/regulators/society) will not permit that. This is a vague notion, with actual level of acceptable risk not specified.

_They're not gonna give me something and then I grow tumours. You know what I mean?_ 08-25

The existence of trust allows subjects to feel generally safe about participation. There is trust that the information provided by researchers will be truthful and complete, and trust in the professionalism of the staff to have the knowledge, ability and responsibility to safeguard their health and to look after them if something goes wrong.

Subjects expressed both concrete and abstract forms of trust. Concrete trust is trust based on evidence acquired through personal experience, whereas abstract trust reflects assumptions based on the status of the trusted party (143). In the case of concrete trust, subjects used a number of criteria to determine trustworthiness. Subjects also appeared, however, to have abstract trust in the study staff because they were doctors and nurses, and in the research enterprise, because the research had been approved by various regulatory bodies.
8.3.1.1 The Basis of Concrete Trust

Concrete trust was enhanced or reduced, based on subjects’ assessments of their interactions with the research staff, and their reactions to the research environment. Trust is enhanced when the staff and facilities are perceived as professional, when sufficient information is provided, and when subjects feel valued by the staff and the facility.

8.3.1.1.1 Professionalism

The assessment of staff and facilities as professional is based on a broad list of criteria. Staff are judged as more professional when they appear knowledgeable, confident, skillful (for example when taking blood samples), and are friendly but focused on their tasks. When staff seem professional, subjects feel their safety will be protected.

*I mean you still feel safe, you know. Because I just think maybe the staff is more qualified or maybe they have more experience, or something—I’m trying to think of the best way to explain it. Like they have a lady down there who used to work at [specialized medical facility], so for like 20, 25 years she was there, and she worked with drug addicts, and alcoholics, and stuff like that, and she’s fantastic. She just really knows how to handle people...I was there once, the one I just did, and the drug itself, it’s a sedative, so you can get high off it, basically. And so when you think you’re gonna be in a room of people that you don’t know taking a drug that you can get high on, you do—having someone there that seems in control and confident in themselves helps you mentally, I think. 07-01

Facilities are judged as more professional if they are clean, organized, and have some degree of strictness. Impressions about professionalism in one aspect of facility operation are generally assumed to carry over to other aspects of operation. Subjects reason that if a facility cannot adequately manage the basic functions, such as cleanliness, it cannot be trusted with more important study procedures that may threaten safety.

[It was dingy, like this is a place where there’s needles, there’s blood, there’s my personal health, there’s random medications, stuff like that. And ya, you know, if the place doesn’t present itself well, then I’m going to be, like that’s going to you know, give me a negative impression. And, like that plays into any aspect of it, the phone manner of the people I talk to when I call up, the way that like I get treated during the physical, the way people seem to be interacting like, professionally, you know these are all things I feel definitely play into the perception some where, like in the case of this one particular place, like I never really kept calling them up and seeing what they had cause like the studies they...
had didn’t seem very good and the place when I went didn’t really leave me with a very good impression. Whereas other places, like ah, looked really clean, really bright, very well organized, like one large central room for doing physicals and you know, the organization is sort of reflective on like the level of professionalism. 07-03

Although subjects interpret some flexibility with the rules as respectful and caring, an overly casual environment is seen as potentially sloppy and therefore unsafe. Strictness applied to screening criteria in some cases enhances subject trust that they will only be included in studies that are safe for them.

Yah, that’s why they told me I wasn’t qualified anymore. They were concerned about my health. So I um, so I just left. And I think, my impression was that um—you know they follow strict guidelines about who they take, and they’re very cautious and they try to be very um, they trying to be safe, trying to take safety precautions, you know, for the subject’s health. 07-13

8.3.1.1.2 Information
The provision of detailed study information enhanced subject trust in the research staff and facilities. Although there is empirical evidence that lengthy consent forms reduce understanding (144,145) and subjects themselves sometimes complained about the lengthy informed consent process, long consent forms, and detailed risk statements also enhanced trust for some subjects.

Um, the more, the larger facilities, like [facility name], they are a lot more professional. They go through everything. They tell you what you have to do, what the procedure is. You know, you come into the lab, you gotta do this, this and this. You have to eat this, this and this. They show you this huge consent form-23 pages. You know, they're professional. It just seems like a better outfit. But, places like [another facility], yah, I thought I was gonna leave without a kidney...And um, they didn't explain—I actually walked out on a study...Yah, they just didn't explain the procedures to me. 08-23

Detailed disclosure is seen as having nothing to hide. It also allows subjects to verify the information against other sources.
S: You know they do give you a lot more—I was surprised, I don't think they have to give you THAT much information. So I think they do give you quite a bit, so if you haven't found anything more on the web—
I: So that's reassuring?
S: YAH. Yes. 08-24

No, I trust them, cause they have a strict protocol and they have, like, a lot of the time they have the schedule written down around the place, like on boards. And you can check see when your dosage is and you can go check see when, you know, check when’s your next blood draw or whatever. So it’s really good cause you can also—like even if they’ve made a mistake, which I haven’t encountered yet—but there’s always a schedule for you to also check and see. 07-06

Most subjects trusted the veracity of information provided. In some cases this trust was present at the outset, but for other subjects, trust developed after one or more verifications from outside sources such as family doctor, family members with medical expertise or the internet.

8.3.1.1.3 Feeling Valued
The concept of feeling valued from the perspective of healthy subjects was described above. Feeling valued by research staff also promotes trust. Subjects expect that staff who respect and care about a subject will look after their welfare. Where subjects do not feel valued, they do not have trust.

It’s a, I would say it’s a cold kind of running so the only motivation to go there [commercial research facility] is cash. Otherwise, you don’t get anything out of it. They don’t really care who you are, what you do. They just want you to put the drug in you, see what happens and get you out of there…it’s not respectful in one sense, and it doesn’t give you a sense of trust in them. Because when you go for experiments it’s trust that you build with your subjects that this is a safe procedure, we will take care of you if anything goes wrong, don’t worry about it, we’ll make sure you get home safely. That package isn’t there. 07-10

When framed in this way, it seems that feeling valued is a necessary component of trust. An exception to this is when trust is based on the cynical view that researchers protect subject safety to avoid being sued. In this latter case, however, it could be said that the trust is not in the researcher, but in protective regulations, which reflect societal valuing
of research subjects. Trust, on the other hand, is not necessarily the outcome of feeling valued. It may be possible, for example, to feel valued and not have trust if a staff member is seen as kind but incompetent.

Trust is enhanced when research staff show concern about a subject’s health beyond it’s impact on the research study, as demonstrated in the following excerpt.

*S: I saw the doctor, and he told me that the results of my blood—the hemoglobin was too low, and they were worried because they were keeping track of my meals, how much I was eating, right. And they said I wasn’t getting enough calories... So the doctor told me that it wasn’t healthy and he told me the number of calories within the normal range I should be eating... he also made suggestions about what I should be eating. I should get more protein in my system, and he just explained to me about nutrition.

*I: For the study, or for your own health in general?

*S: Just for my own health, right... And he suggested that I should see my doctor, right... And then I was sent home and they told me to come back in 30 days, just to do a follow-up, to see how I was doing. So after 30 days I went back, and um I gave them my blood, and I saw the doctor again. It was a different doctor. And he just suggested, he asked me if I you know, had any eating disorders, things like that. And he also told me that I should also try to, I don’t know, he explained to me something about osteoporosis and how I should get more calcium in my bones, and he explained to me about that.

*I: This was the study doctor?

*S: Yah. So um, and he seemed very knowledgeable too. So I felt like they actually took precautions. They were actually cautious about my own health there, and they were worried...I feel safe because they just want to make sure that I, that I’m healthy. 07-13

Another subject described how his trust is increased when he sees staff put his health before their interest in completing the study.

*I: I woke up and they were taking my blood pressure, doing my ECGs, and all that, and it was too low. Like I’m healthy, so it was really low, and that time of the morning—I’m like, come on. So, what they did, is said you can’t be in the study. So they removed me... The reason why I do trust is because of those situations at [facility name]. Like, how do I know if my heart rate’s too low, so I shouldn’t take the drug. They’ve got me. They’ve got a guy that’s gonna do it, and they’ve got obligations to the sponsor but they’re still willing to pull me out for my own safety. 07-01
The focus on subject welfare instead of or in spite of the interests of the study makes subjects feel valued as persons beyond their utility as research subjects, and confirms their trust that the research staff will protect their safety. These experiences also reinforce the role of the researcher as doctor. As described below, this may further enhance trust, as physicians are often afforded some degree of trust simply on the basis of their position in society.

### 8.3.1.2 Basis of Abstract Trust

Some degree of trust appeared to be based on assumptions about the general trustworthiness of doctors, nurses and the research enterprise. For some subjects, white lab coats inspired trust that the staff were qualified to protect their safety.

> ...there are so many people around wearing lab coats. You just get a feeling it’s OK. You’re safe. Like there’s enough people here that are qualified to do something if something does happen. You know what I mean. Like say if it was 2 lab coats and a bunch of guys running around in blue jeans, then you probably would be—I don’t know—. 07-01

Some instances of apparent concrete trust seemed to be predicated on subjects already having abstract trust in the study doctors.

\[ I: \text{Did you feel like you trust them?}\]
\[ S: \text{Yes, I would say trust is huge for someone going into a study. Yah, I would say I had a certain amount of trust in the doctors. In the people I was dealing with, cause at the screening I did ask them if the people that are gonna be working on me are professionals or trainees—people in training. So, that was a big issue for me. And when they told me it was professionals—that’s what people were telling me over and over, that made me feel more comfortable. 07-11} \]

Although the reassurance required by this subject could be interpreted as an instance of concrete trust that had to be earned, his acceptance of the study doctor’s word required some level of baseline trust. This subject’s abstract trust was also supported by interactions with the staff promoting the development of concrete trust.
I: Mm hmm. And then did that seem to follow—did you feel that they were professional? Did you get what they promised?
S: Yah, I did.
I: OK. You said it was important to trust. Anything else about what they did that made you feel that you could trust them?
S: Um, just the way, just the way that they were handling me. It was better treatment than I’ve gotten before. Not with clinical trials but with other places, like what happens in hospitals, things like that. The treatment was much better. The way that they handled my hand when they were giving the injection. They did it with care, and they were so soft, you know. So that made me have a lot of trust in them. 07-11

Thus subjects may enter research participation with a baseline degree of abstract trust that is subject to confirmation or refutation based on subsequent experience. The following excerpt is an example of a subject whose initial abstract trust was changed to concrete distrust after a bad experience during blood sampling.

