PRESSURES AT THE FRONT LINES: INVESTIGATIVE SITES AND CONTRACT RESEARCH ORGANIZATIONS IN CANADIAN CLINICAL TRIALS

by

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Abstract

Commercialization of medical research, and clinical trials in particular, has been the subject of scrutiny by policy makers and academics. However, little attention has focused on a more recent but now dominant actor: the contract research organization (CRO). Over the past twenty-five years, CROs have assumed much of academia’s role in the conduct and control of clinical trials, and are now the de facto face of industry sponsors for those working at investigative sites. This dissertation examines sites, their relationship with CROs, and the extent to which Canadians are protected by Canada’s clinical trials oversight framework.

This dissertation includes both empirical and normative components. First, and based on an extensive review of industry and academic literature, I describe the lay of the land of clinical trials in Canada and set the regulatory and economic context. Second, a qualitative interview study explores the relatively unexamined interface between site and CRO to identify key areas of concern from the perspective of those working at the frontlines of Canadian clinical trials. This is based on 24 semi-structured interviews. Participants were recruited so as to provide a range of perspectives relevant to the practice realities at the frontlines and the challenges that arise in relation to site-CRO interactions. It includes participants working at sites, CROs, pharmaceutical companies and in consultancy roles with clients across these categories. Third, a critical legal and ethical analysis of the regulatory and policy frameworks governing clinical trials in Canada is undertaken to determine areas of weakness in light of the issues identified in the qualitative study. A number of shortcomings with Canada’s approach to clinical trial oversight in relation to both investigator and industry-initiated trials are identified. Key among these is an overreliance on sponsors for trial oversight, which raises different concerns in industry and investigator-initiated trials. These and other critical issues are explored and recommendations to address such concerns are made. This study supports the growing call for an evidence based approach to protecting human subjects in research and is particularly timely given the intense efforts currently underway to attract more industry funded clinical trials to Canada.
Preface

This dissertation is an original intellectual product of the author, Christina Preto. The fieldwork reported in Chapters 4-6 was approved by the University of British Columbia’s Behavioural Research Ethics Board and is covered by UBC Ethics Certificate number H10-00289.
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List of Abbreviations

ACRO: Association of Clinical Research Organizations
ACRP: Association of Clinical Research Professionals
AHC/AMC: Academic Health Centres/Medical Centres (used interchangeably)
ARO: Academic Research Organization
BCCRIN: British Columbia Clinical Research Infrastructure Network
BCEHI: British Columbia Ethics Harmonization Initiative
CFR: Code of Federal Regulations (U.S.)
CHS: Centring the Human Subject (Research Study)
CIHR: Canadian Institutes of Health Research
CITI: Collaborative Institutional Training Initiative
CMA: Canadian Medical Association
CME: Continuing Medical Education
CNA: Canadian Nurses Association
CNE: Continuing Nursing Education
CPI: Certified Principal Investigator
CRA: Clinical Research Associate (or Monitor)
CRC: Clinical Research Coordinator (or Coordinator)
CRF: Case Report Form
CRO: Contract or Clinical Research Organization (used interchangeably)
CTA: Clinical Trial Application (equivalent to the U.S. IND application)
CTSU: Clinical Trial Support Unit
CTU: Clinical Trial Unit
CV: Compliance Verification
EDC: Electronic Data Capture
EPL: Effective Patent Life
EU: European Union
FDA: Food and Drugs Act (Canada)
FDA: Food and Drug Administration (U.S.)
FSP: Functional Service Provider
GCP: Good Clinical Practices
GMP: Good Manufacturing Practices
HC: Health Canada
HPFBI: Health Products & Food Branch Inspectorate
ICH: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICH-GCP: Guidelines for Good Clinical Practice established by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC: Independent Ethics Committee
IND: Investigational New Drug Application (U.S.)
IOM: Institute of Medicine (U.S.)
IRB: Institutional Review Board
LRCC: Law Reform Commission of Canada
MSFHR: Michael Smith Foundation for Health Research
N2: Networks of Networks
NACTRC: Northern Alberta Clinical Trials & Research Centre
NCCA: National Commission for Certifying Agencies
NCIC-CTG: National Cancer Institute of Canada-Clinical Trial Group
NDS: New Drug Submission
NOL: No Objection Letter
NRC: National Research Council
NSERC: Natural Sciences and Engineering Research Council
OCREB: Ontario Cancer Research Ethics Board
PI/QI: Principal Investigator/Qualified Investigator (used interchangeably)
PM: Project Manager
PREB: Private Research Ethics Board
R&D: Research and Development
REB: Research Ethics Board
Rx&D: Canada’s Research-Based Pharmaceutical Companies
SAE: Serious Adverse Event
SMO: Site Management Organization
SoCRA: Society of Clinical Research Associates
SOP: Standard Operating Procedures
SSHRC: Social Sciences and Humanities Research Council
SUADR: Serious Unexpected Adverse Drug Reaction
TCPS2: Tri-Council Policy Statement 2
TIMI: Thrombolysis In Myocardial Infarction (ARO affiliated with Harvard University)
TPD: Therapeutic Products Directorate
WMA: World Medical Association
Glossary

The definitions included below are based largely on the *ICH-GCP Guidelines* and Health Canada’s *Guidance Document For Clinical Trial Sponsors: Clinical Trial Applications*.

**Adverse Drug Reaction:** Any noxious and unintended response to a drug that is caused by the administration of any dose of the drug.

**Adverse Event:** Any adverse occurrence in the health of a clinical trial subject who is administered a drug, that may or may not be caused by the administration of the drug, and includes an adverse drug reaction.

**Case Report Form (CRF):** A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject.

**Clinical Research Associate (or Monitor):** An employee of, or contractor to, either the Sponsor or CRO who is responsible for monitoring the conduct of the trial. The Monitor essentially becomes the representative of the Sponsor to the Site. In particular, the purpose of the Monitor is to ensure (a) the rights and well-being of human subjects are protected; (b) the reported trial data are accurate, complete, and verifiable from source documents; and (c) the conduct of the trial is in compliance with the currently approved protocol and amendment(s), with GCP, and with the applicable regulatory requirement(s).

**Clinical Research Coordinator (or Coordinator):** The person at the site responsible for most of the day to day conduct of the clinical trial activities. They are at once the primary contact at the site for participants and also for the monitor. Among the many tasks that now generally fall within a coordinator’s job description are patient recruitment, screening, enrolling, document management (including regulatory documents) and even budget and contract negotiations in some instances.

**Clinical Trial:** An investigation in respect of a drug for use in humans that involves human subjects and that is intended to discover or verify the clinical, pharmacological or pharmacodynamic effects of the drug, identify any adverse events in respect of the drug, study the absorption, distribution, metabolism and excretion of the drug, or ascertain the safety or efficacy of the drug.

**Contract Research Organization (CRO):** A CRO can be described as an organization that is contracted by a sponsor to manage various steps in the drug development process, including conduct of preclinical studies, clinical study design and execution, data management, analysis, medical writing, and regulatory submission. For the purpose of this dissertation, the focus is on the use of CROs in relation to clinical trials. The terms Clinical Research Organization and Contract Research Organization are referred to interchangeably throughout this document.

**Good Clinical Practices:** Generally accepted clinical practices that are designed to ensure the protection of the rights, safety and well-being of clinical trial subjects and other persons.
**Industry-Initiated Clinical Trial**: A clinical trial that is funded, designed and controlled by a pharmaceutical or biotechnology company.

**Investigator-Initiated Clinical Trial**: A clinical trial that is initiated and conducted by an individual investigator (or research institution). For such trials, the investigator (or institution) is considered to be the sponsor of the trial and must fulfill all the regulatory obligations of the sponsor as outlined in the Division 5 Regulations under the Food and Drugs Act, and the GCP Guidelines. See also: Sponsor-Investigator.

**Investigative Site (Site)**: An investigative site is a company or clinic that conducts studies, often though not exclusively, through contracts with pharmaceutical companies or other funders or CROs. These can be located in a wide range of settings, from large academic health centers and teaching hospitals, to community research institutions to smaller community health clinics and physician practices.

**Monitoring**: The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

**Protocol**: A document that describes the objectives, design, methodology, statistical considerations and organization of a clinical trial.

**Principal Investigator/Qualified Investigator (PI/QI)**: The investigator in charge at any given site is referred to in the ICH- GCP Guidelines as the Principal Investigator, and this term is widely used in the literature. Health Canada, under the Division 5 Regulations, terms this position the Qualified Investigator. I use the terms PI and QI interchangeably throughout this dissertation.

**Research Ethics Board**: A body that is not affiliated with the sponsor, and the principal mandate of which is to approve the initiation of, and conduct periodic reviews of, biomedical research involving human subjects in order to ensure the protection of their rights, safety and well-being.

**Serious Adverse Drug Reaction**: An adverse drug reaction that requires in-patient hospitalization or prolongation of existing hospitalization, that causes congenital malformation, that results in persistent or significant disability or incapacity, that is life threatening or that results in death.

**Serious Unexpected Adverse Drug Reaction**: A serious adverse drug reaction that is not identified in nature, severity or frequency in the risk information set out in the investigator's brochure or on the label of the drug.

**Sponsor**: An individual, corporate body, institution or organization that conducts a clinical trial as per Division 5. The sponsor must comply with its obligations as set out in the Division 5 Regulations.
Regulations under the *Food and Drugs Act* and the *ICH-GCP Guidelines* in adhering to good clinical practices for the proper use of the drugs, drug labelling requirements, record keeping, submission of information, reporting of ADRs, and trial discontinuation reporting requirements.

**Sponsor-Investigator:** An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (e.g., it does not include a corporation or an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator.

**Standard Operating Procedures (SOPs):** Detailed, written instructions to achieve uniformity of the performance of a specific function.
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This dissertation would not have been possible without the efforts and energies of many people. I want to start by thanking the participants in my study who gave so generously of their time and shared their experiences and insights with me, and whose passion for their work brought this study to life. My supervisor, Dr. Michael McDonald, and committee members, Dr. Susan Cox and Professor Timothy Caulfield, have guided me through this process and generously offered me the immense benefit of their expertise and insights as I moved forward. My experience as a co-investigator with the CIHR funded Canadian Network for the Governance of Ethical Health Research Involving Humans: Evidence, Accountability and Practice, was invaluable. Through the Network, I had incredible opportunities to learn from, and collaborate with, many of the leading scholars in research ethics in Canada. Dr. Pierre Deschamps and Dr. Ray Saginur in particular provided suggestions and insights during the research phase of this dissertation. In addition, I had the privilege of being part of the CIHR Ethics of Health Research and Policy Training Program, which also provided invaluable opportunities to work with key figures in bioethics in Canada and introduced me to an inspiring group of peers. My colleagues at the Centre for Applied Ethics at UBC were also instrumental in shaping my doctoral training and providing rich food for thought. I am particularly grateful for the opportunities I had to work with Dr. Mike Burgess and Dr. Anita Ho. My colleagues and friends Dr. Holly Longstaff and Dr. Alice Virani have been important sources of inspiration and encouragement throughout this process. I also want to thank Dr. Rana Ahmad, Dr. Heather Walmsley and Veronica McCaffrey for our many conversations over the years, and Heather for her extremely helpful comments on an early chapter of the dissertation. I am extremely grateful to CIHR for the Doctoral Research Award that helped support this research.

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Dedication

I dedicate this dissertation to my parents. Without all of your love, support (in so many ways!) and encouragement I would not have been able to do this. I also dedicate this to my son Zachary who has been (mostly) patient as I have pursued this goal, and who is a source of endless wonder and amazement.

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Chapter 1: Introduction

The drug development industry involves high stakes for a wide range of parties. Pharmaceutical companies spend billions of dollars developing and testing drugs in clinical trials and stand to make or lose billions on those investments. Host countries like Canada and many others around the world actively seek out clinical trials because they are major economic and scientific drivers. The range of companies and service providers who have evolved to meet industry’s needs now constitute a multi billion dollar industry with the dominant service provider (the contract research organization (“CRO”)), alone having a projected market share of $37.4 billion in 2013. Academic health centers and research institutions, despite having lost much of their share of clinical trial activity to the private sector, continue to rely in large part on industry sponsored research for their survival and to help fund a wide range of important basic research initiatives. Physician investigators, both in academia and private practice, are motivated by a number of factors to participate in clinical trials as they strive to improve the care and treatment options available for their patients and in their field. And of course, the patient populations living with and dying from a wide range of conditions and diseases are hoping that those billions of dollars in drug development translate into some therapeutic benefits or cures that positively affect their quality of life and/or prognosis.

As illustrated above, a number of complex and profound interests converge in the drug development process. As will be described further in Chapter 2, this convergence takes place within a broader context and one that is dominated by the commercialization of science (and more specifically for present purposes, of medical research and clinical trials). McDonald & Preto (2011), observe that,

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1 Association of Clinical Research Organizations (ACRO) website (Market Share). Available at: http://www.acrohealth.org/cro-market1.html. Accessed September 7, 2013. ACRO explains on its site that it is extremely difficult to get an accurate sense of the market share for CROs, since “the definition of "CRO" and the scope of services included in market size may differ from source to source.” Interestingly, accuracy of terminology is a challenge throughout this industry. For example, variations in job descriptions and titles for research coordinators have been discussed in the literature. Grady & Edgerly (2009) note that research coordinators may be called research coordinators, study coordinators, clinical trial nurses-among other labels. Roberts et al.,(2006) suggest that improving clarity of job descriptions could be an important step in formalizing the position and having it better understood.
Various factors (e.g. slow commercialization of research by public research institutions, lack of government support for research, and an increasingly powerful private sector) support a shift away from science as a ‘public calling which research findings should be shared and made publicly accessible’ (Lemmens, 2004, 644) to a field dominated by a heavy commercial focus on patents and other intellectual property protections. Many governments have encouraged this as part of a deliberate shift towards a growing, competitive knowledge-based economy. (327)

The extensive literature relating to the dangers associated with commercialization of science addresses a variety of concerns (Downie, Baird & Thompson, 2002; Krimskey, 2003; Labonte & Torgerson, 2005; Lemmens, 2004). Key among these are the negative effects on exchange of information and sharing of ideas resulting from a focus on protecting and capitalizing on intellectual property, as well as conflicts of interest that erode the objectivity and disinterestedness of those designing and conducting the research and reporting the research findings (McDonald & Preto, 2011). It is important to highlight the difference in funding of clinical research as between public and industry sources. Whereas the Canadian Institutes of Health Research (CIHR) invested a total of $129 million for all clinical research in 2010-2011, industry invested $465 million in phase I-III clinical trials. Given the difference in numbers, it is not at all surprising that approximately 80% of all clinical trials are funded by industry (Lexchin, 2012). Moreover, and as will be discussed further in Chapter 2, since the mid 1990s there has been a dramatic shift of clinical trials out of public or academically affiliated sites and into private community based physician practices, clinics and research units. In fact, 70% of all clinical trials in Canada are now being done in the community and only 30% done in academically affiliated sites (Ogilvie, 2012). The rise of the CRO has been an integral part of this shift, with such organizations assuming many of the responsibilities previously filled by academic institutions and investigators (Mirowski & Van Horne, 2005; Shuchman, 2007).

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2 CIHR is the dominant public funder of health research in Canada (Ogilvie, 2012; Vanderwel, 2012). See also: Canadian Institutes of Health Research (CIHR) Moving Forward: CIHR Performance Across the Spectrum: From Research Investments to Knowledge Translation, 2011. Available at: http://www.cihr-irsc.gc.ca/e/44585.html

3 These numbers refer specifically to the investments reported by companies to the Patented Medicines Prices Review Board (PMPRB).

4 As will be explained further in Chapter 7, these numbers are low because they do not reflect expenditures that do not qualify for tax credits. Such exemptions include, among other things, grants to universities and hospitals for investigator-initiated trials (Vanderwel, 2012).
implications of this shift are described throughout this dissertation; however, and as will be discussed in Chapters 2, 6 and 7, key consequences include a much more limited role for academic investigators in industry sponsored trials (Angell, 2008; Lemmens & Bouchard, 2007; Lenzer, 2008; Mirowski & Van Horne, 2005) and reduced public oversight, as the majority of clinical trials are now subject to review by private-for-profit instead of public research ethics boards (Koski et al, 2005; Lemmens & Freedman, 2000; Lexchin, 2008; Shuchman, 2007).

In this high-powered, high stakes, and ever-evolving context, Canadians need to know that their health and well-being, both as potential research subjects and as future consumers of the products being developed, are protected for two important reasons. First, this is quite simply something Canadians rightly expect and something that Health Canada as the relevant regulatory body holds itself out as doing. This expectation is part of a trust-based obligation that the state has to protect the interests of its citizens. As Miller & Weijer (2006a) put it, the state relies on volunteers “to advance the public interest in science”, and “as a result…the state is morally obliged to exercise its powers to protect their interests.” Second, and perhaps more practically, when Canadians lose trust that their interests are being protected, the very fabric that supports research and makes medical advances possible is threatened (Cohen, 2001; McDonald et al., 2008; Yarborough & Sharpe, 2002).

But how is one to assess the extent to which the interests of Canadians are being protected? Certainly, this can be ascertained in part by analyzing the legal and ethical frameworks that govern drug development in this country; however, such an investigation would only provide a limited perspective revealing at best what is supposed to happen and what protections are supposed to be in place. To obtain a more realistic picture, it is necessary to look not only at the normative aspects—that is, what should happen—but also at the descriptive elements to determine what is in fact happening. This is because contextual and practice realities shape how the regulations, rules and standards are interpreted and implemented both at the frontlines and at all levels of the research endeavor.

5 As indicated on their website, “Health Canada is the federal regulator responsible for authorizing the importation and sale of drugs for the purpose of clinical trials…One of the objectives of Health Canada’s review is to ascertain that subjects participating in the trial will not be exposed to undue risks.” http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdonclin/index-eng.php. Accessed September 7, 2013.
This dissertation takes a number of steps in this direction. My goal in conducting this study is threefold: (1) to explore the ethical and legal issues that arise at the interface between the investigative site (both academic and community based) and CRO in commercialized clinical trials; (2) to situate these issues against the framework governing clinical trials in Canada to determine whether and where there are gaps or weaknesses; and (3) to suggest improvements in the governance framework. I could have focused my study in a number of different ways; for example, by exploring the interactions between the regulator and industry sponsors, or between the sponsors and the organizations to whom they now regularly outsource some or all components of clinical trials and their management—namely, CROs. However, I instead focus on the frontlines and specifically on the interface between CROs and investigative sites. This is done for a number of reasons. In part, I find the frontline focus compelling. The challenges and issues reported by those at the frontlines have an immediate impact on clinical trials and are therefore a good starting point to assess how well the governing frameworks reflect and address the realities of clinical trial research. This frontline approach also makes it possible to compare how the presence of the CRO—an entity that has dramatically changed academia’s role in clinical trials and yet one that has received relatively little academic attention—affects what challenges are reported by the site. Finally, there is also an element of convenience and accessibility. As will be discussed further in the methods section, I am an outsider to the clinical world and to clinical trials. However, through my work with a separate CIHR-funded study entitled Centring the Human Subject in Health Research: Understanding the Meaning and Experiences of Research Participation⁶, I had the opportunity to meet with and present to different sites and professional organizations for those working at the frontlines of clinical trials. This basic level of familiarity with sites and site staff, combined with anticipated obstacles in terms of accessibility and secrecy with those more upstream (e.g., and in ascending order: CROs, sponsors, regulators), also informs the frontline focus of this study.

One additional point to highlight is that while I refer to “sites”, the perspective I focus on almost exclusively within this category is that of the research staff—be they research coordinators, site managers or other research staff—but not the investigators. The reasons for

⁶See, for example, McDonald et al. (2008) for a description of this research study.
this are described in Chapter 3, but very briefly the key reasons have to do with the importance of the coordinator’s role in CRO-site interactions, very limited accessibility to physician investigators, and the fact that I did not want to risk compromising the openness and frankness of the coordinators participating in my study. Particularly on these last two related points, it became clear to me that if I wanted to interview physicians an important point of access would be through the coordinator. While I did initially consider this approach, I ultimately chose not to pursue it. This was because, as the data collection process unfolded, I realized that coordinators were being quite frank with me about some of the challenges they experience within their own site. Instead of jeopardizing this frankness with a request to speak to their investigator, I focus solely on the staff perspective, and on the coordinator’s perspective in particular.

In addition to the intended focus on the CRO-Site interface, a second compelling area emerges from the data that led me to broaden my scope and inquire more deeply into issues and concerns raised by my site-based participants. These are not issues between sites and third party CROs, but within the investigative sites themselves. Most of the participating site staff work with their respective investigator(s) across both commercialized and investigator-initiated clinical trials—with CROs typically being involved with the former, but not the latter. In my interviews, I ask participants specifically about their experiences working with CROs—what works well, and what doesn’t—for example. But I also ask more generally what challenges they encounter in their day to day clinical trial activities, and (in later interviews) what (if any) ethical issues they encounter. In response, and also through generally unprompted comparisons between commercialized and investigator-initiated clinical trials, a number of interesting issues emerge. My participants highlight that the internal dynamics of a site have important implications not only for the staff working there, but also (& as corroborated by participants in other categories) for the site’s external relationships (e.g., with the CRO). Moreover, and as I will argue later in this dissertation, some of these findings suggest some important weaknesses in Canada’s research oversight system—particularly in relation to investigator-initiated trials. As such, I have decided that these site-based issues deserve detailed exploration in their own right.

While there is industry and some medical literature discussing the CRO-Site interface, such articles tend to focus primarily on the logistical challenges, obstacles and proposed solutions to maximizing efficiency and speed of trial conduct, without considering the broader
implications (Getz, 2005; Getz, 2007a; Lamberti et al., 2011; Pierre, 2013; Smed & Getz, 2013). There is also relatively little academic literature (empirical or otherwise) exploring or discussing the broader legal and ethical implications that can follow from CRO-site interactions (Fisher, 2009; Mirowski & Van Horn, 2005), although there is a growing literature looking at this interface in the context of clinical trials in emerging markets (i.e. in less developed and developing countries), (Adobor, 2012; Petryna, 2009; Schipper et al., 2011). My study contributes to this limited literature and does so with a Canadian focus—something that has been lacking to date.

In contrast, there is a richer literature exploring the kinds of internal site issues that I describe in Chapters 4 and 5 of this study. That being said, my findings are interesting in part because they again provide a Canadian perspective (something that has been largely missing in this context), and in part because they emerge so strongly despite not being part of the original focus of the study. Related to this last point, and as noted above, my data also suggest a relationship between the internal functioning of a site and the effectiveness of its relationship with CROs.

By way of brief overview, then, this dissertation is an outsider’s exploration of a portion of the complex domain of clinical trials in Canada. Chapter 2 reviews industry and limited academic literature about the pharmaceutical industry in order to provide a “lay of the land” within which to situate clinical trials in Canada. Because the pharmaceutical industry is truly a global one and one dominated by the U.S., this chapter describes this broader international context as well. Chapter 3 describes the research question and rationale, as well as the methods and processes adopted in this study. These include a qualitative interview-based study across multiple categories of participants, and a critical legal and ethical analysis situating the findings within the specifics of the Canadian regulatory and policy frameworks governing clinical trials. The dissertation then reports on the findings of this study. First, the challenges and pressures that research staff encounter within their own site as they compete for and conduct clinical trials in this high pressure environment are explored. These findings are divided into two chapters, with the first chapter (Chapter 4) examining in detail issues related to gaps in investigator training and the second (Chapter 5) exploring challenges associated with lack of investigator involvement, gaps in staff training and insufficient institutional support. In Chapter 6, the
dissertation shifts its focus to the CRO-site interface and the challenges encountered therein. Ultimately, the findings detailed in this chapter suggest that while the CRO may have a critical role to play in making clinical trials possible and profitable for sponsors in today’s global economic and regulatory climates, they also at the very least exacerbate existing (and may even create new), ethical tensions and concerns in their interactions with sites. These concerns must be addressed in order to ensure the safety and integrity of clinical trials in Canada.

It should be noted that while the primary vantage point across all three data chapters is the investigative site7, this is supplemented and enriched by insights from CROs, sponsors and industry consultants where participants in these categories commented on the issues in question. This site-centered but multi-faceted approach not only serves as a sort of verification through triangulation of the key issues, but also results in much more nuanced and detailed insights and findings.

Shifting somewhat away from the strictly data driven chapters, Chapter 7 provides a detailed examination of the law and policy landscape that shapes how clinical trials in Canada are conducted and informs how those involved in clinical trials understand and define their roles and responsibilities, and then in turn how those responsibilities are enforced. In addition, potential gaps or weaknesses in the legal and policy frameworks that pertain to the key issues raised by participants in earlier chapters are highlighted. Specific questions pertaining to liability and legal exposure are briefly discussed in Chapter 8.

The concluding discussion (Chapter 9) revisits the key findings in the report, but does so by situating them against three commonly held ideas or narratives that the findings challenge. Specifically, these are that:

- If clinical drug trials could be extricated from the profoundly commercial interests of the pharmaceutical industry there would be a return to a golden age of high quality, publicly funded objective, unbiased research;
- The regulator (namely, Health Canada), is the key authority that ensures sites (and CROs) are meeting the established legal requirements and ethical standards, thereby protecting human subject and public interests;

7 The reasons for this choice are described in detail in Chapter 3.
- Clinical trials bring medical benefits both in their own right and in terms of the drugs they ultimately support to market.

Drawing on my findings and analysis in the preceding chapters, I challenge these narratives and offer a more nuanced, realistic picture of clinical trials in Canada. This concluding chapter also discusses the ways in which this research contributes to the existing literature, highlights some possible practical applications for its findings, acknowledges and describes its weaknesses and limitations and suggests possible areas for further inquiry.