Well I assumed that it was gonna be OK, that it was not gonna be bad…but I didn’t expect it to be—you would be just left out. They would just throw you out if something was wrong. They panicked. You know, you don’t want them to panic if something goes wrong to you. That’s a bad sign…It tells me that they don’t know what they’re doing… And ah, so I think that’s more the mistrust than how they handle an adverse event. It kind of puts you off from them, for—I would say forever. 07-10

McDonald and colleagues used the term “dynamic trust” to describe trust that must be built and can easily be broken, which they observed in their study of trust among subjects taking part in various biomedical, behavioural and public health studies (143). In this current study, healthy subjects appear to enter the research experience with a tentative abstract trust, which they build upon, and sometimes break, through information gathering and interaction with research staff. The initial baseline trust observed in this study may reflect both societal expectations about doctors and nurses as trustworthy, and the desire to frame the experience in a positive light, to make participation work.

Some subjects placed trust in the belief that there was some type of regulation or oversight of the research. This seems to be an abstract type of trust, because it was not
based on a thorough understanding of research governance, but on general assumptions that research activities must be regulated by someone.

I assumed that there was somebody else who was there, acting on behalf of the subjects-their best interests as well as protecting the research company. I assumed it but I haven't thought of it, about what's happening. 07-06

I don't worry about it. I just figure that-we're not living in the 1700s. People know what they're doing. I mean, I assume. I'm putting my trust in them. They know. Maybe I'm naive and that sort of thing, but I think they know what they're doing. I trust them. 08-21

8.3.2 The Impact of Trust on the Participation Experience
Having trust in the research staff, research facility, and research enterprise reduces the burdens of research participation for healthy subjects. Trust promotes feelings of safety and puts subjects at ease. The start of this section noted that the concept of trust includes the willingness to become vulnerable. Thus it is typically viewed that when an individual places trust in someone or something, they are giving up control. The understanding of research participation emerging from this study, however, suggests that, like feeling valued, trust may enhance personal control by facilitating accepting, rationalizing risk and emphasizing autonomy. When there is trust, these cognitive mechanisms for finding control are supported. Moreover, trust may enhance personal control by allowing for an extension of personal control through others. The act of bestowing trust on research staff or the research enterprise remains the autonomous decision of the subject, thus is an exercise of personal control.

8.4 Framing the Process of Participation
In Chapter 6, I described how the desire to earn payment led healthy subjects to frame the process of participation as work. I also described how the financial motivation drives and shapes the various stages in the process of participation. In many ways this process resembles the process of a person looking for and completing other types of temporary employment. Research participation, however, also differs from other types of
employment, perhaps most notably because the work that subjects do is traditionally viewed as a passive allowing of their bodies to be used as objects of experimentation. Participation of healthy subjects is further distinguished from other forms of work by the impact of trust in shaping subjects’ framing of their research participation.

The description of trust in this chapter indicates that healthy subjects rely on the research staff to ensure their safety and well-being. The language used to describe research staff suggest that they are seen as health care providers.

...they’re very—it’s medical, and there are doctors and nurses. But their first concern is your health. Which should be number one, right? 08-18

Thus, while healthy subjects are aware that the purpose of their research participation is not to benefit their own health, they are still very much aware they are in a medical context and are putting their health in the hands of the staff and study doctor.

The patient-health care provider orientation seems strongest with regard to the study doctor. This may be the result of the traditional association of physicians as protectors of health rather than as researchers, but is likely reinforced by the fact that interaction between subjects and the study doctor is usually limited to pre-study screening, post-study follow-up examinations, and assessment and treatment of any adverse events arising during participation. These interactions are very much like the routine clinical interactions a patient has with their family physician. In most cases the actual research activities such as drug administration and blood sampling are handled by staff other than the study doctor, allowing preservation of the traditional image of doctor as health care provider.

The perception of an employee-employer relationship in research participation seems to be focused more on the research sponsor and the administrative staff at the research

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31 While the passive view of research participation may be the traditional view, as described in Chapter 7, the strategies subjects use to mentally and physically cope with research requirements suggests a more active view of research subjects.
facility. Subjects know that the research is being carried out on behalf of the sponsor, as illustrated by references to the staff just doing their job and having to follow the protocol as required by the sponsor. At the research facility it is the administrative staff who schedule appointments and hand out the payments.

It has been previously suggested that a labour model may best describe the healthy subject-researcher relationship, rather than the patient-doctor model used to describe clinical research involving patients who may benefit from participation. The theory of making participation work developed here supports, in part, the labour model (76). The importance of caring and trust, however, suggest a more complex model for research with healthy subjects, involving a labour type relationship with the sponsor and possibly the research facility as an organization, and a health care relationship with the study doctor, and possibly a mixed role for study nurses and other staff.

8.5 Feeling Valued and Trust Summary

In this chapter I described the meaning of feeling valued and of trust for healthy subjects in phase I drug trials. I also described how feeling valued and trust affect the experience of research participation. Finally, in this chapter I suggest that, although subjects frame participation as work, the relationship with study doctors and to some extent nurses, is more like patient-health care provider than employee-employer. In Chapter 9, the final chapter of this thesis, I will discuss the contributions of these empirical findings to current knowledge about the participation of healthy subjects in phase I drug trials at commercial research facilities. I will also discuss the ethical implications of these findings, focussing on the issues raised in Chapter 3.
9 Discussion: Making Participation Work—Implications for Research Ethics

9.1 Overview

In the preceding chapters I have described a grounded theory study of the experience of healthy subjects in phase I drug trials and the resulting theory of making participation work. The theory *Making Participation Work* provides an account of how healthy subjects frame their research participation as work, and the impact of this framing on their behaviour. This theory also describes net burden and finding personal control as the main factors affecting the experience of participating. Through finding personal control, subjects reduce the net burden associated with participation, making it easier. Interactions with research staff also affect the participation experience, by making subjects feel more or less valued and by building or eroding trust in the staff and the research enterprise. Most subjects trust that their participation is relatively safe. Although healthy subjects frame their participation as work, the study doctor is seen as having the role of safeguarding subject health, rather than of researcher or employer.

Consideration of the contributions or implications of research findings requires some trust that the theory presented in the previous chapters is a plausible account of the experience of healthy subjects in phase I drug trials. This question will be considered in the section below. Following that, in the remainder of this chapter I will consider the contribution of this theory to current knowledge and discuss several implications of this theory to research ethics regarding healthy subjects.

9.2 Trustworthiness of the Findings

The criterion “validity” is frequently used in quantitative research as an indicator of the degree to which an instrument or test measures what it was intended to measure. In order, however, to ask the question of validity, one must start with knowing what one is looking for. In other words, the thing being measured or assessed must be defined externally to
the findings, so that there is something against which to compare the findings. In the case of qualitative research examining experience, the subject, rather than the researcher, defines the phenomenon. “The truth value of a qualitative investigation generally resides in the discovery of human phenomena or experiences as they are lived and perceived by subjects, rather than in verification of a priori conceptions of those experiences (146). Thus it is common in qualitative research to speak of trustworthiness of the findings, rather than validity.

Establishment of trustworthiness, however, is not a simple matter. A review of the literature regarding methodological rigour in qualitative research revealed a broad range of opinion (146-151). A major challenge to the establishment of generally applicable criteria for judging quality is the fact that qualitative research is not a unified field, with a large variety of methodological approaches classified as “qualitative” (151, 148). Some researchers suggest that it is inappropriate to try to develop general criteria to assess quality when there is no “uniform body of theory, methodology, or method that can collectively be described as qualitative research” (148). Others suggest that some generalized criteria might be developed, although there is no consensus on what they should be (148). Sandelowski suggests that “Trustworthiness becomes a matter of persuasion whereby the scientist is viewed as having made those practices visible and, therefore, auditable” (147).

Mays and Pope suggest a number of criteria which seem consistent with Sandelowski’s focus on persuasion and auditability, namely: clear exposition of methods of data collection and analysis, reflexivity, attention to negative cases, fair dealing, triangulation, and respondent validation (149). The trustworthiness of this empirical study will be considered below in terms of each of these criteria. In this section I will also consider the issue of generalizability.

9.2.1 Clear exposition of methods of data collection and analysis
This criterion refers to provision of adequate detail regarding the process of data collection and analysis, including providing “sufficient data to allow the reader to judge
whether the interpretation proffered is adequately supported by the data.” (149) The process of data collection and analysis for the current empirical research is described in detail in the methods section, Chapter 5. Numerous quotes are included to support the development of the theory, described in Chapters 6 through 8.

9.2.2 Reflexivity
Reflexivity refers to consideration of the ways that the researcher shaped the findings. Chapter 5 of this thesis provides an account of my prior assumptions about phase I research with healthy subjects and on the role of the literature in framing the research question and the interpretation of the data.

9.2.3 Attention to Negative Cases
Seeking out cases or incidents that seem to contradict the emerging explanation of a phenomenon has been suggested as a way to increase the quality of a developing theory (149). This criterion contributes to persuasiveness because it tests the theory as well as aiding in its development. A grounded theory that accounts for so-called negative cases shows it is robust enough to explain extreme variation in the phenomenon. The grounded theory *Making Participation Work* accounted for the behaviour of subjects who were very satisfied with their experience, as well as those who were very dissatisfied, including one subject who decided against further participation and several reluctant subjects who participate despite their dissatisfaction. The ability of the theory to hold up for such divergent cases hopefully persuades the reader that the theory will also be relevant to other cases.

9.2.4 Fair Dealing
Fair dealing means ensuring that the research includes a wide range of different perspectives (149)32. As described in the section Theoretical Sampling, Chapter 5, an effort was made to include a variety of perspectives, guided by the principle of theoretical

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32 Although it may be questioned whether this criterion is applicable to certain qualitative methods that use in-depth studies of fewer cases, such as phenomenology, it is applicable to the grounded theory method used in this study.
sampling. In addition to the inclusion of a range of attitudes about participation described above, the database from which my grounded theory was developed included the perspectives of subjects from a wide range of income levels, ages, and ethnic backgrounds. The financial reasons for participation ranged from desperation to buying “extras” such as luxury items or travel. The frequency of participation ranged from as often as possible, to once or twice a year, to once only. Moreover, the subjects held a range of attitudes about risk, study burdens and the adequacy of the payment.