Finally, although some of the issues discussed by my participants in both commercialized and investigator-initiated trials have been described to varying degrees in the industry and/or academic (nursing, medical, bioethics, health law) literature, there has been very little academic empirical research exploring these issues in a specifically Canadian context. This study addresses this gap and then builds on the data to identify weaknesses in Canada’s regulatory and policy frameworks that could have important implications at the frontlines, especially in light of concentrated efforts currently underway to attract more industry-funded clinical trials to Canada.
Chapter 2: Clinical Trials In Canada: A Brief Overview

The clinical trials industry is at once vast, complex and global in scope. While this dissertation focuses on a very narrow sliver—namely investigative sites and their interactions with CROs in Canada—it is important to situate this narrow sliver within the broader context. The purpose of this chapter is to provide that context, based on a review of (mostly) industry and (some) academic literature about the pharmaceutical industry. More specifically, this chapter describes key pressures facing the pharmaceutical industry and briefly explains how these pressures have affected clinical trials in Canada. It then looks at the evolution of pharmaceutical outsourcing into a multi-billion dollar industry, introduces the key actors in this regard and then situates these actors within the Canadian context. Together, these elements provide the big picture or lay-of-the-land within which the findings of the qualitative interview study (Chapters 4-6) and critical legal and policy analysis (Chapters 7 and 8), must be situated in order to be properly understood.  

2.1 The Pharmaceutical Industry: Down, But Certainly Not Out

There are a number of challenges facing the pharmaceutical industry today. So-called blockbuster drugs are few and far between, numbers of potential products in later stages of development are dropping, patents on many of the critical money-making drugs have or are about to expire, regulatory requirements are numerous and complex, and costs associated with drug development are increasing in leaps and bounds. As one recent industry report states, “the average cost of bringing a new product successfully to market has increased by 21 percent from

8 It is worth highlighting that in relation to this “lay of the land” chapter, my literature searches yielded more in the way of industry and grey literature than academic sources and I have relied heavily on these throughout this chapter in particular.
10 This patent cliff started in 2011, with Pfizer’s Lipitor going off patent. As has been noted elsewhere, “[f]aced with more than 110 drugs losing patent exclusivity in the U.S., including 14 "blockbusters”, the world's leading pharmaceutical companies face considerable risk to their revenue streams in next three years.” See R&D Spending, Approvals Down in 2011. Available at: http://www.dddmag.com/news/2011/06/r-d-spending-approvals-down-2011
$830 million in 2010 to $1.048 billion in 2011.” 11 Other estimates put the cost at closer to 1.9 billion in 2012 (Carroll, 2012). 12 Given that clinical development is the most costly part of the drug development process (Roy, 2012; PhRMA, 2013), it is informative to look at the increased expenditures in this domain to get a sense of the pressures facing industry and the costs they are trying to control in order to remain competitive and profitable. For example, of the $48.6 billion USD PhRMA13 member companies invested in research and development in 2011, 57% (~$28 billion) was spent on phase I-III clinical trials, of which 35.8% (almost $17.4 billion) was on phase III clinical trials (PhRMA 2013). Other figures highlight the substantial increase in per patient clinical trial costs that have plagued the industry in recent years, with some figures putting the increase in per patient costs for phase III trials between 2008-2011 as high as 87% (Santos-Serrao, 2012). 14 The key factors cited as major contributors to this increase include higher enrollment costs for patients, increasing vendor fees, recruitment of clinical trial sites as well as increasing costs in technology. Increased staffing for clinical trials was also a major contributing cost, with all phases of trials at minimum doubling in their staffing levels in this time period, and phase I and II increasing by 108 and 106% respectively. 15

12 It is important to note that these numbers are not uncontested. Critics (Collier, 2009; Light & Warburton, 2005) highlight that there is a profound lack of transparency around how such numbers are reached and point to a number of other concerns. For example, the inclusion of lost opportunity costs (instead of limiting it to actual out of pocket costs), lack of identification of government funding and failure to deduct amounts saved in tax breaks are identified as serious flaws.
13 PhRMA, the Pharmaceutical Research and Manufacturers of America, is the organization that represents the country’s leading biopharmaceutical researchers and biotechnology companies. See more at: http://www.phrma.org/about#sthash.4FRfVGJ0.dpuf
14 This article cites data from a 2011 report entitled “Clinical Operations: Benchmarking Per-Patient Trial Costs, Staffing and Adaptive Design Cutting Edge Research” by Cutting Edge Information consultants. Unfortunately, as with much industry based data detailing the economic and business trends in the industry, access was prohibitively expensive (a copy of the report would have cost nearly $8000). As such, the figures cited herein are taken from summaries of the report provided by other sources.
15 As noted by Silverman (2011), an increase in clinical research associates was a major factor in this regard as “[i]n 2008, the average Phase II trial employed 3.6 clinical research associates, but that rose 9 in 2011. The average ratio of CRAs per site was 10 in Phase IIIb and 6.3 in Phase
Despite these and other challenges, however, the pharmaceutical industry is still going strong. Global sales were projected at $880 billion USD\textsuperscript{16} in 2011 and research and development spending reached $68 billion USD\textsuperscript{17} which, while a three year low within the industry, is second only to computing/electronics and far ahead of the third place automotive industry.\textsuperscript{18} In terms of international investments, global members of Canada’s Research Based Pharmaceutical Companies (Rx&D) alone invest $110 billion annually to support their research related activities in countries around the world, including $1 billion in Canada.\textsuperscript{19} As has been the case for nearly 3.5 decades then, the pharmaceutical industry continues to be a very powerful and influential force. Countries around the world, including Canada, are working hard to make themselves more attractive to the industry in order to compete for ever shrinking—though clearly still substantial—research dollars, the bulk of which are associated with clinical trials.\textsuperscript{20}

The above is a reminder that the pharmaceutical industry is at once an international high stakes, high pressure environment that is currently facing unprecedented challenges, and yet—relative to other global industries—one that continues to yield almost unparalleled influence on a global level. The remainder of this chapter is comprised of a series of sections that provide the important background information to support the analysis and discussion chapters. The first section briefly situates the discussion in the Canadian context and provides some illustration of how the economic challenges facing the pharmaceutical industry globally are being felt and

addressed in this country. This is followed by a description of why and how outsourcing has evolved in the drug development arena and an introduction to the key actors in this domain.

2.2 Clinical Trials: A Brief Overview

Clinical trials are a critical phase of the drug development process, and they come in many shapes and sizes. As noted previously around 80% of clinical trials in Canada are industry funded. Most industry-funded trials are also designed and conducted by industry sponsors or the CROs to whom they delegate such responsibilities. Such so called industry-initiated trials are often conducted to gather information about the safety and efficacy of new drugs in order to meet regulatory requirements necessary to have their products admitted to market in a given country or to be able to market the drug to a new population or for a new indication. However, clinical trials are also undertaken for a number of other reasons, including for example, to test newly approved drugs against standard treatment, or simply to learn more about drugs on the market within the terms for which they are approved. In contrast to the clinical trials supporting a new drug’s initial market approval, these other kinds of clinical trials may be funded and conducted by parties other than the pharmaceutical company who developed the drug in question. For example, such clinical trials may be funded by groups who have a special interest in a specific disease or condition, or by a public funding agency. Such funders might then issue a grant to a physician investigator (or collective of physician investigators) to design and ultimately conduct the trials. In such cases (called “investigator-initiated” or “grant-funded” trials), the physician investigator is called the “sponsor-investigator” and is responsible for both their investigator based duties, but also for sponsor based duties. The responsibilities associated with these various roles and the implications thereof, are discussed further in Chapter 7. The point here is simply to explain that there is a wide range of clinical trials, and that whereas some are funded and controlled by industry, others are funded, designed and conducted by a range of other kinds of stakeholders.

21 Although, and as is discussed elsewhere in this dissertation, such trials may also be funded in whole or in part by industry.
22 The Canadian Cancer Research Alliance (CCRA) provides a more concrete illustration of the ratio of investigator to industry-initiated trials. In its 2011 report (State of Cancer Clinical Trials
Although there are some nuances, and regardless of who is funding or conducting the trial, clinical trials generally fall into one of four categories. Very briefly, and as described by Health Canada, the categories may be defined as follows:

**Phase I trials**
Initial safety studies on a new drug, including first administration of the drugs into humans, usually conducted in healthy volunteers.

**Phase II trials**
Clinical trials to evaluate the efficacy of the drug in patients with medical conditions to be treated, diagnosed or prevented and to determine the side effects and risks associated with the drug.

**Phase III trials**
Controlled or uncontrolled trials conducted after preliminary evidence suggesting efficacy of the drug has been demonstrated.

**Phase IV trials**
All studies performed after the drug has been authorized by the regulator for the market, and related to the authorized indication.

The above description suggests a sharp demarcation between the various phases; however, in actual practice there is a great deal more overlap. The figure below (Figure 2.1) illustrates that clinical trials tend to extend along a continuum and evolve over time. The dark spots indicate the main objectives of a given kind of study and what phase these goals are concentrated in, but the clear spots illustrate that such goals can cross phases. For example, while phase III studies

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24 Copyright International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). This figure is copied directly from the ICH-E8 guideline, General Considerations for Clinical Trials, p.5.
are the main point in which therapeutic aspects of the drug are being confirmed, this process evolves out of the therapeutic exploratory stage (phase II) and continues through to phase IV.

Figure 2.1: Phases of Clinical Trials

Recalling the dramatic figures outlined above in relation to the cost of studies, it is also worth highlighting that not all compounds or products that start the clinical testing process will proceed through all stages. In fact, the attrition rate from pre-clinical phases to market is quite astounding. As described by Rx&D (the industry association representing research based pharmaceutical and biotechnology companies in Canada), for every 250 compounds that go through preclinical testing, 5 will enter the clinical testing phase. From those 5, only 1 will ultimately be approved. Figure 2.2 helps illustrate the attrition process, as well as the time and number of subjects typically involved in each phase.²⁵

²⁵ Used with permission from Canada’s Research Based Pharmaceutical Companies (Rx&D). Available at: http://www.canadapharma.org/en/our-industry/industry-facts/saving-lives---transforming-care/info-graphics
For all phase I-III clinical trials, the sponsor must submit a clinical trial application to Health Canada (this is not a requirement for phase IV studies). While the legal and ethical frameworks for the oversight of clinical trials will be described in great detail in Chapter 7, it is helpful here to just very briefly introduce the key documents. Health Canada’s authority to regulate clinical trials and approve new drugs in Canada is established in the *Food and Drugs Act* (“the Act”), and further described in its *Division 5 Regulations* (Drugs for Clinical Trials Involving Human Subjects, hereinafter “the Regulations”)

\[26\]. In addition, Health Canada has adopted the *ICH-Good Clinical Practice (GCP) Guidelines* as a guidance document.

\[27\] The guidelines constitute an international standard for the ethical and scientific conduct of clinical trials, providing principles and practices related to the protection of clinical trial subjects rooted in the Declaration of Helsinki

\[28\], as well as standards to ensure the integrity and reliability of

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\[26\] *Food and Drugs Act*, R.S.C. 1985, c. F-27; *Division 5 Regulations* C.R.C., c. 870

\[27\] These are the *Guidelines for Good Clinical Practice established by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH-GCP)*, E6 (R1), June 10, 1996.

\[28\] It is important to note that while the *ICH-GCP Guidelines* may be rooted in the Declaration of Helsinki, the extent to which they are ethical documents is limited (Goodyear et al, 2009;
clinical trial data. Whereas the Division 5 Regulations outline sponsor responsibilities, the GCP Guidelines describe the roles and responsibilities of other key parties including the CRO, the Monitor, the PI and the REB. The Regulations and GCP Guidelines apply to all clinical trials in Canada, regardless of whether they are industry or investigator-initiated. Finally, the standards established for the ethical conduct of research by the Tri-Council Policy Statement 2 (TCPS2)²⁹ apply to all clinical trials funded in whole or in part by one of the three federal funders (CIHR, SSHRC, NSERC), or which studies take place in whole or in part at institutions receiving such funding. The principles and standards of the entire document apply to clinical trials; however, Chapter 11 also addresses considerations specifically relevant to clinical trials. While not an exhaustive list³⁰, taken together these legislative documents and guidelines constitute the mainframe of the legal framework governing clinical trials in Canada.