Despite the wide variety of perspectives described above, as described in Chapter 5, there were limitations in the sampling and this sample is not meant to be construed as a “representative sample” of healthy subjects. For example, although the majority of subjects in this study find participation to be a relatively positive experience, these findings could not support any comment regarding the prevalence of positive experiences in a different sample of healthy subjects. As described in Chapter 5, the finding of mostly positive experiences was somewhat of a surprise, as it was anticipated that subjects with “an axe to grind” might be more likely to want to talk about their experience. Possible reasons for the higher prevalence of positive experiences in this study are: 1) Most subjects who have had a bad experience do not participate again, and therefore do not read the websites where I posted my advertisements; 2) It is possible that some subject characteristics that were selected against by my recruitment methods (e.g. non-English speaking, not using the internet), may also be associated with decreased ability to find personal control or increases perception of burden, leading to decreased likelihood of including subjects who had a bad experience; and 3) It is possible that, contrary to my expectations, those who had a negative experience were less likely to want to be in my study. It should be noted that in the current study, having a positive experience was not found to be associated with any particular demographic variables.

9.2.5 Triangulation
Triangulation refers to using two or more different approaches to answer the research question. This may involve different methods for data collection (e.g., observation and interviews), different data sources (e.g., interviewing different groups), different research
methods (149), or different researchers (150). Only one research method was used. Interviews with other interest groups were not included, as the purpose of the research was to examine the perspective of healthy subjects. As access to the study facilities was not permitted (see Chapter 5), data collection through observation was not possible. Several alternative information sources consulted during the data collection and analysis, however, provided a quasi-triangulation. These alternative sources were first person accounts of healthy subjects, published as “blogs” on the internet, web sites of phase I research facilities, web sites directed at healthy subjects, and a visit to a phase I research facility.

Blogs were reviewed during the data collection and analysis period. These blogs were not included in the formal analysis (i.e. subject to thorough coding and incorporation of resulting codes into the emerging theory) for several reasons. The blogs generally included little or no demographic information about subjects, and were often unclear about the nature of research participation, such as whether the study was a phase I drug trial, and whether participation took place at a commercial research facility or an institutional setting. In addition, content of the blogs was limited to what the authors chose to write about, including digressions about friends or work and detailed description of the meals, or particular fellow subjects. I could not ask about topics of relevance to my developing theory, ask for clarification or request elaboration on topics raised by the writer.

Given these significant limitations, the blogs were not considered as “data sources” per se, but were read to enhance my theoretical sensitivity. Theoretical sensitivity refers to “the ability to recognize what is important in data and to give it meaning” (109). For example, in her blog about participation in a 23-day drug interaction study, a healthy subject expressed her frustration that, three days before the scheduled check-in, she had not yet been told whether or not she had qualified to take part. “I am getting a bit panicky…If I’m in, I need to do some shopping and pack and stop eating chocolate and other products with caffeine. Not knowing makes me feel out of control.” (152) It was this statement that led me to identify the concept of personal control as important to healthy
subjects. Once aware of personal control, it became a sensitizing concept that I was able to recognize repeatedly as I analyzed subject accounts of their experiences.

Similarly, I reviewed the content of the web sites of the research facilities in the Greater Toronto Area, where most of the healthy subjects in my study had participated. I also reviewed two web sites directed at healthy subjects—Guinea Pig Get Paid (20) and Guinea Pig Zero (153). Finally, in my role as an REB member I toured one of the phase I commercial research facilities represented in my sample. These various sources provided me with a better understanding of the context in which the research took place. Although none were used as data in the same way as the interviews were, to the extent that they enhanced my understanding of the context in which healthy subjects participate, they were consistent with the theory of Making Participation Work that was developed from the interviews.

9.2.6 Respondent Validation

Also known as “member checking”, respondent validation refers to bringing the research findings back to the research subjects to see if the findings correspond with the subjects’ experiences. The usefulness of respondent validation is controversial (149). The major criticism of respondent validation as a criterion for trustworthiness in grounded theory, is that the developed theory reflects a conceptualization or abstraction based on many experiences, and an individual subject may therefore not recognize their experiences within this overall theory. In addition, a grounded theory represents the researcher’s interpretation of what is going on in the data, and is not intended as a forum for the subjects’ voice regarding a phenomenon. It is quite possible that a respondent in a grounded theory study may not agree with the researcher’s interpretation, for example if the finding is unflattering, or difficult to accept. Thus, lack of subject agreement does not necessarily render the findings untrustworthy or invalid (115).

In contrast to respondent validation of a final theory, asking subjects for their response to developing concepts can be useful during data collection to stimulate discussion, leading to a richer understanding of a concept. I used this approach throughout the interview.
process. As new concepts emerged in my analysis, I introduced them as topics during the next interview. For example, asking subjects about things they might do to make participation better elicited a variety of strategies such as use of supplements to stay healthy and knowing which staff member to approach with problems. Subjects were also probed about the impact of these strategies on their experiences. Subjects were never asked explicitly about “finding personal control”, but the less abstract lines of questioning contributed to the development of this concept.

9.2.7 Generalizability

Generalizability is a term usually associated with quantitative research, and refers to the degree to which study findings are considered to be applicable to a wider population. Generalizability is achieved by ensuring that, as much as possible, the study sample is representative of a larger population. In quantitative research, representativeness is achieved through careful inclusion and exclusion criteria and sampling strategies such as randomization.

Grounded Theory methods, on the other hand, use theoretical sampling, with the objective of fleshing out the developing theory, rather than maximizing the degree to which the study sample is representative of a particular population. Strauss and Corbin have described this sampling goal as a concern with “representativeness of concepts” (109) rather than of populations. To achieve this representativeness of concepts, the grounded theorist looks for varying instances of a given concept, to produce a dense description of that concept, and how it varies under different conditions. The goal is not to “generalize as such, but to specify… the conditions under which our phenomena exist, the action/interaction that pertains to them, and the associated outcomes or consequences” (109). Grounded theories then, can be considered generalizable not to populations but to conditions, as specified within the theory. Where conditions change, the theory must be modified to accommodate the new condition.

The grounded theory Making Participation Work accounts for a variety of conditions relevant to healthy subjects in phase I drug trials at commercial research facilities as
described above and in Chapter 5. It is expected that the theory will therefore apply to other instances of research with healthy subjects where the conditions are similar; that is, paid participation for relatively burdensome non-therapeutic research. As was described in Chapter 6, this study involved a highly educated group of subjects. Empirical examination would be needed to determine how the concepts forming the theory *Making Participation Work* would vary in different conditions, such as a lower education level of subjects. As representativeness relates to concepts, however, and not populations, it is expected that where there is the general condition of being paid to take part in burdensome non-therapeutic research, the theory will apply. Additional variations in conditions may require further specification of concepts, but that would be an enrichment of the concept, rather than an indictment of the original theory.

Certain parts of the theory may also apply in other circumstances where similar conditions are encountered. For example, as described in Chapter 7, finding personal control is a response to the condition of deprivation of control, and it is expected that some variation of finding personal control will be applicable to other situations, such as hospitalization or imprisonment, where people feel deprived of control.

The remainder of this chapter discusses the research findings. Key findings are summarized in section 9.3. Section 9.4 examines the contribution of the findings to current knowledge and section 9.5 discusses the ethical implications arising from this research.

### 9.3 Summary of Findings

In Chapters 6 through 8 I presented a grounded theory, *Making Participation Work*, that describes the perspectives and experiences of healthy subjects in phase I drug trials at commercial research facilities. Some of the key findings are listed below. These will be discussed further in subsequent sections.
Healthy subjects are motivated to participate in phase I drug trials at commercial research facilities to earn money. This motivation results in a framing of the participation process as work, and shapes behaviour regarding participation.

The decision to be a healthy subject is usually made separately from and in advance of the decision to take part in a particular study.

Healthy subjects seek out and select suitable studies using personal criteria. Decisions about specific studies are made using a burden-pay calculus.

The experience of being a healthy subject varies among subjects, from very easy to very hard. The main factors determining whether participation is easy or hard is the perceived net burden associated with participation and the degree to which subjects are able to find personal control during participation.

Experience is also affected by whether subjects feel valued (respected and cared for) by research staff, and whether they have trust in the research enterprise.

Most subjects who participate in more than one study trust that they will be safe. This trust is associated with a view of the study doctor’s role as protecting subject health, rather than carrying out the research.

9.4 Contribution to current knowledge

Current empirical data regarding the experience of healthy subjects is limited mostly to survey data. A few qualitative studies have been carried out, but have either not focused on the general experience of participation (83) or have examined the experience in a context other than phase I drug trials (108,154). Abadie’s ethnographic examination of research participation among healthy subjects did examine subject experience to some extent, but the focus was on the social/economic/political context of research participation and the study population was a single social group (12). This thesis is the first research to produce an integrated, empirically grounded theory about the experience of research participation among a heterogeneous group of healthy subjects in phase I drug trials at CROs.

A key contribution to current knowledge is the finding that for all healthy subjects who do more than one study, and for most subjects even in their initial study, the motivation to participate is to earn money. As described in Chapter 4, previous empirical research has
suggested payment is an important motivator, or even the most important motivator for participation. The findings from this study, however, suggest that earning payment is the motivator. Other factors, such as interest or contributing to science, may make participation more palatable, but they are not what drives a person to become a healthy subject\(^{33}\). This is important as the identification of participation as an earning opportunity is what shapes the process of participation.

A number of commentators have suggested that payment “nullifies our appreciation” for research subjects (155) by eliminating the social good that results from research participation as a “gift” (60,155). Payment is seen as a commodification of research participation and a threat to the integrity of medicine (67,155). To avoid these harms it has been suggested that researchers find ways other than financial inducement to engage volunteers and show appreciation for their contribution (156). While the healthy subjects in this study did find that caring and respectful treatment enhance their experience, the theory of making participation work described in this thesis does not support the suggestion that subjects would be motivated by, or satisfied with, only non-financial shows of appreciation.

The process of participation describes how healthy subjects frame participation, from the initial opportunity identification, to opportunity shopping and the use of a burden-pay calculus to select suitable studies, culminating in getting through participation. The process of participation described here provides a unique conceptualization of the phases of research participation. The phases of opportunity identification and opportunity shopping do not fit current assumptions about research decision making as related to a particular study and originating with the invitation to a given study.

Another contribution of this research is the development of the concepts of net burden and finding personal control. These findings expand on earlier empirical data regarding

\(^{33}\) As noted in Chapter 6, a few individuals appeared to be motivated by interest or curiosity the first time they participated, but this was not a reason to continue participation in subsequent studies.
the importance of environmental factors (66) and social interactions (108) to the experience of research participation in healthy subjects. The concept of net burden describes what burdens have the greatest impact on healthy subjects and how these burdens affect both decision making and the experience during participation. Deprivation of control, with consequences of boredom, loss of privacy, and discomfort, emerged as one of the significant factors affecting the participation experience. The burden resulting from deprivation of control has received little prior attention with respect to healthy subjects.

Subjects in this study expressed a range of attitudes about participation, from finding it “easy money” to “very, very, hard”. Previous surveys of healthy subjects have identified a number of factors that impact the experience of participation, but provided no information regarding how these factors affect the experience. The theory of making participation work offers a more in-depth account of some of the ways that subjects are affected by study burdens as well as by interaction with staff. Furthermore, the theory of making participation work suggests that differences in attitudes about the experience of research participation are accounted for mainly by differences in subjective response to study burdens, and that the response to burdens is determined to a great extent by the degree to which subjects find personal control over the participation experience.

The importance of finding personal control to the well-being of healthy subjects in phase I drug trials at commercial research facilities has not been raised by previous research with this study population. In previous studies, personal control has, however, been identified as important to the well-being of hospitalized patients (157,158) and fathers of very premature infants (159). As was the case with the healthy subjects in the current study, finding personal control seemed to be an important coping strategy in situations where deprivation of control was experienced.

Given the concurrent findings of personal control as important to the well-being of healthy subjects, hospitalized patients, and fathers of premature infants, it seems possible or perhaps even likely that the theory of finding personal control described in this study
will be relevant to other populations of healthy subjects, as well as patients taking part in research that offers the possibility of direct medical benefit. Moreover, the behaviour of finding control as a response to situations where there is deprivation of control may prove to be abstractable to a formal theory. Further research is required to determine the applicability of the concept of finding personal control beyond this current study.

The finding that healthy subjects have a significant impact on their experience through finding personal control suggests that subjects who have an internal locus of control are more likely find personal control and to have a better participation experience. Locus of control is a widely-studied psychological characteristic, which

> refers to the degree to which persons expect that a reinforcement or an outcome of their behavior is contingent on their own behavior or personal characteristics, versus the degree to which persons expect that the reinforcement or outcome is a function of chance, luck, or fate, or is under the control of powerful others, or is simply unpredictable. (160)

Those who put greater emphasis on the role of their own behaviour on outcomes are said to have an *internal* locus of control, while those who look to outside factors are said to have an *external* locus of control. Finding personal control as described in this study, may correlate with an internal locus of control, since subjects’ own behaviours appear to have an important impact on the nature of their experience.

Caution should be used in making this assumption, however, as empirical studies have shown that behaviour is not always associated in expected ways with measures of locus of control. In a review of studies examining the relationship between locus of control and health related behaviours, an internal locus of control often, but not always, was associated with more positive behaviours. No relationship was found, for example, between locus of control and compliance among myocardial infarction patients or plans to take future preventative precautions among patients with gonorrhea (161). Empirical research specifically examining the relationship between locus of control and behaviour among healthy subjects might provide additional insight into the psychological characteristics of healthy subjects who take part in phase I drug trials, and in considering strategies that help subjects maximize their personal control.
This study has also provided a description of feeling valued as experienced by healthy subjects in phase I drug trials. The research shows the importance of respect and caring by research staff in making healthy subjects feel valued. In medical research, the ethical principle of respect for persons is mainly expressed as respect for individual autonomy, which is operationalized through the process of informed consent. Although autonomy was important to healthy subjects in this study, respect was interpreted as being treated as an individual who had value other than being an object of research. This finding is consistent with the findings of Joffe et al, who found that for hospitalized patients, being treated with respect and dignity was of significant importance to their hospitalization experience (162). The findings in this study of healthy subjects support the argument for an expanded view of the principle of respect for persons in research and health care (162).

Some commentators have suggested that many drug trials, including phase I drug trials, are disrespectful to subjects because the research is serving the economic interests of the sponsoring company, rather than the health interests of society. Drug trials investigating “me-too” drugs so that companies can have a share in a lucrative market, and trials that serve to fill certain regulatory requirements for marketing approval, but generate no new knowledge, are criticized as having little scientific value. These studies are seen as disrespectful to subjects, who endure burden and risk not for the benefit of society, but for the financial benefit of the drug companies (12,76,163,164).

Healthy subjects in a previous study expressed cynicism about the medical benefit accruing from phase I drug trials. These subjects saw themselves as exploited by the pharmaceutical industry and used this as a justification for non-compliance, such as sneaking food when they were supposed to be fasting (12). In contrast, the healthy subjects in this thesis research study did not raise concerns about the scientific value of the research, except for the occasional comment about how various factors, such as cheating among other subjects, might compromise the study results. Issues of scientific
value did not appear to play a significant role in the decision making or behaviour of subjects.

The difference observed in subject attitude between the two studies may largely be explained by the fact that the subjects in Abadie’s study were self-identified anarchists who examined most aspects of their lives through a political lens. The subjects in my study, on the other hand, seemed to regard research mainly as it impacted them personally as an opportunity to earn money, and focused their attention on the participation experience. The lack of comment on scientific value may also indicate that subjects in this study did feel that there was societal benefit to the research. As this issue did not emerge as important to subjects, it was not pursued in the current study. Future research might directly examine what subjects think is the scientific value of the research in which they participate, and how attitudes about scientific value correlate with selection of studies and the participation experience.

This research has also contributed to an understanding of the nature of trust as expressed by healthy subjects in phase I drug trials. Subjects begin participation with some degree of abstract trust which is confirmed or refuted by interaction with staff. Subjects who choose to participate in more than one study generally trust research staff and the research enterprise to protect their safety. This finding is consistent with McDonald et al’s conceptualization of dynamic trust observed among subjects from a wide variety of research experiences (143). The finding of trust among healthy subjects, however, contrasts with reports of mistrust of the pharmaceutical industry in the general population (37), and among the group of anarchists living in the Philadelphia area (described above) who frequently participate as healthy subjects (12).

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34 A few subjects did raise concerns about fellow participants, such as whether they understood the study information sufficiently to provide a meaningful informed consent. These concerns, however, were related to the participation experience, rather than the broader social or political issues such as whose interests are served by drug trials.

35 As noted in Chapter 1, the goal of this research was to examine the participation from the perspective of the healthy subject, and to permit the subject to identify which issues were important.
The finding of trust among research subjects despite distrust in the general public may indicate the need for research subjects to have trust in order to choose to participate in a study. This may reflect the development of trust during the process of deciding to be a research subject (opportunity identification)\(^{36}\), a selection for members of the general public who do trust the pharmaceutical industry, or a difference between distrust in “big pharma” as an anonymous business entity and trust in a specific research facility or research staff. The finding of distrust among the anarchist group is not surprising, given their political beliefs, and may represent a special subgroup of healthy subjects. More research aimed at obtaining a more in-depth understanding of the nature and objects of trust among research subjects and the general population is needed to explain the various findings.

There is to my knowledge, no empirical data that specifically addresses the subject-study doctor relationship from the view of the healthy subject in drug trials. Empirical and anecdotal data on the financial motivation of healthy subjects taking part in drug trials at commercial research facilities has led to emphasis on how this research differs from clinical research involving patients, and prompted the suggestion that research involving healthy subjects might be more similar to a labour relationship. The findings from this study, however, suggest a more complex relationship.

The grounded theory accounting for the experience of healthy subjects developed in this research may provide hypotheses not only for future examination, but to suggest possible interpretations of findings from other empirical studies, such as quantitative surveys. For example, the study of highly educated healthy subjects by Fortun et al. (91), described in Chapter 3, found poor understanding of procedures and risks, but near perfect knowledge of study duration and compensation amount. The authors focused the discussion of their findings on the impact of increasingly lengthy and complex consent forms on subject understanding, and suggest the need for shorter consent forms, and other approaches to improve understanding. The results of this qualitative study, however, suggest other

\(^{36}\) Development of trust during the process of opportunity identification maybe concrete, based on learning about the research process, or may reflect a rationalization to support the desire to participate, or some combination of both.
possible interpretations of Fortun et al’s findings. The finding that, despite poor
understanding of most other information, subjects had excellent understanding of the
study duration and payment, is not surprising in light of the finding in this thesis research
that subjects are motivated almost entirely by payment, and that time and payment are
key components of the burden-pay calculus used to decide about participation.

The concept of rationalizing risk developed in this study suggests that once subjects
determine the risk to be acceptable, for many subjects, the study is classified as safe. In
the informed consent study described above, subjects may have, to a greater or lesser
extent, noted the risks described in the consent form, but, determining them to be
acceptable, may have set them aside and therefore quickly forgot the specifics. Moreover,
if subjects feel valued and have trust in the research enterprise, then detailed review of
procedures and risks may not be perceived as important to those subjects. Finally, the
concept of opportunity identification suggests that, as healthy subjects have made some
commitment to the decision to find a study before they ever see a study specific consent
form, the role of the consent form in their decision making, hence their attention to the
consent form details, may be less than expected by REBs, researchers, and policy makers.

9.4.1 Contribution to Knowledge Summary
The findings from this empirical study about the experience and perspectives of healthy
subjects in phase I drug trials are consistent with and expand upon previous empirical
data regarding motivation to participate, and the importance of environmental and social
factors on experience. This research provides further insight into how these contextual
factors affect the experience and provides a theory of how these various factors relate to
one another and to the process of participation. The identification of the central role of
payment in motivating and framing the research process helps to remove the ambiguity in
discussions about motivation. Moving forward from this point, it is suggested that future
debates regarding payment acknowledge that it is integral to the process and not a moral
contaminant that can be removed to produce a more pure participation experience. The
implications of these findings on the ethical debate about payment and other issues will
be discussed below.
9.5 Implications for Research Ethics

The theory of making participation work has a number of implications for research ethics. The discussion here will focus on four main issues: 1) the impact of opportunity shopping on the distribution of subjects doing different types of phase I trials; 2) the concept of undue inducement; 3) optimizing the research experience for healthy subjects; and 4) the setting of an upper limit of risk for research involving healthy subjects.

9.5.1 Subject Selection Pressures

Opportunity shopping describes how healthy subjects seek and select suitable studies, using a number of criteria. As noted in Chapter 6, the majority of healthy subjects interviewed in this research select first by ruling out studies that exceed their burden threshold, leading to a preference for studies with confinement periods on the weekends, of one to three nights confinement, involving investigational drugs in the later stages of development, and excluding “serious” indications/mechanisms of action such as HIV, immunosuppressants and psychoactive drugs. In the group of subjects interviewed for this study, phase I drug trials involving longer confinement periods, and first-in-humans or early phase testing of new drugs, for “serious” indications, were left to a minority of subjects who selected first for maximal payment. This latter group of subjects also participates frequently, earning a significant portion of their income from participation, and are more likely to ignore the 30-day or longer washout period required between studies.