2.3 Clinical Trials In Canada: Feeling The Pinch

Although clinical trials are perhaps most often thought of in a health context, and while some have profound implications for the health and wellbeing of Canadians³¹, they are also extremely important economically. For example, and as illustrated by Figure 2.3³², the activities of Canada’s Research Based Pharmaceutical Companies alone contribute over $3 billion to the

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³⁰ For example, other relevant aspects include privacy legislation and consent legislation (among others) that address the research context within a broader focus.
³¹ Not all clinical trials are created equal. As will be discussed further in Chapter 9, critics point out that some trials (both phase IV and earlier) are much more about furthering a sponsor’s economic interests than they are about bringing new or improved health benefits. For example, one recent report suggests that 77 out of the 109 newly patented drugs in Canada in 2011 offered “little or no therapeutic benefit” over current therapies. (PMPRB, 2011; Gagnon, 2012)
³² Figure copyrighted to Canada’s Research-Based Pharmaceutical Companies (Rx&D). Used with permission (granted September 3, 2013).
Canadian economy each year, from research and development spending to direct employment and contributing to the creation of additional jobs across the country.\(^\text{33}\)

**Figure 2.3: Economic Impact of Rx&D Companies**

However, Canada has been impacted by the hard times hitting the pharmaceutical industry, with industry investments in Canada decreasing since 2008. Whereas total investment

\(^{33}\) According to a 2013 report by KPMG (SECOR-KPMG analysis of simulations by Statistics Canada based on internal data provided by Rx&D) Rx&D and its members contributes $1.08 billion to Research and Development in Canada, which translates into contributions of more than $3 billion to the Canadian economy — $2 billion directly and $1 billion indirectly. The report finds, for example, that the research based pharmaceutical industry supports 46,000 full time jobs across Canada. KPMG (2013). Summary of 2012 R&D Spending and Investments by Rx&D Members Available at: [http://www.canadapharma.org/CMFiles/Media%20Centre/News%20Releases%20and%20Statements/20130514_KPMG_Summary_2012_Spending_Investments_EN.PDF](http://www.canadapharma.org/CMFiles/Media%20Centre/News%20Releases%20and%20Statements/20130514_KPMG_Summary_2012_Spending_Investments_EN.PDF). Accessed September 13, 2013.
by patentees in 2007 was $1.32 billion, this same group invested $991.7 million in 2011, a decrease of 15.8% over 2010. Of this $991.7 million, $525.1 million went to applied research, of which 75.2% was allotted to clinical trials.34

While clearly an important economic driver in the Canadian economy, Canada’s share of the overall pharmaceutical research and development market is quite small. By way of illustration, the map below (Figure 2.4) shows the global distribution of all clinical trials listed in the clinicaltrials.gov database.35 As can be seen, Canada hosts only a small fraction (11322 of 151261—or about 7%) of such trials. The U.S. holds the largest share (71147, or approximately 47%). According to these figures, in terms of countries Canada actually places second behind the U.S., with Germany following in third place with about 6.9%. Within Canada, the bulk of the clinical trial activity is in Ontario (7099) and Quebec (4183) with only 2950 taking place in British Columbia. This echoes findings from the 2011 annual report of the Patented Medicines Prices Review Board (PMPRB) which indicates that Ontario and Quebec account for 86% of total pharmaceutical R&D expenditure, with the western provinces accounting for just 12.6% of total R&D expenditure.36

Given the significant implications and potential benefits for both the health and prosperity of the country, it is no wonder that there has been a great deal of interest and attention paid to reports that Canada’s share of clinical trials is in fact dropping (Saryeddine et al., 2011) and that the competition for industry dollars is getting more fierce as industry sponsors reap the benefits of hosting their trials in developing countries with their dense, often treatment naïve populations, lower costs, and in many cases lighter regulatory requirements (Saryeddine et al., 2011; Schipper et al., 2011). The President of Rx&D noted in June 2012, that international competition for research dollars is fierce and it has become more and more difficult for Canadian CEOs to win global investments for Canada… Without question, we must attract more international investment – a larger share of the $110 billion being invested by our global companies annually.38

37 This is the background document (Canadian Clinical Trial Summit: Starting the Conversation) from the Clinical Trial Summit hosted by Canada’s Research Based Pharmaceutical Companies (Rx&D), Canadian Institutes of Health Research (CIHR) and the Association of Canadian Academic Healthcare Organizations (ACAHO) on September 15, 2011 in Ottawa. A number of examples of initiatives that were underway at the time of the summit are listed by province. The report is available at: http://www.acaho.org/?policy_2011. Last accessed September 12, 2013.
Canada’s concern about regaining and growing its share of the clinical trial market was also clear at the clinical trial summit held in Ottawa in September 15, 2011. As reported by Vanderwel (2012),

Health Canada data on the decline in the number of clinical trials in Canada were presented by Rx&D, CIHR and ACAHO. These three orgs believed that while patients are available in Canada to be enrolled in trials, the cost/performance, operational environment and recruitment reliability are seen as areas in which Canada has “lost our edge”….A call was made to improve the research infrastructure to maintain Canada’s attractiveness for fast, efficient and reliable research. (p.17)

Fewer industry dollars for pharmaceutical research and development affects not only research and clinical trials directly funded by industry, but also has a huge impact on grant funded or investigator-initiated trials since these too are partially supported by industry through fees charged by research institutions as well as through financial and in kind contributions, university chair endowments, charitable donations, grants or sponsorships (Vanderwel, 2012). As such, it is not surprising that this sense of urgency to regain and grow the contract (i.e., industry sponsored) clinical trial industry in Canada is being felt and broadcast not just by industry organizations, but also by federal and provincial regulators, federal and provincial research funders, academic institutions, private or community research units and sites, and others.39

2.4 Keeping Canada On The Map: Initiatives To Attract Clinical Trials

A wide variety of national and provincial initiatives and networks are being undertaken to try to make Canada a more inviting place in which to conduct trials—these include (among others) efforts to harmonize the ethics review process, to improve infrastructure and streamline regulatory requirements and develop and share tools, training opportunities and best practices to enhance Canada’s research capacity (Rx&D et al., 2012a; Saryeddine et al., 2011). Health Canada for example has made changes to the regulatory framework under the *Food and Drugs Act* and *Division 5 Regulations*. These changes are discussed in Chapter 7, but include (among

39 As discussed further in chapter 9, it is important to note that the vast majority of drugs tested in clinical trials will not offer much in terms of improved therapeutic benefit. As such, the main value of these trials is to the pharmaceutical companies, in terms of being able to get their new drugs onto the market.
other things) faster review times and penalties for the regulator for failure to meet those review times. Other national level initiatives include the Network of Networks (N2), which creates networks and connections between existing disease networks, universities, institutions, sponsors and other stakeholders specifically to enhance Canada’s research capability and capacity. CIHR’s Strategy for Patient-Oriented Research (SPOR) is another national level effort to build capacity and also to:

(a) establish an integrated, leading edge, pan-Canadian clinical research infrastructure along the full continuum of patient-oriented research; and
(b) to strengthen organizational, regulatory and financial support for clinical studies in Canada and enhance patient and clinician engagement in these studies.

While not directly geared at attracting industry clinical trials, making Canada more competitive and attractive to industry partners to support the commercialization of research is certainly among its explicitly stated goals.

There are also a wide variety of provincial initiatives underway across the country to entice industry sponsors. In British Columbia, for example, the BC Clinical Research Infrastructure Network (BCCRIN) is a major collaboration between provincial health authorities, research institutions, universities, industry associations and funding agencies to help increase B.C.’s competitiveness in the global clinical trials market. As explicitly stated on their website, BCCRIN was formed in direct response to the decreasing numbers of industry sponsored clinical trials coming to Canada and declining levels of government support for clinical research in

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40 The penalties for failure to meet the review times were implemented in 2004 and are outlined in the *User Fees Act* (S.C. 2004, c. 6). These and other changes and associated concerns are discussed in Chapter 7.
41 For more information on N2, please see: [http://n2canada.ca/](http://n2canada.ca/) (last accessed September 12, 2013).
42 Please see CIHR’s description of this important national level initiative at: [http://www.cihr-irsc.gc.ca/e/44000.html](http://www.cihr-irsc.gc.ca/e/44000.html)
43 As is discussed in more detail in chapter 7, the ever increasing commercialization of research has a number of important implications at a global level, not the least of which is a lack of attention to, and prioritization of, global health inequality and much needed health policy and systems research. See for example, Pratt & Loff (2012) and McDonald & Preto (2011).
44 As described on the BC CRIN website, available at: [http://www.bccrin.ca/what-were-about/](http://www.bccrin.ca/what-were-about/).
While still relatively new (launched in 2010), a broad range of important initiatives are well underway and include, among others, capacity building and training efforts, patient recruitment efforts (including research participant survey to identify relevant factors influencing decisions regarding research participation), contract and tool development, and business development.

Another important initiative in this province is the BC Ethics Harmonization Initiative (BCEHI), funded and facilitated by the Michael Smith Foundation for Health Research (MSFHR). The initiative involves BC’s six provincial health authorities and four major research universities (University of British Columbia, Simon Fraser University, University of Victoria, University of Northern British Columbia). Also running since 2010, the goal is to improve BC’s attractiveness as a location for multi-site, multi-region health research (including clinical trials) by streamlining ethics review processes and reducing duplication. Lack of REB standardization, accreditation and transparency—problems that have been discussed in detail elsewhere and which suffer from a profound lack of national level leadership in Canada—are among the hurdles this initiative needs to overcome (Glass, 2006; Hebert & Saginur, 2009; McDonald, 2000; McDonald et al., 2011). An important, though preliminary, milestone in this effort was achieved in May 2013 when an agreement was reached granting the 14 review boards under the jurisdiction of the various BCEHI collaborators authority to work together to develop processes by which to streamline ethics review between participating institutions. Whether and how this agreement leads to the hoped for results remains to be seen.

Perhaps one of the most comprehensive and multifaceted provincial initiatives is Clinical Trials Ontario, which aims “to make Ontario a preferred location for global clinical trials, while maintaining the highest ethical standards.” As indicated on their website, this is an integral part of Ontario’s Life Sciences Commercialization Strategy and has been allocated a 3-year commitment from the Ministry of Economic Development and Innovation with an annual budget of $1.5 million. Key partners providing input and additional support are drawn from the

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45 BC CRIN Website: http://www.bccrin.ca/who-we-are/ Last accessed September 1, 2013.
47 Ibid.
provincial community of stakeholders involved in clinical trials in Ontario from the public and private sectors. The main goals of this initiative, which launched in 2012, are threefold: to reduce time and cost of conducting trials in Ontario by harmonizing the ethics review and other administrative processes; grow strategic partnerships with and between investigators, industry and government to attract clinical trial investment to Ontario; and to engage patients and the public to recognize the benefits of clinical trials for their own health and that of their families and society and to improve recruitment through education.

The above is just a sample of some of the many initiatives currently underway to help promote Canada to industry as an attractive place to conduct clinical trials. A relatively brief review of the literature did not yield many academic critiques of these various efforts—either individually or collectively. However, Vanderwel (2012) in her report to Health Canada entitled *International and Canadian Activities Related to the Ethical Review of Clinical Trials* does provide an overview of national and provincial efforts in this regard and offers a few observations in relation thereto. Many of her comments address the important issues and concerns raised by others (Anderson et al., 2011; McDonald, 2000; McDonald 2001) that ethics review, oversight and accreditation efforts still tend to be too narrowly limited to the research ethics board instead of adopting a broader, system wide approach. More specifically related to the efforts to attract clinical trials to Canada, she observed an important disconnect; that is, that while most efforts currently underway target the streamlining and harmonization of activities and structures for research taking place within academic or public institutions—the vast majority (65-75%) of clinical trials are taking place in private or community based settings. One aspect of this is that, as Vanderwel notes (and as echoed by some of my participants) community based sites have strengths and successes that public sites could perhaps learn from. However, this also raises the question as to whether private, community based sites as a group are being overlooked in

48 The website ([http://www.ctontario.ca/](http://www.ctontario.ca/)) lists the following partners: the Council of Academic Hospitals of Ontario, [Ontario Council on University Research](http://www.ucr.on.ca/), Council of Ontario Faculties of Medicine, [BIOTECanada](http://www.biotecanada.ca/), Canada’s Medical Technologies Companies through MEDEC and Canada’s Research-Based Pharmaceutical Companies through [Rx&D](http://www.rxandd.com/).

49 In addition to the examples described in the text above, another important effort includes the [Ontario Cancer Research Ethics Board](http://www.cancerresearchethicsboard.ca/) that functions as a single REB in that province to facilitate scientific and ethical review of multi-centre oncology trials.
other kinds of ways too—in terms of oversight, for example. Some of the challenges and weaknesses of the Canadian approach to clinical trial oversight are discussed in Chapter 7.

As suggested earlier, however, it is not just Canada’s share of the market pie that is shrinking—the pie itself is getting smaller (Vanderwel, 2012). In order to stay competitive in these circumstances, the pharmaceutical industry has undergone some profound changes in the last 3 decades. These changes include, among others, transitioning away from working closely with academic institutions for the design and conduct of clinical trials to a heavy reliance on a variety of private sector service providers, including contract research organizations (CROs). This transition is described in more detail below.

### 2.5 Structure Of The Clinical Trials Industry

Prior to the 1980s, “industry grants to academic institutions to fund studies by faculty members gave investigators total responsibility” (Angell, 2008), including control over study design, data collection, analysis, and reporting of results. Since the 1980s, a number of factors have come together to create a very different reality, and have lead to a dramatic increase in the overall level of industry control and influence over the drug discovery and development processes (Angell, 2008; Krimsky, 2003; Lemmens & Bouchard, 2007; Lenzer, 2008; Mirowski & Van Horne, 2005). A key factor in this shift has been an increased reliance on industry funding and a blurring of boundaries between the public and private sectors in the scientific enterprise. As has been discussed in the extensive literature on the commercialization of science, this process began in earnest in the economy of the 1980s when many countries including the U.S., the UK and Canada instituted major budget cuts for public services, including universities (Brown, 2002). In addition to cutting funding support, various governments also introduced incentives to bring industry and academia into closer contact. For example, in the American context, the passage of the Bayh-Dole Act in 1980 is widely recognized as a primary cause of the commercialization of medical research in the U.S. (Lemmens, 2004; 2004a). By allowing universities and researchers to obtain patents on the results of their publicly funded research, this legislation encouraged academics to enter into relationships with industry to help them develop commercial applications for their discoveries (Krimsky, 2003; Lemmens, 2004, 2004a). Around this same time period, the pharmaceutical industry was experiencing significant growth with the development of blockbuster drugs for a wide range of diseases and disorders. With profits in the
billions, the pharmaceutical industry’s sphere of influence and incentive to exercise such influence, increased dramatically (Lemmens, 2004a).