While additional research is necessary to confirm whether this theory holds true in larger subject populations, the theory suggests that the higher risk studies are populated by a subset of healthy subjects who have had numerous exposures to various investigational products, sometimes with insufficient washout between dosings. Although there is limited evidence from the data in this study, there is some suggestion that this sub-set of subjects is also more likely to conceal adverse events and is more skilled at doing so.
Thus, the highest risk studies are populated by a subset of subjects whose behaviour amplifies the risk to their health and to the integrity of the study results.

This concentration of risky behaviour associated with higher risk trials suggests the need for increased vigilance with regard to human subject protections, as well as study integrity. A proportionate approach to research ethics review has been widely promoted, for example by the TCPS (1). This study provides empirical evidence for a specific subset of phase I research that requires increased vigilance. At the level of research ethics review, REBs should be aware that higher burden as well as higher risk studies are more likely to attract a population of subjects whose behaviour may place them at increased risk. This should be a factor, for example, in the consideration of risks associated with potential drug interactions.

At the level of the research facilities, strategies for increased vigilance might include increased medical screening, such as shortening the time window between the full medical screening and study entry, and expanding the testing performed at each entry into confinement. The development of a database to track healthy subject participation across various phase I research facilities might help stop subjects from participating without sufficient washout between studies. This approach has been discussed previously, but is not widely practiced. In France, a national registry, established in 1988, has been challenged by a group of scientific societies and patient associations, who feel that the requirement has become a barrier to biomedical research (165). Other concerns can be envisioned such as subjects’ concerns about privacy, and technical as well as confidentiality concerns related to sharing information between individual private companies.

9.5.2 Undue Inducement

Of all the ethical concerns regarding research with healthy subjects, undue inducement has been the most prominent, generating significant debate reflecting a wide range of opinions. In this section I will consider how the findings of this empirical study inform the debate about undue inducement. The discussion is organized into two parts. The first
part will focus on reluctant participation as a test case for undue inducement. In the second part I will revisit the ethical discussion regarding undue inducement in light of these current research findings, to support my position that concern about undue inducement should not play a role in the ethical review of phase I drug trials in research with healthy subjects.

9.5.2.1 Reluctant Participation
Ethicists concerned about payment worry that it may interfere with decision making, in terms of understanding and voluntariness. There are various suggestions regarding moderating payment to reduce its interference in decision making. The theory of making participation work suggests that, rather than interfering with decision making, payment is central to the decision about research participation as a healthy subject. The theory of making participation work further suggests that decreasing payment will not decrease the importance of payment in decision making. Decreasing payment will only change whether individual subjects choose to participate in a given study, based on their individual burden-pay calculus.

Discussions about the ethical acceptability of payment have largely centred on what level of payment is an “undue inducement”. A few voices have brought to the discussion the more fundamental question of whether the concept of undue inducement is a useful way to think about payment to subjects (38,53,58,65). Two definitions of undue inducement were discussed in Chapter 3. The first, and broader definition, is that undue inducement is an influence that gets people to do something they would not otherwise do. Some critics have suggested that this definition also applies to any inducement, rendering the qualifier “undue” as superfluous. A slightly more stringent definition of undue inducement is that an undue inducement is an inducement that gets someone to do something to which they are averse or that goes against their better judgment.

In this study, all repeat participation was driven by the desire to earn payment. Without this payment, subjects would not be taking part in phase I drug trials. Thus, all subjects were “induced” to participate. If the general definition of undue inducement is accepted,
all subjects were unduly induced to participate. As discussed in Chapters 6 and 7, several subjects participated with great reluctance, and were clearly averse to their participation, but participated nonetheless because they needed the money. This scenario of reluctant participation would seem to fit the more stringent definition of undue inducement, as subjects were induced by the payment to do something to which they were averse.

As described in Chapter 3, the discussion about undue inducement has focused on the amount of payment as the variable that can make a payment due or undue. Where payment is considered an undue inducement, reduction in the amount of payment should resolve the ethical concern and return payment to merely an inducement. Applying this reasoning to the case of reluctant subjects reveals several problems. First, the finding that a payment is an undue inducement in this current example applies to specific subjects, rather than to specific studies. The particular studies in which some subjects participated reluctantly, were of short duration (no more than two consecutive nights of confinement) and were generally of lower risk. These are the same types of studies that most subjects preferentially select as having the most favourable burden-pay ratio. These other non-reluctant subjects were not averse to participation and therefore, according to the more stringent definition, were not unduly influenced to participate. If undue inducement renders participation unethical, it would seem that the same study, with the same payment, could be ethical for some and unethical for others. Thus it is not so clear to say that a particular payment level is undue or inappropriate.

Undue inducement is seen as an ethical problem because it threatens the understanding and voluntariness of the informed consent to participate, and therefore threatens individual autonomy. It is expected that those who have less education might have a poorer understanding of the study information and of their rights as research subject, and therefore would be most vulnerable to undue inducement. In this study, all three subjects who participated reluctantly had at least one university degree. They all indicated that they read the consent forms carefully and thoroughly consider all the risks. They have declined participation in studies that were deemed too risky or otherwise undesirable.
Thus, in this example, understanding does not appear to have been affected by the payment.

For the group of reluctant subjects in this study, it might be concluded that voluntariness was altered by the payment, as the payment induced the subjects to do something to which they were averse. The concept of undue inducement is based on the principle that payment becomes undue when it is excessive; the larger the payment, the harder it is to resist. The reluctant subjects, however, all felt that the payment was too low for what was expected of them, and participated despite the low payment, because they were financially desperate. They indicated they would feel less averse to participation if they felt fairly compensated for enduring the burdens of participation and felt devalued by the low payment. Thus it was not that the amount was irresistible, but the opportunity to earn any money. It is possible that the payment could be reduced so that these subjects would find participation not worth it, but this would lead to situations of unfair compensation, and some desperate subject may nonetheless be willing to participate for extremely little compensation. As one reluctant subject noted:

> Just because people are coming in for a thousand dollars doesn’t mean it’s fair. You know, I could probably get somebody to work for a dollar an hour. Somebody in a poor financial situation, who just arrived in the country, or an illegal. So, it doesn’t make it fair. 08-28

It seems likely that making the compensation unattractive will only limit the subject pool to the most desperate, rather than improve the quality of the decision to participate.

This scenario of reluctant subjects makes a good test case for the concept of undue inducement. Although the fact of participation in the face of aversion fits the definition, the assumptions and implications of undue inducement do not work when applied to the specific case. The concept of undue inducement assumes that the problem is study specific, and is the result of an offer of payment that is too high. Proposals to address the concern of undue inducement reflect these assumptions, by suggesting methods to

37 It might be supposed that all subjects would say that the payment was too low, when in fact most other (non-reluctant) subjects expressed that the pay was fair, although many would also be happy to receive more.
calculate what is a reasonable payment for a given study (55). The example of reluctant subjects in this study, however, finds a situation that fits the definition of undue inducement, but that is subject rather than study specific, and is the result of a financially desperate situation, exacerbated by a payment that is too low. In this example of the reluctant subjects, lowering the payment will not lead to a more ethically acceptable circumstance for participation.

9.5.2.2 Abandoning Undue Inducement
The above section described how undue inducement did not fit the case of reluctant subjects. In this section I will take the argument further, and suggest that guarding against undue inducement should be abandoned as a normative guideline for phase I research with healthy subjects. It should be noted that this argument applies only to competent adult healthy subjects.

This discussion of undue inducement centres around three main arguments: 1. Keeping payment low will not change the role of payment in decision making; 2. Limiting payment does not enhance autonomy or respect for subjects; and 3. It is morally acceptable for healthy subjects to use payment in their decision making.

9.5.2.2.1 Role of Payment in Decision Making
There is a general discomfort with the idea of paying research subjects, while at the same time there is the realization that payment is needed for adequate recruitment, and perhaps as compensation for subjects’ time and expenses related to participation. In an attempt to balance the practical need for payment with the aversion to it, it is commonly suggested that subjects be paid, but not too much (76). The concept of “undue” as opposed to “due” inducement suggests that payment is acceptable, as long as it does not play too large a role in the decision making process. According to this logic, the lower the payment, the smaller its role in decision making, and the greater the role of other more “ethically acceptable” factors. That is, keeping payments low will make the decision to participate in research less about money and more about something other than money. The grounded theory developed in this study, however, suggests that payment is central to decision
making, and lowering the amount of payment to avoid undue inducement will do nothing to remove the commercial nature of the transaction. Instead, keeping payments low will decrease the pool of potential subjects who find the outcome of burden-pay calculus sufficient to participate and may lead to exploitation of financially desperate subjects, who are willing to accept even unfair compensation for their participation.

9.5.2.2.2 Autonomy and Respect for Subjects
It has been argued that payment may decrease subject autonomy, by reducing the quality of decision making about participation. The data from this study suggest that subjects are making autonomous choices about participation, weighing the various study burdens—including, but not limited to, risk—against the size of the payment offered. Subjects were fully aware of the voluntariness of participating, including their right to withdraw at any time, and aware of the role of payment in their decision. There was evidence that many subjects were aware of, and considered, study associated risks in their decision making, although the extent of understanding was not assessed in this study. Thus it seems that payment does not necessarily inhibit voluntariness or understanding.

Although there is no clear evidence that payment interferes with understanding, there is ample evidence of insufficient understanding among research subjects who are not distracted by payment (145,166-168) as well as healthy subjects (91). Thus, rather than approaching the problem indirectly by focussing on payment, which may or may not be adversely affecting understanding, attention should focus directly on understanding. The need for a higher threshold for understanding for non-therapeutic research involving payment has been proposed by Grady (39). One way to ensure that this threshold is met, is by requiring some form of testing to demonstrate that each subject has sufficient understanding of study-associated risks or other information prior to participation.38

Concerns about undue inducement also imply that payment may interfere with voluntariness more than other factors used in decision making. It is not clear, however,

38 Of course many challenges related to the concept of understanding and its measurement exist, but even a simple recall test could at least address the concern that paid subjects have no awareness of the risks.
that a patient subject who is motivated by the prospect of direct therapeutic benefit is making a more autonomous decision than a healthy subject motivated by money. Each is weighing the burdens and risks of participation against what they personally stand to gain.

In addition to concerns about autonomy, it has been suggested that payment for research participation may be demeaning, and that participation based on altruism would be more respectful of subjects (60,67). The empirical data from this study, however, suggest that reducing payment is likely to make subjects feel less respected, by undervaluing their contribution and sacrifice, and taking advantage of their financial need to obtain their participation at less than a fair price. Thus, limiting payment with the intent of protecting autonomy and increasing respect for subjects appears to be overly paternalistic, and based on assumptions that are not supported by empirical evidence, and in some cases contrary to the available evidence.

### 9.5.2.2.3 Payment as an Acceptable Factor in Decision Making

The finding in this study that subjects use of a burden-pay calculus implies that payment affects risk acceptance. In other words, payment is inducing subjects to take on risk. Concern over undue inducement is based in part on the position that financial gain is not an appropriate factor for decision making about research participation and should not be used by subjects to balance research risks. This prohibition has been contrasted with many other occupations where there is societal support for increased payment in exchange for the assumption of risk to the individual for the benefit of society, such as in policing or the military (38,44,53,63,64,73). As Grady has noted, all sorts of decisions are routinely influenced by a variety of factors (39). Why should payment be singled out as inappropriate? The moral difference between payment and other factors has been assumed—we don’t worry about subjects being excessively or unduly influenced, for example by altruism—but not adequately defended. Objections on the basis of autonomy or respect have been rejected above. The differentiation between research participation and other types of risky work may reflect the fact that research participation has been governed according to a different set of ethical principles than is used for labour, and that
research principles do not accommodate payment. This, however, is an explanation, rather than a justification for the differentiation.

Challenges with accommodating payment as an acceptable factor in subject decision making may also reflect the finding in this study that healthy subjects use a burden-pay calculus for evaluating studies, which is different from the risk-knowledge calculus that REBs or other governing bodies use. In research with patient subjects, both REBs and patients are presumed to use a risk-benefit calculus, making it more likely that each group uses similar factors in decision making. The use of a burden-pay calculus by healthy subjects, however, represents a radical departure from the criteria used by REBs—risk is not necessarily paramount, and knowledge (i.e. benefit to society) is not a factor of any significance. Given this profound difference, it is no wonder that the behaviour of healthy subjects cannot be readily accommodated by current models for research decision making. In the absence of a sufficient rationale for what Wertheimer and Miller have labeled “the parochialism of research ethics” (44), however, payment should be regarded as an acceptable factor in subject decision making.

9.5.2.3 Undue Inducement Summary
The data from this study suggest that the theoretical concept of undue inducement is overly simplistic and not consistent with empirical reality. This lack of fit with the real world may explain why the concept of undue inducement has always seemed stuck at the level of a theoretical construct that we can’t figure out how to put into practice. Concerns about undue inducement have persisted for decades, and are difficult to abandon. For the reasons discussed above, however, I suggest that the question of undue inducement should not enter into the ethical assessment of research with healthy subjects. Instead, we should ask whether compensation is adequate and fairly distributed (such as ensuring that payment is accrued evenly over the participation period). The quality of the informed decision could be promoted by requiring subjects to demonstrate adequate understanding of relevant information. In addition, as will be considered later in this chapter, subjects should be protected from excessive risk.
9.5.3 Optimizing the Participation Experience

The identification of factors affecting the experience of participation provides the opportunity to optimize the experience for healthy subjects. The findings suggest that discomfort could be reduced by, for example, increasing the minimal training requirements for technicians performing blood draws and increased responsiveness of the facility to complaints about poor technique. Facility requirements could include minimal square footage per subject, which might be adjustable, with increased space for studies having longer confinement periods, and an upper limit on the number of beds in a room. Approaches for allowing some privacy might be developed, although the need to continuously monitor subjects for both compliance and safety may present limitations. Control could be provided in little ways, such as providing facilities for subjects to make tea or other beverages where not prohibited by study requirements or allowing subjects access to blankets without having to negotiate for them. Although it is difficult to legislate respectful behaviour among staff, the study results suggest that an environment and organization that appears to value subjects has a direct positive impact on the participation experience, and may promote respectful and caring behaviour among staff.

At the level of research ethics review, sensitivity to the burdens associated with getting through participation might allow reviewers to make suggestions to study design to minimize burdens as well as the risk from the study drug. Such considerations during protocol review would likely require inclusion of details regarding study procedures that are currently not included in REB submissions.

As summarized in Chapter 3, community consultation has been suggested as one mechanism to avoid exploitation (76) and raise the status of research participation from “hard” to “meaningful” work (77). The results of this study provide evidence of what conditions a community of healthy subjects considers fair. The results of this study suggest that healthy subjects would generally welcome such requirements to optimize their participation experience. Given the extra resources that would be needed to meet these requirements, however, it seems equally likely that many clinical research
organizations that run the phase I studies, and the REBs that review phase I protocols, would not welcome the extra requirements.

Although many facilities would have to invest resources to meet some of the standards suggested above, some facilities seem to operate at or near this ideal already, based on the descriptions of subjects in this study. When I asked one reluctant subject if participation would be more acceptable if conditions were more comfortable, such as better food and more skilled blood sampling technicians, he responded—“you just described [facility name]. Cause for the most part—better food, better facilities, better staff, better location.” Thus, it seems the requirements are not inconsistent with a viable business operation. It should be noted that the facility referred to is a larger organization. It is possible that meeting the above requirements may be more difficult for newer or smaller facilities with a smaller operating budget.

The reasonableness of minimal requirements to optimize the participation experience is supported by the Association of the British Pharmaceutical Industry (ABPI), that includes the following recommendations in their 2007 Guidelines for Phase I Clinical Trials (34).

*Beds should…be fitted with curtains or screens for the subjects’ privacy, have lockers for the subjects’ belongings…During periods of residence, trial subjects should have access to leisure areas with facilities such as comfortable seats, television, video, internet access, board games, newspapers, magazines, books, and facilities to make approved drinks, such as decaffeinated coffee.*

Currently, however, these recommendations have not been endorsed by other guidelines or required by regulation. One reason for this may be the lack of empirical data regarding the importance of study conditions to subject well-being. The findings from this study may be useful in this regard. The lack of focus on optimizing the participation experience may also relate paradoxically to both the fact that healthy subjects are paid for participation, and to a reluctance to acknowledge that payment is the motivation for participation.
The fact that healthy subjects are paid may be used to support the justification that subjects freely choose to endure study conditions in exchange for payment (68). According to this reasoning, as long as subjects are informed about what they are getting into, and freely agree to it, the situation is considered fair. As discussed in Chapter 3, however, a subject is exploited if the net sum of benefits and burdens is unfair, regardless of whether or not there was voluntary consent. Furthermore, letting the “market” determine the conditions can lead to a slippery slope, with conditions only being as good as necessary to get adequate recruitment. This justification is not acceptable in other types of employment, where minimum working standards are required regardless of the availability of individuals willing to accept less.

Participation for payment may also cause subjects or their contribution to society to be socially devalued—there is less appreciation for the “mercenary” subject who is in it for the money, compared to the esteemed altruist who wants to help others. Evidence about subject deception seen both in this study and previously, may also lead to social devaluing of paid healthy subjects. The focus on the commercial transaction takes away focus on healthy subjects’ contribution to drug development and perhaps unconsciously permits a lack of attention to “softer” ethical issues such as subject comfort.

The lack of attention to optimizing the experience may, at the same time, reflect the reluctance on the part of ethicists to view participation of healthy subjects as a type of work (75). “[T]he research community has been unable to divorce themselves from the idea of the research subject as altruist”(72). Participation of healthy subjects is considered under the current framework governing research with patients, that has no provisions for negotiations and considerations of fair pay or working conditions. That subjects feel this lack of power is demonstrated in this quote from one reluctant subject:

_Yah. I want to leave because I don’t have any blankets. What would that do to the study data? Would that mess it up? Or what if we all decided to go? Wow, wouldn’t that be empowering? But we all need the money so badly it won’t happen._ 08-24
A number of authors have suggested that healthy subjects need to be empowered to negotiate working conditions and payment, for example through forming a union or through the creation of labour-type legislation \((19,72,75,76)\). This would require explicit framing of research with healthy subjects as a type of work.

The importance of factors such as emotional comfort and personal control are unapologetically recommended in the nursing literature with regard to patients \((157,158)\). The link is easily made in the health care context, as these factors have been associated with improved well-being and recovery, which is the goal of hospitalization and treatment. Participation of healthy subjects, while still an intervention mediated by medical staff, has no therapeutic intent, and therefore there is not so obvious a link between the goals of the activity (the research) and the promotion of subject comfort through the optimization of the experience.

Thus research with healthy subjects at the moment seems to be caught in a void where both lack of official recognition regarding the commercial aspect of this activity, as well as stigma resulting from the commercial aspect, stand in the way of consideration of the optimization of the participation experience. The results from this study provide empirical support for the importance of environment in subject well-being, and details regarding the types of environmental features that would optimize the participation experience. Comments from the subjects in this study further suggest that some research facilities already provide an environment that promotes their well-being.

9.5.4 Upper Threshold for Risk
The above sections discuss some of the implications of the framing of research participation as work. The conflicting views of research involving healthy subjects as both similar to and different from clinical research with patients was also considered. The findings of this study may be seen as adding to this complexity, as they suggest that, although subjects are motivated by and frame their participation as work, their relationship with the study doctor and possibly other research staff more closely resembles patient and health care provider rather than employee and employer. If this
theory is supported by future research, however, the specification that the “working” relationship applies to the research sponsor or research facility as a business entity, and the “clinical” relationship is associated with the research staff, and particularly the study doctors and nurses, may provide clarification and a path for further policy development.

As suggested by others, issues related to facility conditions and compensation might best be examined through a labour framework. This section will consider how the clinical relationship might be accommodated through limiting risk. As noted in Chapter 3, an upper threshold of minimal risk has been recommended by the London Royal College of Physicians (2) and endorsed by the ABPI (34), and some of the discussion regarding participation of healthy subjects in research seems to presume some upper limit of risk. Emanuel (53) has noted that

\[
\text{current regulations appear to be flawed by failing to specify that net research risks can only be justified when these risks are comparable to what society can reasonably expect...a person to undertake to benefit others.}
\]

There is no consensus, however regarding an upper limit on risk for research involving healthy subjects, nor even consensus on the need for such a limit. Indeed, with the few exceptions noted above, the issue is essentially absent from the research ethics literature. A number of findings in this study, however, suggest that this issue deserves consideration.