Although the industry sphere of influence was growing in leaps and bounds through the 1980s and early 1990s, the bulk of industry dollars for clinical research were still going to academic health centers (AHCs) (CenterWatch, 2008; Gelijns & Thier, 2002; Mirowski & Van Horne, 2005; Rettig, 2000). This started to shift significantly in the mid-late 1990s. Some statistics indicate that academia’s share of industry sponsored clinical research went from 80% in 1988 to 40% in 1998. Other statistics suggest that the AHCs share of the industry clinical trials market fell from 71% in 1991 to 23% in 2006 (CenterWatch, 2008; Mirowski & Van Horne, 2005). As one industry analyst notes,

> Up until the early 1990s, academic medical centers (AMCs) were the primary and predominant home of industry sponsored clinical trials. As these programs became larger and more complex and costly, industry sponsors grew tired of the inherent inefficiencies in working with academia, including protracted contractual and budget negotiations, bureaucratic and slow moving institutional review boards (IRBs), and higher relative costs associated with poorer performance.” (Getz, 2007a)

As will be described below, a range of for profit auxiliary service providers—dominated by the contract research organization (CRO)—picked up the slack created by industry’s dissatisfaction with their academic partners. Hence, “in a trend that has received surprisingly little attention, contract research organizations have gradually taken over much of academia’s traditional role in drug development over the past decade” (Shuchman, 2007).

The shift away from academia has taken place in at least two different ways. First, and as illustrated above, there has been an exodus of clinical trials being conducted in academic sites in favor of private community based sites. Approximately 80% of all clinical drug trials in Canada are funded by industry (Lexchin, 2012) and roughly 2/3 or almost 70% of clinical trials in Canada now take place in the community at privately owned and operated facilities, as opposed to academic sites or hospital settings (Ogilvie, 2012). However, not all clinical trials can be

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50 This is the report by the Standing Senate Committee on Social Affairs, Science and Technology (2012). Canada’s Clinical Trial Infrastructure: A Prescription for Improved Access to New Medicines. This report can be downloaded at: [www.senate-senat.ca/social.asp](http://www.senate-senat.ca/social.asp). Last accessed September 12, 2013.
conducted in the community\textsuperscript{51} and yet even for those clinical trials that take place in the academic setting, there has been a shift in the locus of control. Whereas academic investigators used to have significant control over the trials with which they were involved, they are now much more likely to simply be collecting data and, as others have described, “at the extreme…have become little more than hired hands, supplying patients and collecting data according to the company protocol.” (Angell, 2008) Control over the design, management, trial conduct, results reporting and other key aspects, has been transferred from academics to CROs. Hence, even those industry-initiated\textsuperscript{52} trials that still take place in academia are largely out of the hands of the investigators.

\subsection*{2.6 Outsourcing In The Pharmaceutical Industry}

It is worth noting that industry sponsors might have decided to (more or less) abandon academia in favor of a more in-house approach wherein the individual pharmaceutical companies would assume responsibility for (e.g.,) design and conduct of clinical trials required to test and develop their products. However, as the pharmaceutical industry was looking for more attractive alternatives to their relationship with academia, there was also a larger trend in the broader business community towards outsourcing, which has seen the large, diversified “mega-corp” being replaced by an organizational form in which a nucleus of ‘core’ activities is performed permanently in-house by full time employees, the rest being supplied through contract with other organizations or individuals. Its hallmark is a relatively narrow focus…concentrating on activities in which it believes it has a distinct advantage, or that are essential to its competitive survival. (Domberger, 1998, p.18)

In very general terms, the goal of outsourcing is to support the “enhancement of the financial performance” (Nichol, 2006, p.409) of the outsourcing company. Outsourcing is today

\footnote{For example, some clinical trials target diseases or conditions which are commonly treated in an academic and/or large tertiary care setting.}

\footnote{As described previously, academic investigators tend to conduct a combination of industry-initiated trials (i.e., trials that are funded, designed, controlled by industry) and investigator-initiated trials, wherein the investigator designs and controls all aspects of the study. Such studies are funded by a variety of sources-government, not for profit organizations, and are also frequently funded in whole or in part by the pharmaceutical industry.}
considered by pharmaceutical companies to be “strategically critical to their long-term viability” (Getz, 2012).

2.6.1 Outsourcing In The Pharmaceutical Industry: Drivers

There is no question that the Contract Research Organization (CRO) industry has grown up fast. Revenues of about $50 million in the late 1970s have advanced to about $10 billion [in 2004] alone...the size of the outsourcing market to CROs is continuing to rise. By any measure we are a healthy, growing industry that has a significant role in the drug development process. (Gillings, 2004, p.6)

Nine years later, this statement is just as accurate. While figures vary quite widely in terms of assessing the size of the global CRO market (Getz et al., 2012), some estimates put the worldwide CRO market at $37.4 billion in 2013. Other assessments looking specifically at the U.S. pharmaceutical contract services market valued it at $39.5 billion USD, with 16% ($6.5 billion) of that attributed to clinical research services (Getz et al., 2012). In terms of numbers, 3244 individual contract research organizations were identified as functioning in the U.S. across the entire range of services related to the pharmaceutical industry, with a sub total of 643 being active in clinical research (Getz et al., 2012). As others have noted, “there is no doubt that pharmaceutical R&D outsourcing is big business” (Scott, 2008). Despite the prominence of the CRO, it has been noted by Mirowski & Van Horne (2005), that apart from some scattered comments in industry literature and some aggregate industry data, it is extremely difficult to get information about the history of their development and evolution. One source puts the origins of the first commercial contract services provider in this industry around 1975 (Nichol, 2006). Another source claims that generally speaking, the CRO did not exist before 1980, and observes that, of the four largest pharmaceutical CROs, Quintiles Transnational was incorporated in 1982, and Parexel International was founded in 1983. Covance was formed in 1987…CROs differ profoundly from earlier for-profit toxicology, bioassay and pharmaceutical testing firms, which they have tended to drive out of business.” (Mirowski & Van Horne, 2005, p.538 (fn 5))

What history is available suggests that CROs have arisen at least in part in response to increasingly stringent regulatory requirements around the drug development process that date back to the Thalidomide controversy and resulting legislative amendments. In the U.S., these were the 1962 Kefauver-Harris Amendments under the Federal Food Drug and Cosmetic Act (1938), through which the FDA exercised their jurisdiction and set the standards and format of drug testing from the pre-clinical stage through to final human clinical trials (Lemmens & Bouchard, 2007; Mirowski & Van Horne, 2005). Under the new regulations, drug companies had to demonstrate both the safety and efficacy of a drug before marketing it, and the standards set out ultimately shaped accepted international standards (Nichol, 2006). CROs emerged, at least in part, as a result of the increased regulatory stringency and regulatory requirements that demanded more and higher quality data to support new drug applications (Thomis & Desai, 2006).

Another driver of the outsourcing trend is simply the need for speed in the drug development process. The development of a new drug is a lengthy (6-10 years)54, expensive process with estimates of the associated cost ranging from $200 million to $1.9 billion.55 Moreover, the cost of every day of delay in getting a drug approved has been quoted at $1.3 million (Brody, 2007). Reducing the time that it takes to get a drug through the various development stages is a key factor in reducing overall costs, and allowing maximum realization of profits. The patent protection system is a critical factor in this regard. While a detailed exploration of the patent considerations in the drug development process exceeds the scope of this dissertation, it is important to recognize that the time of market exclusivity from the time a drug is admitted to market (known as the effective patent life (EPL)) is central to a company’s ability to recover costs and make a profit on the substantial R&D investments that go into drug

55 http://www.fiercebiotech.com/story/economists-cite-soaring-costs-behind-average-19b-price-tag-drug-rd/2012-12-03?utm_medium=nl&utm_source=internal. It is difficult to get reliable numbers in terms of costs in this industry. For a good discussion on this point, see Collier (2009).
innovation. Given that the life of the patent is generally 20 years\textsuperscript{56}, and that the drug
development process from the time the patent is filed can take more than 10 years, in effect the
EPL is generally about 10 years in the Canadian context (Grootendorst, 2007). To address this
shortfall, some jurisdictions such as the United States, the European Community and Japan, have
implemented ‘patent term restoration’ legislation.\textsuperscript{57} As has been noted elsewhere, the very
purpose of the CRO in clinical trials is to speed up the process (Wadman, 2006) and they are
apparently effective in this regard. According to one independent analyst, “clinical trials
conducted by CROs are completed an average of 30 percent more quickly than those conducted
in-house. This results in an average time savings of some four or five months, translating to
$120 million to $150 million in increased revenue potential.”\textsuperscript{58}

However, while a key factor encouraging outsourcing is certainly the potential for
increased speed, and while in some ways, this consideration underlies most of the other factors,
there are other considerations. For example, outsourcing also can be an effective way of easily
increasing or decreasing capacity while maintaining constant levels of personnel and overhead
in-house. This can be particularly important in smaller companies that are moving into new
areas of specialty or biotechnology firms who find themselves at the point of needing to conduct
clinical research (Getz et al., 2012; O’Donnell, 2007). Instead of developing the skill sets and
infrastructure necessary to do this, they can instead choose to contract this out to others
specializing in these areas (Getz et al., 2012; Rettig, 2000). Globalization also supports the
move towards outsourcing to international CROs that are more familiar with the regulations and

\textsuperscript{56} Pursuant to the \textit{Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS)},
patent life for any product is 20 years from the date that a patent application is filed in all World
Trade Organization member countries.

\textsuperscript{57} As explained by Grabowski (2006), in the U.S. the \textit{Drug Price Competition and Patent Term
Restoration Act (Public Law 98-417, otherwise known as the Hatch-Waxman Act)} was passed in
1984. This essentially makes it possible to seek patent extensions for up to 5 years over the
normal 20 year patent lifespan; however, the total patent life for the product in question cannot
exceed 14 years from the product’s approval date.

\textsuperscript{58} This information is from the Association for Clinical Research Organizations (ACRO) website
at \url{http://www.acrohealth.org/industry-ataglance.php}. The quote is attributed to KMR Group,
Inc., a management consulting firm specializing in resource management, benchmarking, process
analysis and decision making for the pharmaceutical industry. As explained on the ACRO site,
the “quoted profits are based on market expectation that an average product generates $1 million
in revenues per day: PAREXEL’s Pharmaceutical R&D Statistical Sourcebook 2004/2005.”
requirements of emerging markets (Schipper et al., 2011; Thiers et al., 2008). Having an understanding of the locale within which a trial is situated can be critical for ensuring it runs as smoothly and efficiently as possible. Moreover, the international CROs can often address regulatory and other requirements in multiple jurisdictions effectively and efficiently (Getz, 2007b; Rainville, 2002; Rettig, 2000; Schipper et al., 2011). In addition, sponsors are increasingly looking to run early phase clinical trials (Phase I/IIa) in special populations in order to make quicker go/no go decisions thereby saving significant time and resources by avoiding going too far down an ultimately unsuccessful path. As such, it is beneficial to sponsors to be able to draw on CROs that have access or databanks of special patient populations and particular expertise in a range of relevant therapeutic areas in all phases of clinical trials (Rettig, 2000). Not unreasonably, some commentators have also opined that in the 1980s and 1990s there was “a growing hostility of the FDA towards free-market pharmaceutical manufacturers...[and that] the use of contract researchers seem[ed] to enhance FDA’s perception of the objectivity of a trial” (Olmstead, 1992). However, this claim that outsourcing was in part an effort to insulate pharmaceutical companies from the conduct of the clinical trial process, and thereby mitigate, or appear to mitigate, conflicts of interest, is not unchallenged. Azoulay (2003), for example, rightly indicates that CROs do not shift the locus of responsibility for trial integrity away from the sponsor. Azoulay (2003) also points to the fact that pharmaceutical sponsors do not seem to appeal to the mitigation of conflicts of interest as a rationale for their decision to outsource, and the fact that FDA medical examiners reviewing trial data are often unaware of whether a study they are reviewing has been outsourced. For these reasons, Azoulay (2003) concludes that mitigating real and apparent conflicts of interest was not a driving force for outsourcing in the pharmaceutical context, but that this move was much more about work-force cohesion and bottom-line considerations. Finally, outsourcing to CROs also allows the sponsoring companies to maintain greater control over clinical trial data. Unlike academic investigators, CROs are not interested in publishing and therefore do not make any demands on their clients to release data in a timely fashion or at all (Mirowski & Van Horne, 2005).

59 This is alluded to in the marketing materials for Quintiles International that I received at a conference in 2009.
2.6.2 Outsourcing In The Pharmaceutical Industry: The Cast

For all the reasons discussed above, the contract research industry has become a key resource for pharmaceutical companies in their efforts to trim costs, speed up drug development and maximize available profits. A wide range of “auxiliary agents” have emerged “to mitigate pharmaceutical companies’ losses from R&D development” (Fisher, 2009, p.8). These include among others investigational sites, site management organizations (SMOs), contract research organizations, academic research organizations and private research ethics boards. While the dominant player, and often responsible for engaging, coordinating and monitoring the activities of the others, CROs are only one part of this larger industry. Although sponsors typically rely heavily on CROs (Getz, 2012), CROs are not involved in all clinical trials and sponsors may only delegate some subset of their responsibilities. It is impossible to capture the nuances in these relationships without a specific example; however, figure 2.5 illustrates in general terms the relationships and lines of communication in an industry-sponsored clinical trial wherein the CRO has been delegated all of the sponsor’s clinical trial responsibilities. As explained by Mello & Joffe (2003), the study protocol is typically part of the clinical trial agreement (denoted by purple line below), which delineates the scope of work for the investigative sites. The list of entities in the bracket on the right represent a selection of other outsourced service providers that may also be contracted by either the sponsor or CRO.

60 Fisher (2009) provides a helpful discussion of the various “auxiliary agents” and their relative place on the contract research organizational hierarchy, and I have drawn on her work here. In addition to the parties discussed above, she also mentions more peripheral service providers such as study brokers, clinical advertising agencies, and central patient recruitment companies. Of these more secondary service providers, the patient recruitment organizations are most relevant to our discussion and could be considered a niche service CRO. One example of such an organization is HCG (Health Care Communications Group), who specifically state they “[have] one specialty—professional clinical trials recruitment services. We help pharmaceutical companies involved in drug development build their subject recruitment plans upon a foundation that will enroll and retain patients in Phase II - IV research studies.”

http://www.hcg.com/default.asp While there are such niche service providers, patient recruitment is a service that is also a staple offering of the full service CROs.
2.6.2.1 Investigative Sites

Fisher (2009) describes a contract research industry hierarchy in which the investigative site is placed at the base as “the most basic level organization” (p.9). Investigative sites are companies or clinics that conduct studies through contracts with pharmaceutical companies or CROs. These can be located in a wide range of settings, from large academic health centers and
teaching hospitals, to community research institutions to smaller community health clinics and physician practices (Fisher, 2009). In each domain, sites may be more or less sophisticated or structured, be more or less well integrated with the clinical practices that are often run out of the same space and provide access to at least some of the study subject population, and have access to more or less external research support.

In many instances, the (largely U.S. based) literature tends to describe a dichotomy between academic and community based sites; however, in the context of the Canadian publicly funded health care system, it is perhaps clearer to describe sites as falling inside or outside the public system. For example, according to the 2011 Clinical Trials and Preclinical Infrastructure Asset Map published by Genome B.C., there are at least 59 clinical trials units (CTUs), centres and study sites across 5 of the 6 health authorities in B.C. (the 6th health authority, Northern Health does not yet conduct clinical trials). The asset map identifies a range of levels of infrastructure within the sites it lists. For example, some sites are identified as clinical trial units or centres, which the report defines as “a cohesive entity with dedicated study nurses and data managers. It acts as an independent management unit even if it has no dedicated space.” In addition to investigators and staff, such units also offer “quality control/assurance procedures, of which Standard Operating Procedures (SOPs) and Good Clinical Practice (GCP) regulations and guidelines provide an integral part” and a variety of administrative support.

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61 As noted in the glossary at the start of this dissertation, for the purposes of this document I use academic and public interchangeably; likewise, sites not falling into the public/academic category are identified interchangeably as “private”, “community”, “independent” or “non-academic”.

62 As will be described in the next chapter and Chapter 9, while B.C. is a distant third to Ontario and Quebec in terms of clinical trial activity, this research study looks at the Canadian clinical trials industry through a B.C. lens. For example, many of my participants in the qualitative interview study were located in B.C., and my first hand exposure to the industry has really been limited to this province. That being said, I have attended industry conferences in other parts of the country and a number of my participants brought a more trans Canadian perspective to their interviews as a result of having had experience working in other provinces.

63 As noted by Genome B.C., “the CTUs, centres, and study sites included here are probably not all-inclusive. The listings contain only those facilities that the authors were able to discover through extensive searches and discussions with hospital and health authority personnel.” In fact, they also specify that this number (59) does not include individual physicians conducting clinical trials out of some of the smaller regional hospitals—even though they list some of these investigators in an appendix to their report.
including contract services, budget negotiations, accounting, REB submissions, and regulatory requirements among others. 64

Other sites, while not qualifying as units or centres, still “employ study nurses or coordinators” and many can access additional support from the appropriate Clinical Trials Support Unit (“CTSU”), though access and available services vary across health authorities. 65 CTSUs in turn offer a range of services, which generally include assistance with study design, methodology and protocol development, budget planning, REB submissions, regulatory documentation and training in clinical trials procedures and Good Clinical Practices, among others. 66 In addition, the report notes that some of the province’s smaller hospitals also have individual investigators who perform clinical trials, but does not indicate whether they have research staff or support available to them. 67

Hence, within the context of public sites— across universities, large academic hospitals, smaller community hospitals, and other medical units within the various health authorities— there are numerous investigative sites of varying degrees of structural complexity and infrastructure. In addition to the sites working within the public system, the Genome B.C. asset map reports that there are also at least 25 independent organizations that provide a range of clinical trial support services, including at least 8 for-profit independent investigative sites working outside the public system, 5 of which are disease-specific (cancer, urology, endocrinology, gastrointestinal, and cardiology). 68 Extrapolating from the U.S. literature (Fisher, 2009; IOM, 2012) and the data from the present study, the variation in terms of site infrastructure

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64 Genome B.C. Asset Map, p. 7.
65 For example, a review of the report suggests that investigators who are in Interior Health do not have access to a formal Clinical Trial Support Unit.
66 For a full list of the services provided, please see: Clinical Trials and Preclinical Infrastructure - Asset Map, available at: http://www.genomebc.ca/profile/publications/asset-maps/
67 It seems reasonable to assume, however, that while some of these investigators would have some level of support or research staff, others likely do not. Again, depending on where they are located, these investigators would also have varying levels of access to services provided by Clinical Trial Support Units.
68 The 17 other for-profit organizations offer clinical trial support across a variety of services, including among others: a few CROs, one for profit REB and a range of analytic and preclinical service providers. As previously noted, there are undoubtedly many other investigators participating in clinical trials out of their private offices and/or small regional hospitals who have not been counted.
and sophistication in terms of research readiness and support also varies significantly within the private context. Much as the less sophisticated sites within the public domain can sometimes seek support or assistance from the Clinical Trial Support Units, sites working within the private sector may have the option of working with a Site Management Organization (described later in this section), to gain access to additional support including training, staffing and regulatory assistance among other services.

An important distinction between the public and private sites is in relation to research ethics review. Whereas clinical trials taking place at investigative sites that are part of the public system must be approved by the appropriate institutional research ethics board (there are 23 in B.C.) private investigative sites may use private research ethics boards. The use of centralized or private research ethics review is a significantly faster and more streamlined process than the institutional review board reviews and provides the industry sponsor or CRO much greater control and predictability in terms of timeline for approval. As such, whether or not a site is free to use a private REB can often be an important consideration for industry sponsors or CROs in the site recruitment process.\(^6^9\) Concerns and challenges associated with both commercial and institutional research ethics boards are discussed later in this chapter (2.9.11), as well as in Chapter 7.

### 2.6.2.2 Site Personnel

The investigative site is the key point of interaction between human subjects and the study. It is the place where the study procedures occur and data is collected and reported. The key personnel at investigative sites include a single Qualified or Principal Investigator (PI) for the site, who by Canadian law must be a physician for all clinical drug trials\(^7^0\), and a study coordinator (or Clinical Research Coordinator (CRC)).

#### 2.6.2.2.1 Qualified/Principal Investigator (QI/PI)

The PI is the individual responsible for the conduct of the clinical trial at the investigative site. He or she is also responsible for ensuring that the data that is ultimately reported back to the

\(^6^9\) It is important to clarify that where an independent site needs to access hospital services as part of the clinical trial (for example, for surgical services or imaging services) then the research will have to be approved by the institutional REB.

\(^7^0\) This is the case, except where the drug in question is to be used for dental purposes only, when the PI can be a dentist. (Division 5 Regulations, pursuant to the *Food and Drugs Act*)
study sponsor is accurate (Nesbitt, 2006). Although the PI has a range of responsibilities, these are not described in Canadian regulations\(^71\), which focus solely on the sponsor; instead, one has to look to the ICH-GCP Guidelines. \(^72\) Pursuant to the guidelines, the investigator must (among other things) be thoroughly familiar with the specifics of the trial, conduct the trial according to Good Clinical Practices and “other regulatory requirements”, and ensure that all individuals assisting with the trial are qualified to complete the tasks delegated to them. Investigators are also responsible for reporting serious adverse events (SAEs) to the sponsor, for timely communication with the REB, and for complying with the protocol among a myriad of other duties. In addition, legislated responsibilities may accrue to Canadian PIs who are participating as a Canadian site in a trial under an Investigational New Drug (IND) application to the U.S. Food and Drug Administration.\(^73\) Further legal responsibilities can also be delegated to the PI under the terms of the contract signed with the sponsor or CRO. These examples simply serve to illustrate some of the range of potential sources of obligation for the PI. The discussion of the legal framework within which those responsibilities accrue will be addressed later in Chapter 7.

2.6.2.2.2 Clinical Research Coordinator (Coordinator or CRC)

While the study coordinator’s (or CRC’s) position can vary tremendously depending on how many other research staff are on site, a key and constant element of the role is that the coordinator is the “person with whom subjects interact the most, and the one most able to identify their needs and employ necessary procedural safeguards” (Davis et al., 2002, p. 418). Originally conceived as a clinical manager for research subjects with a relatively limited range of duties (Speicher et al., 2012), the many tasks that now generally fall within a coordinator’s job description include “recruiting patient subjects, screening and enrolling patient-subjects into particular studies, managing the regulatory documents like IRB submissions and FDA forms, and overseeing the financial end of contract negotiation and fee collection” (Fisher, 2009, p.67). In

\(^71\) The relevant regulations would be the Division 5 Regulations under the Food and Drugs Act. R.S.C. 1985, c.F-27; Division 5 Regulations, C.R.C., c.870

\(^72\) TCPS 2 also described investigator responsibilities that are relevant in the context of clinical trials that fall within its jurisdiction.

addition, coordinators are often responsible for performing study related procedures that don’t require a physician. In essence, and different from any other position in the clinical trials industry, coordinators are very much the face of pharmaceutical drug development. It is primarily through coordinators that patients interact with the clinical trials industry and come to trust that they are being cared for. Coordinators understand that the quality of their interactions with patients and the rapport they build with them affects how well they are able to recruit, enroll and retain those patients in studies. (Fisher, 2009, p. 68)

Coordinators also are often the ones that transcribe source documentation such as medical records, clinic and lab notes etc, into case report forms (CRF) supplied by the study sponsor (Nesbitt, 2006). In terms of the relationship between sites and the CRO or the sponsor, coordinators again hold a very key position in that they are often the ones that interact with the clinical research associate (CRA or monitor), appointed by the CRO or the sponsor to monitor the various clinical trial sites. Just as the coordinator becomes the face of the research for the human subject, he or she also becomes the personality with which the sponsor or contracting CRO interacts and therefore has significant influence in the relationship between the site and the CRO/sponsor (Nesbitt, 2006; Speicher et al., 2012). This in turn can have significant implications for the site’s ability to attract future research.

2.6.2.3 Site Management Organizations (SMOs)

SMOs are private organizations that essentially provide a range of services to individual primary care physicians conducting clinical trials. They create networks of trained, supported community based (primary care) physicians that sponsors and CROs can access to conduct clinical trials. This is of value for sponsors because it streamlines site recruitment and often improves overall quality of community sites. The Trial Management Group (TMG) is an example of a Canadian SMO. As advertised on their website, TMG “is Canada’s leading clinical investigator network with the largest number of high-performing primary care investigators across the country. Our experienced investigators are trained in Good Clinical Practice (GCP) and have successfully completed hundreds of Phase II-IV trials across multiple therapeutic areas.”74 I do not discuss SMOs in much detail here because my research tends to focus more on

74TMG website is available at: http://www.tmginvestigators.com/
academic sites. It is my understanding that because such sites tend to have access to their own internal infrastructure (CTSUs, for example) they do not typically work with SMOs.

2.6.2.4 Contract Research Organizations (CROs)

As alluded to earlier, the dominant auxiliary organization in the pharmaceutical outsourcing business is the CRO. These organizations in turn are certainly not a homogenous group and range widely in size, services provided, and expertise. In fact, CROs have expanded into nearly every stage of the discovery, developing and marketing of new pharmaceuticals… Their activities range from initial screening of molecules for biocompatibility, in vitro screening, pharmacokinetic modeling, chemical synthesis and analysis, all phases of clinical testing, dosage formulation and pharmacy services, to all aspects of the regulatory process. (Mirowski & Van Horn, 2005, p.507)

Three levels of CRO have emerged: the small niche CRO, the mid-size CRO, and finally, the full service, multinational CRO (Nichol, 2006; Getz, 2007b). However, as has been observed by others, “small and mid-size contract research organizations have largely been left behind while major CROs-the only organizations with sufficient scale to and diverse talent” are dominating (Getz, 2012). This trend is echoed by the Association of Clinical Research Organizations (ACRO), which observed that “the industry is evolving toward a full-service model, where CROs offer services from the earliest stages of development through clinical trials and post-approval research.” Full service CROs offer a full range of services related to clinical trials (phase I-IV), including: trial design, project and site selection and management, investigator and subject recruitment, monitoring, data management, biostatistics and bioanalysis, medical affairs, medical writing, regulatory affairs and submissions. It is becoming increasingly common for full service CROs to handle post-marketing concerns now as well, including phase IV trial design and management, post marketing surveillance, data management issues and others (Getz, 2012; Thomis & Desai, 2006). In addition to this full range of services spanning both the discovery and development stages, another key feature in the increasingly globalized context of the pharmaceutical industry is the ability of these organizations to effectively recruit subjects, physicians and run trials across multiple jurisdictions (Adobor, 2012; Schipper et al., 2011).