The findings from this study suggest that the adoption of an upper threshold for research related risk where there is no prospect of therapeutic benefit would help to address a number of ethical concerns regarding research with healthy subjects. Careful consideration is required to determine just what level of risk might be reasonable, but current regulations and guidelines, which require only that the risk be balanced by the knowledge gained, are too permissive. Within the current rules, even significant risk could be judged as acceptable, if there is promise of significant scientific value. Support for the setting of an upper threshold for risk comes from findings in this study related to trust, and to the impact of payment on risk perception and/or acceptance. These will be discussed below.
9.5.4.1 Trust
The account of trust developed in this research suggests that, although healthy subjects view research participation as an earning opportunity, the relationship with the study doctor and possibly other research staff more closely resembles patient-health care provider than employee-employer. Furthermore, this research demonstrates how trust and feeling valued promote a feeling that participation in phase I drug trials is generally safe. The feeling of safety expressed by subjects in this trial does not appear to be an expectation of guaranteed safety, but a trust that study doctors and others governing research will not place them at unreasonable risk. Similar findings of trust that the research enterprise will keep them safe have been documented among patients and healthy subjects taking part in a variety of research studies (143,169). This trust is necessary for people to make the decision to participate in research. As eloquently stated by Kass et al (169), the trust exhibited by subjects creates obligations for those responsible for human subjects protections:

Human subjects research allows scientific and medical progress to move forward, which is in the best interest of all of us. To be entrusted with the authority to conduct human subjects research is a privilege. Yet only through vigilance and humility will we as investigators be able to live up to the trust that is placed in us; and only if that trust is deserved can the research enterprise survive. (p. 28)

The healthy subjects in this study trust the research enterprise to keep them reasonably safe. Although further research might more precisely define the degree of safety subjects expect, it is clear that subjects in this study would not expect to be placed at significant risk for the pursuit of scientific knowledge, no matter how important. For the research enterprise to live up to this trust, an upper limit on research risk for healthy subjects must be considered.

9.5.4.2 Impact of Making Participation Work on the Informed Consent Process
The setting of an upper threshold for risk might also address some of the concern reflected in the concept of undue inducement. This suggestion will be considered in the following section by arguing that payment of healthy subjects impacts the informed
consent process, that this impact does not fit into traditional notions of vulnerability, and that it cannot be accommodated at the level of informed consent.

In Chapter 3 it was noted that several regulations and guidelines identify research with healthy subjects as possibly requiring “special attention” (27) or “extra safeguards” (170). It was also noted that the concern related to the potential impact of payment on informed consent. Where a specific recommendation is provided to address this concern, it is to limit payment to a level that is not undue. As described above, however, the data from this study suggest that limiting payment will not eliminate it’s impact on decision making, and, as suggested by others, may promote exploitation of the most desperate prospective subjects.

A potential impact of payment on decision making is also suggested by the account of rationalizing risk described in this study. The data from this study suggest that subjects generally are informed of and consider the research-associated risks. Subjects appear to use this information to choose studies according to their personal comfort level with regard to risk. These actions are consistent with a process of meaningful informed consent. Yet through rationalizing risk, it seems that once subjects make the decision to participate, they feel safe. Being aware of a risk then, may not mean feeling personally at risk. Through rationalizing risk, subjects feel a sense of having controlled to some extent the research-related risks, thereby contributing to their feeling that participation in phase I drug trials is relatively safe.

By definition the outcome of rationalizing risk is a reduction in feeling at risk (although this is not necessarily the same as a reduced objective awareness of risk). This finding is consistent with psychological research regarding risk perception. There is an extensive body of empirical evidence that risk perception is affected by subjective factors, independent of disclosure (e.g. (171,172)). Factors that appear to reduce perceived risk include the presence of a perceived benefit (49,50), or the perception of control over a given risk (95). In addition, people tend to have an “optimistic bias” concerning many
types of personal risk, meaning that in general people believe they are less at risk of certain harms than their peers (172).

In the situation of research with healthy subjects, payment is clearly perceived by subjects as a benefit, and rationalizing risk as well as other mechanisms offer subjects a sense of personal control over the risk, supporting the suggestion that any subjective effect will be a reduction rather than an increase in perceived risk. The positive view of participation promoted by rationalizing risk supports the objective of making participation work. Thus the financial incentive appears to be a causal factor in rationalizing risk.

One response to this finding is to make a determination that rationalizing risk is a problem that needs to be corrected, through reduction of the causal factor (i.e. payment) or through improvements in the informed consent process. The problems with reducing payment have been discussed a number of times above. Although additional empirical research is needed for confirmation, it seems likely that changes to informed consent cannot eliminate the rationalization of risk, as it describes how subjects process and use risk information, rather than what information they originally understood. The degree to which subjects were informed or not was not specifically measured in this study, but, given the likelihood that the process of rationalizing is distinct from the process of understanding, changes in understanding may not have a significant impact on the process of rationalizing risk.

Current approaches judge payment as a moral problem that makes subjects vulnerable to bad decision making and conclude that payment therefore has to be reduced until it is no longer a problem. This approach has been considered for several decades and has not provided a viable solution to concerns about payment of healthy subjects (53). Eliminating the impact of payment does not seem possible. I suggest instead that payment should be viewed as morally neutral and simply an inherent part of the context of

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39 Understanding here is defined as it is commonly applied to measures of informed consent as the ability to recall relevant disclosed information.
research with healthy subjects and that any changes to the governance of this research must accommodate this reality.

One way to do this might be to define the context of payment of healthy subjects as one that may decrease risk perception and/or increase risk acceptance. Payment could be viewed as creating a type of vulnerability that is associated with this type of research, rather than with the subject per se. In other scenarios of research with vulnerable groups where vulnerability cannot be “corrected”, for example research with children, subjects are protected by placing a limit on the level of risk that is permitted. Similarly, the setting of an upper limit for research risk is an appropriate protection for the context of research involving payment of healthy subjects.

Although the healthy subjects in this study would not be described as personally vulnerable in terms of capacity for informed decision making, the commercial context of participation may have an impact on the role of risk in decision making. As reduction or elimination of this impact does not seem feasible, a limit to potential risk may be warranted.

The challenges in determining what level of risk should be considered the upper threshold, and whether specific research protocols exceed that threshold, are significant. As noted in Chapter 3, these challenges may be a factor in the previous lack of attention by ethicists and regulators to establish a threshold for phase I drug studies involving healthy subjects. Similar challenges have been described with the application of the minimal risk standard for research involving children that offers no therapeutic benefit, as noted in Chapter 3 (33). Despite these challenges, however, it is doubtful that many commentators would recommend dropping the use of a risk threshold for research with children. Similarly, the challenges of establishing a risk threshold for research involving healthy subjects do not provide sufficient reason to reject this suggestion.

The setting of a risk threshold may or may not have a significant impact on the nature of phase I studies, as most research that is currently undertaken may fall within whatever
limit might be set. Nonetheless, it would address one of the concerns that high payment might induce people to take part in excessively risky research (41). Perhaps more importantly, the setting of a limit may help to re-direct the ethical framework used to consider research with healthy subjects in a way that reflects the reality of this context.

### 9.6 Next Steps

The grounded theory about research participation developed here provides an overview of healthy subjects’ perspectives and experiences. To cover all aspects of the theory within the scope of this thesis, I have to some extent favoured breadth over depth. This choice has allowed me to incorporate all of the key concepts emerging from my analysis into the final theory. This choice also means that I have initiated many discussions that I could not develop to my satisfaction. In many ways, the conclusions are really introductions, begging for further attention. This seems appropriate; one of the most frequently cited attributes of qualitative research is that it is “hypothesis generating”. Some of the issues that I, or others, might develop in future work include:

#### 9.6.1 Empirical Analysis

- Repeat a similar qualitative study involving additional populations of healthy subjects, such as subjects with less education, or who are non-English speaking, or who participate in institutional rather than commercial settings. What modifications to the theory of making participation work are needed to account for these other perspectives?
- Expand on the meaning of trust for healthy subjects to more precisely define the nature of trust and its properties. Do subjects have trust that they will be kept safe, or that staff or others will adhere to certain standards regarding safety? What degree of safety do subjects assume? Whom do subjects trust? How does lack of trust affect the experience or decision making?
- Test the hypothesis that finding personal control is associated with a positive research experience.
• Examine the importance of finding personal control in other research populations. It was suggested above that finding personal control may be important in a variety of circumstances. Future research might include examination of the importance of personal control in populations such as patients taking part in research with potential direct therapeutic benefit. Such research might ask, for example, whether concepts such as accepting, rationalizing risk, emphasizing autonomy and managing the burdens apply to research populations other than healthy subjects.

9.6.2 Conceptual Analysis

• Examine the contribution of findings to the conceptualization of vulnerability as it has been applied to healthy subjects. The notion that payments may affect healthy subjects’ perception of their personal risk was considered in the above discussion as a type of vulnerability that warrants protection from excessive risk. Future exploration of this issue would include an in-depth examination of current philosophical and regulatory conceptualizations about vulnerability. A number of commentators have discussed the current ambiguity regarding the meaning of vulnerability, which populations are vulnerable, and why (173-176). A detailed consideration of vulnerability in light of the current findings may contribute some small increment of clarity to these discussions.

• Propose an upper limit on acceptable risk for research with healthy subjects. I have argued above for the need to establish an upper threshold for the degree of risk to healthy subjects that can justifiably be balanced by potential knowledge alone. I have also considered some of the challenges in determining what is an appropriate threshold. An important next step is to attempt to define this threshold. This effort might include examination of other contexts in which risk to an individual is accepted in exchange for benefit to society. Empirical data regarding the expectations of subjects with regard to safety could also inform this analysis. Limitations on assessing and managing risk in early phase drug research would also have to be considered.
9.7 Discussion Summary

The participation of healthy subjects in phase I drug trials at commercial research facilities has been the subject of considerable discussion, but little empirical study. The predominant ethical concern regarding this research has been the impact of payment on subject autonomy. Responses to this concern have focused on trying to determine what level of payment would compensate subjects for their contribution, without being an undue inducement. With little existing empirical data regarding the experiences and perspectives of healthy subjects in phase I drug trials, both the framing of the ethical concerns and the suggestions to address them, have been based largely on theoretical principles and assumptions about human behaviour.

This study contributes to the ethical discussions, by providing empirical data describing the experiences and perspectives of healthy subjects in phase I drug trials. The results of this study suggest that phase I drug research with healthy subjects at commercial research facilities in many ways does not fit the current model of patient subjects and traditional research ethics framing of processes such as informed consent. Development of a modified model for research involving healthy subjects requires recognition of both the commercial and the clinical aspects of participation. If we as a society expect healthy subjects to take part in phase I research, we need to make sure they are treated with respect, compensated adequately, and protected from undue risk.
References

(64) Savulescue J. The fiction of "undue inducement": why researchers should be allowed to pay participants any amount of money for any reasonable research project. AJOB 2001;1(2):56-58.


(125) Schwartz B. Deprivation of Privacy As a Functional Prerequisite: The Case of the Prison. Journal of Criminal Law and Criminology 1972;63:229-239.


Appendix A. Online Advertisement, University of Toronto

Department: Institute of Medical Science/Joint Centre for Bioethics

Date: date of posting

Headline: Men and Women who have been healthy subjects in phase I drug research wanted to describe their experiences.

Content: English speaking men and women, ages 18 and up, who have taken part in one or more phase I drug research studies as healthy subjects wanted to describe their experiences. Participation involves one meeting, about 30 to 90 minutes. $20 compensation for your time.

For more information, please contact Nancy at:

Email: XXXXXXXX, phone: XXXXXXXXX
Appendix B. Online Advertisement, NOW Magazine

Wanted: Men and Women who have been healthy subjects in phase I drug research wanted to describe their experiences:
- English speaking men and women.
- Ages 18 and up
- Have taken part in one or more phase I drug research studies as healthy subjects wanted to describe their experiences.

Participation involves one meeting, about 30 to 90 minutes to describe your experiences as a research subject. $20 compensation for your time.

For more information, please contact Nancy at:

Email: XXXXXXXX, phone: XXXXXXXXX
Appendix C. Advertisement. Poster Distributed by Research Subject

RESEARCH VOLUNTEERS NEEDED

WHO
Men and Women who have taken part in Phase I drug research as healthy subjects.

PURPOSE
To get the subject’s view on what it is like to be in a phase I drug trial. This research is being carried out as part of the investigator’s PhD thesis.

STUDY PROCEDURES

- One 30 to 90 minute interview.

- You will be asked to describe your experiences as a research subject and whether you have any concerns or suggestions. You can stop the interview at any time.

- The interviews will be audiotaped.

- Must be 18 years of age or older and English speaking.

- $20 compensation for your time.

You may be invited to participate in an optional second interview.

CONFIDENTIALITY
Confidentiality will be protected. Your name will not be included in any reports.

For more information, contact Nancy at:

Email: XXXXXXXXXX Phone XXXXXX
Appendix D. Information and Consent Form

Information and Consent Form

Investigator Name: Nancy Ondrusek (PhD student), University of Toronto, Joint Centre for Bioethics

Thesis Supervisor: Dr. Philip Hébert
Sunnybrook and Women’s College Health Sciences Centre

Study Title: The Experiences, Concerns and Perspectives of Healthy Research Subjects Participating in Phase I Clinical Drug Trials

You are being asked to consider taking part in a research study involving healthy volunteers who have taken part in one or more drug research studies. This form explains the study and what you would be asked to do. If you have any questions, or do not understand anything in this form, please ask investigator (Nancy Ondrusek) to explain.

What is the purpose of this study?

Background
Before people are invited to take part in a drug research study, the study plan must be reviewed and approved by various groups or committees, including Health Canada, and a Research Ethics Board (REB, a group of scientists and non-scientists not involved with the research, who review research studies to help protect the rights and welfare of subjects). These groups and committees follow various laws and guidelines to make their decision about whether to allow a new research study to go forward, but there is very little information about what subjects think about research participation. Knowing more about the experiences and concerns of research subjects would help the people who run the studies, and the groups who review the studies, to do a better job.
During the interview you will be asked to describe your experiences as a subject in a medical research study, and whether you have any concerns or suggestions to make the process better. You will be also asked for some demographic information (age, education, employment, and how often you take part in medical studies). The interviews will be audiotaped (tape recorded) so that the investigator can later analyse the information.

Possible Second Interview
In some cases, after analyzing the study results, the investigator may wish to ask some subjects a few more questions, or to get feedback from subjects about whether the investigator’s conclusions fit with their experiences. At the first interview you will be asked for permission to be contacted a second time. If you say yes, the investigator will ask you for contact information, such as your phone number. You are free to say no to a second contact. If you say yes, you are free to later change your mind. Even if you say yes, you might not be contacted.

If you agree and the investigator would like to have a second interview, the investigator will contact you and arrange to have another meeting at a time that is convenient for you.

What are the risks of taking part in this study?
There are no foreseeable risks in taking part in this study, except for the loss of your time.

What are the possible benefits?
You are not expected to benefit directly from participation in this study. The information gained from this study will lead to a better understanding of what it is like to be a research subject in a Phase I drug trial. This information may help in the protection of research subjects.

Do you have to take part in this study?
Your participation in this study is completely voluntary. You are free not to take part or to withdraw from the study at any time, without giving a reason, even if you have signed this consent form. This research is not associated with any drug studies, and the investigator is not involved in any way with the research facilities conducting those studies. If you decide not to take part, or to withdraw, it will have no effect on your participation in future medical research.
If you wish to withdraw during the interview, simply tell the investigator and the interview will be stopped. With your permission, the investigator will keep the information already collected. If you wish to withdraw your interview from the study, inform the investigator. Your tape will be erased and your information will not be used in this study. Once the interview has been combined with the results from other subjects, however, it cannot be withdrawn.

**Confidentiality**
Your identity will be kept confidential at all times. Unless disclosure is required by law, only the investigator will know the identity of study subjects. Your name will not appear in any reports or publications arising from this study.

Audiotapes will be stored until the analysis is complete (about 2 years). After that time they will be destroyed. The consent form, which contains your name, will be destroyed 3 years after the completion of the analysis.

Transcripts (written records) of the interviews will be labeled with a letter code and not your name. Transcripts, without your name, will be kept indefinitely and may be reanalyzed in the future to address further questions related to the experience of research subjects.

Interview results will be combined in any reports. The names of the research facilities will not be included in any reports. In addition, subjects will be asked to speak about any of their research experiences, at any facility.

**Compensation/Costs**
There are no expenses related to taking part in this study. You will be given $20.00 for your participation.

**Your Rights**
If you have questions about your rights as a research participant, please contact Jill Parsons, Health Sciences Ethics Review Officer, Ethics Review Office, University of Toronto, at telephone 416-946-5806 or by email: jc.parsons@utoronto.ca.
Consent
I have been given enough time to read this form and to ask questions. All of my questions, if any, have been answered to my satisfaction. I freely volunteer to take part in this study. By signing this form, I am not giving up my legal rights or releasing the investigator from her legal and professional obligations. I will be given a copy of this form to take home with me.

_______________________  ______________  _______________________________
Subject Name (printed)         Date         Signature

______________________________________
Investigator Signature

______________________________________
Investigator Signature         Date
Appendix E. Audiotaping Consent Form

Audiotaping Consent Form

Investigator Name: Nancy Ondrusek (PhD student),
University of Toronto, Joint Centre for Bioethics

Thesis Supervisor: Dr. Philip Hébert
Sunnybrook and Women’s College Health Sciences Centre

Study Title: The Experiences, Concerns and Perspectives of Healthy Research Subject Participating in Phase I Clinical Drug Trials

As part of your participation in this study, you are being asked to agree to be audiotaped during your interview. The tapes will be transcribed (typed onto a computer) by the investigator, so that the information collected from this study can be analysed. These audiotaped interviews will be used to get a better understanding of research participation from the perspective of healthy subjects.

You will not be identified by name on these tapes, but by a study number. The tapes will be stored in a secured, locked location until the project is complete. They will be used only by the investigator and will be erased when this research project is complete.

Voluntary Participation
Your participation in this study is completely voluntary. In addition, you may take part in this study without being audiotaped, and the investigator will instead make notes during the interview. You are free not to take part or to withdraw from the study at any time, without giving a reason, even if you have signed this consent form. This research is completely separate from your medical study, and the investigator is not involved in any way with the research facility. If you decide not to take part, or to withdraw, it will have no effect on your participation in the medical study.
If you wish to withdraw during the interview, simply tell the investigator and the interview will be stopped. With your permission, the investigator will keep the information already collected. If you wish to withdraw your interview from the study, inform the investigator. Your tape will be erased and your information will not be used in this study. Once the interview has been combined with the results from other subjects, however, it cannot be withdrawn.

Confidentiality
Your identity will be kept confidential at all times. Unless disclosure is required by law, only the investigator will know the identity of study subjects. Your name will not appear in any reports or publications arising from this study.

Audiotapes will be stored until the analysis is complete (about 2 years). After that time they will be destroyed. The consent form, which contains your name, will be destroyed 3 years after the completion of the analysis.

Transcripts (written records) of the interviews will be labeled with a letter code and not your name. Transcripts, without your name, will be kept indefinitely and may be reanalyzed in the future to address further questions related to the experience of research subjects.

Subjects will be interviewed at more than one research facility, and the results will be combined in any reports. The names of the facilities will not be included in any reports. In addition, subjects will be asked to speak about any of their research experiences, at any facility.

Your Rights
If you have questions about your rights as a research participant, please contact Jill Parsons, Health Sciences Ethics Review Officer, Ethics Review Office, University of Toronto, at telephone 416-946-5806 or by email: jc.parsons@utoronto.ca.

Consent
I have been given enough time to read this form and to ask questions. All of my questions, if any, have been answered to my satisfaction. I agree to
having my interview audiotaped as part in this study. By signing this form, I am not giving up my legal rights or releasing the investigator from her legal and professional obligations. I will be given a copy of this form to take home with me.

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<th>Patient Name (printed)</th>
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Appendix F. Demographic Questionnaire

**Demographic Questions**

Subject Number: 08-____ Subject Name: ____________________________
1. Gender: M F 2. Age: ________
3. Race: ________________
   Prompt: Caucasian; Black/African-Canadian; Asian, Southeast Asian,
4. What is your highest level of education:
   ___ Didn’t finish high school ___ High school ___ College or University Degree
   ___ Post-Graduate/Professional Degree
5. What is your current employment status: ________________________________
   Prompts: Full-time employed, Part-time employed, Student full-time, Student part-time,
   Unemployed, Full-time caregiver
6. What is your main source of income:
   ___ Participation as a research subject
   ___ Employment
   ___ School scholarships/grants
   ___ Other
7. What is your current income level:____________________________________
   ___ Less than $20,000;   ___ $21 to 39,999
   ___ $40 to 54,999;   ___ $56,000 or over
8. Do you have any science/health care background, either through work or school? Yes
   No If yes,__________________________________________________________
9. How many trials have you been in? __________________________
10. What types of trials have you been in?______________________________
    ____________________________________________________________________
    How many drug trials? (if applicable) ____________________
10. When was the most recent study? ________________________________