Finally, in considering the role of the CRO in the drug development process, it is important to distinguish between their role in early clinical trial development (i.e., phase I-IIa
clinical trials) and later stage clinical trials (phase II-III).\textsuperscript{75} Phase I trials involve relatively small numbers of human subjects and generally take place at one site. While traditionally sponsors conducted phase I trials in their own in-house facilities, it has become more common now to outsource these to full service CROs with their own in-house phase I facilities; alternatively, CROs will contract with a single site or unit to conduct the trial.\textsuperscript{76} In contrast, later stage trials (phase II-III and post marketing or phase IV trials) generally involve multiple sites (and therefore multiple PIs) and hundreds or thousands of human subjects, often on an outpatient basis. In addition, such trials can also involve multiple sponsors, CROs, and other auxiliary service providers. A key role of the CRO in these trials is to coordinate all of the various service providers and sites, and provide additional trial related services as contracted for by the sponsor. As alluded to earlier, in all trial phases, sponsors can choose to contract out the running of the entire trial or only certain select services. Where sponsors outsource only select services, these often include patient recruitment, monitoring, data management and medical writing, however new services are also being constantly introduced in response to sponsors demands for faster trials and globalization (Getz, 2012; Nesbit, 2006).

\subsection*{2.6.2.5 CRO Personnel}

Among the many different positions within a CRO, clinical research associates (also referred to as monitors) and project managers play particularly important roles in the interactions with sponsors and with other auxiliary service providers. While an exhaustive look at the changing and evolving roles of each of these positions exceeds the scope of this study\textsuperscript{77}, it is important to gain at least an initial appreciation of these roles to understand how the way in which outsourcing in clinical development unfurls.

\footnote{75} The phases of clinical trials are described near the beginning of this chapter.
\footnote{76} This was a key point that was raised by a phase I recruiter/marketer for a large CRO in a personal communication in 2009. This individual provided me with extensive materials describing the Phase I capacities of his company, including three separate Phase I units in different countries for a total of 275 beds, extensive expertise and emergency simulation units for educational purposes.
\footnote{77} Fisher (2009) does provide a detailed discussion on each of these roles.
2.6.2.5.1 Clinical Research Associate (CRA or Monitor)

As noted in an earlier section, the clinical coordinator is generally the person at the investigative site who interacts with and reports to the CRA or monitor, who in turn is (at least in theory) the representative of the sponsoring pharmaceutical company, but who may be employed by the sponsor or by the CRO, or be an independent contractor hired by either sponsor or CRO for a specific study (Doyle, 2008; Fisher, 2009; Getz, 2007c; Nesbitt, 2006). Pursuant to the ICH-GCP Guidelines, the purpose of the Monitor is to verify that:

- The rights and well-being of human subjects are protected.
- The reported trial data are accurate, complete and verifiable from source documents.
- The conduct of the trial is in compliance with the currently approved protocol/amendments, with GCP, and with the applicable regulatory requirements.

Moreover, the guidelines state that monitors should be appointed by the sponsor, be the main line of communication between the sponsor and the investigator, be appropriately trained, and have the scientific and/or clinical knowledge needed to monitor the trial adequately. While there may be significant diversity in any additional roles a monitor is assigned, the basic process of monitoring a clinical trial involves selecting an appropriate site, monitoring the conduct of the trial at that site, and closing the site. Each of these stages requires the monitor to attend in person. Given that a monitor has a wide range of responsibilities across multiple trials for multiple sponsors in multiple jurisdictions, it is not surprising that burnout and high turnover rates are common problems (Doyle, 2008; Fisher, 2009; Miseta, 2013).

78 As noted by a subgroup of the Interagency Panel on Research Ethics (PRE) working on procedural issues looking at the harmonization of the TCPS and GCP Guidelines, “the assumption on the part of Health Canada inspectors and trial sponsors is that the ICH-GCP guides the conduct of clinical trials in Canada. In addition, it should be noted that the acceptability of Canadian research data in submissions to foreign regulators, such as the U.S. Food and Drug Administration, is based on compliance with ICH-GCP.” Harmonisation of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS) and ICH-Good Clinical Practice: Conflict or Clarification? Submitted by Subgroup on Procedural Issues for the TCPS (ProGroup): A Working Committee of the Interagency Advisory Panel on Research Ethics (PRE).

79 In addition to intense workload, heavy travel requirements and inconsistent training, another challenge for monitors involves lines of communication. While the CRA is supposed to be the sponsor’s representative at the site, project managers and other administrators at the sponsor
Interestingly, despite the significance of this role it seems that there is little consistency in the training received by monitors. For example, some pharmaceutical companies and CROs have formal classroom style training whereas others assign new employees to work with more experienced monitors to learn the system and skills…Other monitors pay out of pocket for training courses offered by the Drug Information Association or the Society of Clinical Research Associates (SoCRA) as a way of obtaining formal credentials and increasing their marketability towards the top CROs or pharmaceutical companies. (Fisher, 2009, p. 106)

This lack of consistency in education and training for monitors is no doubt exacerbated by the fact that “even the Association of Clinical Research Professionals (ACRP), the leading CRA certifier, is still trying to define what the minimum education and training requirements for study monitors ought to be” (Getz, 2007c).

2.6.2.5.2  Project Manager

Another important role within the clinical development outsourcing relational web is the project manager. Like the CRA, this is a position that is evolving as the clinical trials context continues to change and become increasingly complex. The role of project manager is becoming one of strategic oversight and leadership, whose key purpose is “to oversee the entire clinical trial process, often including complex relationships with many stakeholders, including multiple sponsors, CROs, Academic Research Organizations etc” (Burgess, 2008). Sponsors are reportedly shifting away from having large management teams reviewing the work of the CROs, and instead adopting a more removed oversight role. This shift places greater responsibility on the project manager as the key liaison with the sponsor’s key decision makers on a day to day basis. In essence, their role on a given trial is to keep track of the various sites for which their organization is responsible (drawing on the information provided by the monitors, for example), making adjustments as needed to stay on track with timelines, and motivating the team members to accomplish project goals on time and to a high quality. They are then responsible for reporting quickly and effectively to the sponsor and ensuring that their client’s needs and expectations are being effectively met (Burgess, 2008).

and/or CRO often contact the site directly, thereby leaving the monitor out of the communication and undercutting the authority and respect the monitor can command at the site. (Fisher, 2009)
As a very basic summary of the communication lines involved between sites, CROs, and sponsors then: the coordinator is responsible for managing all trial related activities at the site, under the supervision and ultimate responsibility of the PI. The coordinator interacts with the monitor, who comes to review site activities from site selection to conducting the trial, to site wrap up and closure at the end of the trial. The monitor in turn reports to the CRO’s project manager (or to the sponsor’s project manager where no CRO is involved). The project manager serves as the key contact between the sponsor and the CRO.

2.6.2.6 Academic Research Organizations

It is interesting to note that, “whereas the mid 1990s saw a flurry of academic institutions establish clinical trial offices to better handle industry relationships, the late 1990s through mid-2000s saw a reversal of that trend” (Getz, 2007a, p.35). In recent years industry observers have again suggested increasing collaborations between CROs and academic medical centres (AMCs) (Getz, 2007a; Henderson, 2009), though it is not clear how best to structure such relationships (Goldenberg et al., 2011). There are benefits to both academia and industry in increasing their collaborations. For academia, dollars are clearly relevant, but so to is the benefit of being involved with cutting edge innovation (Henderson, 2009). For industry, collaborations with academia are appealing because they offer access to specialized expertise in certain areas, and increased patient access for certain more complex conditions and diseases (Henderson, 2009). Moreover, given growing public skepticism around industry integrity, academia also provides a certain reputational value to industry sponsors; however, as others have warned, “although academic research organizations offer the imprimatur of university based research, like commercial organizations they are beholden to their industry sponsors” (Lenzer, 2008, p.604).

In their efforts to make themselves more marketable as potential collaborators in industry sponsored drug trials some academic centers have been banding together to form networks that provide sponsors and CROs access to multiple trial sites that use a single contract, ethics board and budget. The Duke Clinical Research Institute, for example, is the largest academic research organization in the world. As noted on its website, it is “a comprehensive academic research organization (ARO) and the only one of its kind that can offer all the services of a commercial contract research organization (CRO) with the academic credibility and expertise of an academic
research institute.” Another American example is the TIMI (Thrombolysis In Myocardial Infarction) Study Group which is affiliated with Brigham and Women’s Hospital and Harvard Medical School and conducts and coordinates clinical trials in patients with cardiovascular disease or risk factors for cardiovascular disease. As described on its webpage, its services include “leadership in terms of study design, protocol development, statistical analysis planning, on-going trial supervision, trial closeout, and finally manuscript development.”

In Canada, the Canadian VIGOUR Centre is located at the University of Alberta and is the Canadian arm of the international VIGOUR (Virtual Coordinating Centre for Global Collaborative Cardiovascular Research) Group, an international ARO specializing in clinical trials (phase II-IV) in cardiovascular disease. They offer a wide range of services, including: trial design, development, phase III and IV clinical trial management, and trial monitoring among many others.

Another example, the Northern Alberta Clinical Trials and Research Center (NACTRC), is a joint venture between Alberta Health Services, and the University of Alberta. Partnered with 13 hospitals and 6 primary care centers in Alberta, they offer “access to a network of over 250 qualified researcher and clinicians in all health disciplines” NACTRC creates a “one-stop shopping” option and boasts being the least expensive location to conduct clinical trials in North America in 2004. However, both the above examples still rely on the University of Alberta’s clinical research ethics board for their reviews. This is because in Canada, unlike in the U.S. where institutions may delegate ethics review of commercially sponsored research to private REBs, research collaborations between industry and academy must still be reviewed by the

81 http://www.timi.org/?page_id=782. Another example is the BRANY (Biomedical Research Alliance of New York) network, which promises “to provide a comprehensive solution from start to finish by providing independent IRB and IBC (institutional biosafety committee), educational, consulting, site identification and administrative services to sponsors and investigative sites around the world… BRANY is able to offer its partners a turnkey solution for expedited site identification and study startup, including a single contract, IRB and budget” (www.brany.com/about). Last accessed September 13, 2013.
84 As Koski et al. (2005) explain, commercial ethics review boards in the states have been reviewing an increasing amount of both industry and federally funded research since the
institutional REB. As such, they are still subject to the problems and delays that have been a key and continuing source of frustration for industry in their collaborations with academia. While this will be discussed in further detail in Chapter 6, it is worth noting here that the academic or institutional sites that participated in this study almost invariably expressed a strong preference for working with AROs over private CROs. Among the key reasons cited for this preference were better service and support levels and increased confidence in the ARO abilities and expertise.

2.6.2.7 Private Ethics Review Boards

In addition to investigative sites, site management organizations, contract research organizations and AROs, private or non-institutional ethics review boards have also emerged to support the commercialized drug development industry. Some of the drivers frequently cited for the rise of the CRO in the 1990s have been mentioned earlier in this chapter. However, another important factor that continues to encourage pharmaceutical companies not only to outsource but to choose commercial entities over more traditional academic ones is the perpetual problem of slow and ineffective research ethics review in the university and hospital setting (Gelijns & Thier 2002; Lexchin, 2008; Rettig, 2000).

Under the Canadian and American regulatory frameworks, all federally funded research involving human subjects, as well as all research (regardless of funding source), being used to support an application for approval of new drugs must be approved by a duly constituted research ethics board (REB), whose primary mandate is to ensure protection of the “rights,
safety and well-being” of human subjects. As noted earlier, in the Canadian context, all research that is funded by, or occurs within the jurisdiction of an institution receiving funds from, one of the three main federal funding agencies must be reviewed by a local research ethics board. Where the REB is not satisfied that the research protocol meets appropriate ethical standards as set out in the relevant guidance documents, they can request amendments be made or, if such steps do not resolve their concerns, they can reject the protocol. However, as has been noted elsewhere, “despite general agreement on the aims and guiding principles for research involving human subjects, there is no overarching structure for the governance of research in Canada and, consequently, no process for ensuring that those aims and guiding principles are attained and implemented” (Glass, 2006, p.38). Others have described the law in Canada as applying “almost inadvertently to the enterprise of biomedical research” (McDonald, 2000, p.93). Given the high demand for ethics review, the fact that institutional research ethics boards (i.e., those housed in universities and hospitals) are chronically under-supported and over taxed in their endeavors, and the patchwork approach to governance in this area (McDonald 2000), it is not surprising that there is an ever increasing variety of research ethics boards (both in terms of structure and kind) emerging and functioning within the human subjects’ research arena (Lemmens & Freedman, 2000).

file a clinical trial application prior to undertaking any clinical trial supporting the development of a drug. As part of this clinical trial application, the sponsor must include the name and contact information of each research ethics board that approved the protocol at each clinical trial site. Regulatory requirements are discussed in Chapter 7.

88 *Division 5 Regulations (C.05.001)* pursuant to the *Food and Drugs Act*.

89 For example, in Canada these would be the *GCP Guidelines* which have been adopted by Health Canada as applying to the conduct of clinical trials in Canada, as well as those standards established in the Tri-Council Policy Statement (*TCPS2*).

90 See also Miller (2006) for a good discussion of these concerns.

91 See also, Anderson et al., 2011; Glass & Lemmens 2002; McDonald 2001; McDonald et al., 2011)

92 For example, in addition to the most traditional set up, wherein a research ethics board is affiliated with an academic institution or publicly funded hospital, there are also provincial research ethics boards, REBs attached to administrative licensing bodies, free standing private for profit REBs, and REBs that are situated within or closely affiliated with particular pharmaceutical companies or contract research organizations. For the purposes of this paper, the focus will be on commercial REBs as compared with traditional institutionally based REBs.
While an extensive discussion of the types of boards and their associated strengths and weaknesses exceeds the scope of this paper, it is highly relevant to draw a comparison between commercial research ethics boards and university or hospital-based boards. Commercial boards can be free standing private for profit boards, or they can be situated within or closely affiliated with particular pharmaceutical companies or contract research organizations. An important concern with commercial boards is that their ability to provide an objective and effective review is compromised by their reliance upon their industry clients (Lemmens & Freedman, 2000; Lemmens, 2004). In other words, the survival of such boards is dependent upon keeping their clients (generally, pharmaceutical sponsors or CROs working for the sponsors), happy. While this might arguably be mitigated somewhat in the case of a board with a diverse clientele, it seems heightened for boards which have a close and virtually exclusive relationship with any particular CRO or sponsor. In such circumstances, the fact that the board is technically independent of the CRO seems almost irrelevant in effect.

As Lemmens and Freedman noted, “the difference between commercial and academic IRBs lies primarily in the context in which they operate and, to some extent, in the goals of the medical research that these IRBs are reviewing.” (2000, p. 550) Traditional research ethics boards are generally located in a university or hospital and are set up to review the research that takes place in those (largely) publicly funded institutions or by physicians affiliated with those institutions. Members of these REBs receive little or no compensation or protected time in recognition of what can often be fairly heavy time commitments. Finally, evidence suggests that the levels of training and ongoing education for board members varies tremendously across boards and in many cases is little to none (Glass, 2006; Lexchin, 2008; McDonald, 2000; McDonald et al., 2011).

In contrast, commercial boards mostly review studies on behalf of commercial entities such as CROs or pharmaceutical companies. They are able to target their clientele and ensure they have appropriate expertise represented on their board or boards. Moreover, unlike academic or institutional REBs, these boards are not staffed by volunteers but by individuals for whom it is a significant part of their formal and acknowledged workload. As such, some of the key benefits

93 For example, research I conducted for my Masters degree suggests people can spend up to 15 hours of prep time plus a four hour meeting on a monthly, and sometimes twice monthly, basis.
of working with commercial boards (and which are highlighted in their marketing efforts), include speed of review, the quality and variety of services offered, and the ability to review multi-site projects (Koski et al., 2005; Lemmens & Freedman, 2000).

The lack of consistency and national accreditation standards, combined with patchwork governance and regulation, creates a number of problems. For example, with no real prohibition against so-called “forum shopping”\(^94\), sponsors can take their protocol to sites where they can expect the most favourable and speedy reviews. Moreover, while the criticism is often raised that commercial boards suffer from an inherent conflict of interest that compromises their ability to provide a meaningful review because their continued business depends upon meeting the expectations of their industry customers for fast approval times (Lemmens & Freedman, 2000; Lemmens, 2004; Lexchin, 2008), it is not at all clear that university and hospital boards are not subject to similar pressures. These public institutions are coming to rely more and more heavily on industry dollars and, as such, they too (and their boards) are in a position of being potentially vulnerable to industry demands (Lemmens & Freedman, 2000; Shuchman, 2007). The lack of consistency and clear standards in REB oversight arguably exacerbates this vulnerability.

In addition to the above actors, there are also a number of other auxiliary service providers that support the pharmaceutical industry. These include, among a myriad of others, laboratories, electronic data capture (EDC) companies, and patient recruitment services. Typically these other actors are referred to as vendors, although whether and how they are distinguished from niche CROs is not always clear.\(^95\)

### 2.7 Effectiveness Of Outsourcing Relationships

Domberger (1998) highlights that “successful contractual relationships are not simple spot transactions. Contracting appears to yield greatest benefits when it combines market discipline with longer-term, cooperative relationships” (p.50). However, the progression away

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\(^94\) While there is no prohibition or real controls on forum shopping, under the *Food and Drugs Act*, the sponsor must provide as part of their clinical trial application submissions to Health Canada an account of any refusals to approve the protocol in question by an REB (as well as any refusals by any regulatory authorities outside Canada).

\(^95\) In many instances, these services will also be part of what is offered by full service CROs. For example, many larger CROs have developed their own EDC systems. As described in the industry literature (Babre, 2011; Borfitz, 2009), and as will be seen in Chapter 6, such systems vary tremendously and can dramatically affect site satisfaction levels.
from strictly transactional interactions towards increasingly close and cooperative relationships (for example, preferred partnerships, strategic partnerships and ultimately strategic alliances) requires levels of trust, candor and transparency that have apparently been lacking in the pharmaceutical context (Azoulay, 2003; Azoulay et al., 2010; Getz, 2012; Scott, 2008; Thomis & Desai, 2006). Sponsor size is one relevant consideration in this context, as the trend is for smaller and mid-size pharma and biotechnology companies to primarily use transactional outsourcing, whereas the larger firms have been trying (though frequently ineffectively) to establish integrated relationships with CROs (Azoulay et al., 2010; Getz, 2012).

While a detailed discussion of the outsourcing relationships and tensions exceeds the scope of this dissertation, one aspect of the dynamic is important as it has a direct influence on the relationships between sites and CROs, which is one of the main foci of this study. The point to highlight is that as the pharmaceutical sponsors have been looking to contain costs, they have been asking their CROs (and sites) to do more with less. As others have put it, regardless of the types of relationships that sponsors and CROs form, contract services profitability is being challenged. Sponsors want more flexible and fluid drug development operations at lower relative cost…and are requiring CROs to provide more favorable preferential pricing for both project-based tasks and portfolio based services…Integrated relationship customization is also deeply squeezing large CRO profitability….Every sponsor wants to establish relationships that uniquely suit their culture, their operating style and practices, their systems and their management models…Customization cannot be scaled. It demands more infrastructure and management and eats into the CROs ability to operate efficiently. (Getz, 2012)

CROs, in turn, must look for other ways to improve their profitability and, as will be seen later in this dissertation, this has real implications for their interactions with investigative sites. It might mean, for example, that CROs cut back on their on-site monitoring, or hire fewer and less experienced staff who will work for less, or develop fewer tools to assist sites with the running of trials, or take on more projects and so be spread too thinly to provide much in terms of monitoring or support for the trial site, among other issues. In any event, and not surprisingly, belt tightening at the top levels has implications that reach all the way down to the frontlines. These tensions will be described in further detail in Chapter 6 of this dissertation.

2.8 Conclusion

The purpose of this chapter has been to describe some of the key pressures and influences that have shaped the pharmaceutical industry in recent decades—both globally and then within
Canada. It has also introduced the key actors and relationships that form the backbone of clinical trial outsourcing. This provides the relevant context for the findings of the current study, which is described in detail in the following chapter (Chapter 3).
Chapter 3: Methodology

The previous chapter provides a detailed lay-of-the-land or overview of the clinical trials industry in Canada, including some of the historical context, a description of the key parties involved and a discussion of current trends or challenges. Against this backdrop, the present chapter will (1) describe the goals of the current study, (2) provide a rationale for why I chose to focus the study as I did by briefly outlining some of the broader contextual considerations, and (3) detail the methodological processes and steps I took to complete this research. Finally, I will situate myself within the research by briefly describing my background. I will also explain how having some of my key assumptions challenged by the data ultimately helped shape this study.

3.1 Goal Of This Research

This dissertation examines investigative sites and their relationship with CROs to offer insight into (a) the challenges that arise at this interface and (b) the extent to which Canadians are protected by Canada’s clinical trials oversight framework. This study is comprised of two main components which, while distinct methodologically, build on and inform each other. The first is a qualitative interview study examining the relationship between investigative sites and CROs, predominantly—though certainly not exclusively—from the site’s perspective. The second is a critical legal and ethical analysis of the Canadian legal and policy frameworks for clinical trials, including a review of the obligations, responsibilities, and liabilities under those frameworks, as well as an assessment of their blind spots or weaknesses. This critical assessment is informed by and sensitive to the issues identified in the findings of the interview study, and as such moves beyond a normative account to provide some insight on the extent to which the legal and policy frameworks are attune to current research realities at the Canadian frontlines.

3.2 Rationale: Why Clinical Trials? Why Sites And CROs? Why Now?

Why Clinical Trials?

From both bioethics and popular perspectives, clinical trials are among the most visible and controversial forms of health research. The increasingly competitive, high-stakes clinical trials industry has been the backdrop for a myriad of unethical and even illegal behaviors by

96 The reasons for, and implications of this decision are described later in this chapter.
various parties in this field—from the pharmaceutical sponsors funding the trials, to the CROs running the trials and the investigators interacting with the subjects and collecting the data.\footnote{The range of such behaviors include everything from biased study designs and underreporting of negative results (Krimsky, 2003; Lemmens, 2004), total disregard for inclusion/exclusion criteria and lack of meaningful consent processes (Wilson, 2010), to bribery and other forms of blatant misconduct particularly in developing or emerging markets (McMahon et al., 2013).

\footnote{Such cases include, for example, those involving Nancy Olivieri, Jesse Gelsinger, and David Healy. For more information on each of these cases, please see Thompson, Baird & Downie, 2001; Lemmens and Waring, 2006; Schaffer, 2004 respectively.

\footnote{A very recent example—and one that is being negatively received by some industry associations—is the U.S. Final Rule under the Physician Payments Sunshine Act, which came into force August 1, 2013. The legislation requires the reporting of payments made to physicians by pharmaceutical sponsors and their designates (including, for example, CROs). For some discussion on what this means for industry, please see: Sullivan, T. (2013) Physician Payment Sunshine Act: Opportunities and Challenges for Global Implementation \url{http://www.policymed.com/2013/05/physician-payment-sunshine-act-opportunities-and-challenges-for-global-implementation.html}. Accessed September 16, 2013.}}

This fact, combined with the major contributions such trials have made to medicine and human health and their continued promise in this regard, make this an intriguing and strategic area for study.

*Why Sites and CROs?*

While some aspects of the complex clinical trials industry have been well examined, others have not. The increased commercialization of academic research generally, and medical research and clinical trials in particular, continues to be widely discussed and described in the wake of a number of high profile cases.\footnote{The range of such behaviors include everything from biased study designs and underreporting of negative results (Krimsky, 2003; Lemmens, 2004), total disregard for inclusion/exclusion criteria and lack of meaningful consent processes (Wilson, 2010), to bribery and other forms of blatant misconduct particularly in developing or emerging markets (McMahon et al., 2013).} Such cases have sparked intense debate and initiatives both nationally and internationally that have crossed the domains of law, policy, science and ethics. For example, those working in the field of research ethics have written extensively about the concerns associated with commercialization of research and clinical trials, including conflicts of interest of researchers, research institutions and private research ethics boards, among others (Angell, 2008; Ferris & Naylor, 2006; Krimsky, 2003; Krimsky, 2006; Lemmens & Freedman, 2000; Lemmens 2004; Lenzer, 2008). Central to these discussions are questions around how to manage and rein in the powerful interests that at once drive innovation and drug development, but also threaten to compromise the testing and development of safe, affordable and effective medications. Legislative\footnote{The range of such behaviors include everything from biased study designs and underreporting of negative results (Krimsky, 2003; Lemmens, 2004), total disregard for inclusion/exclusion criteria and lack of meaningful consent processes (Wilson, 2010), to bribery and other forms of blatant misconduct particularly in developing or emerging markets (McMahon et al., 2013).} and policy\footnote{The range of such behaviors include everything from biased study designs and underreporting of negative results (Krimsky, 2003; Lemmens, 2004), total disregard for inclusion/exclusion criteria and lack of meaningful consent processes (Wilson, 2010), to bribery and other forms of blatant misconduct particularly in developing or emerging markets (McMahon et al., 2013).} initiatives promoting transparency and providing...
guidance on the identification and management of conflicts of interest at the individual and institutional levels have been widely implemented, albeit with varying levels of success and impact (Ferris & Naylor, 2006; Shnier et al., 2013; Weinfurt et al., 2006).

However, and somewhat surprisingly, another aspect of the commercialization of medical research, namely the dramatic shift of clinical trials out of academia into private sector CROs, has received relatively little academic attention (Fisher, 2009; Mirowski & Van Horne, 2005; Shuchman, 2007). While there is rich, though often inaccessible, industry data and literature examining both this move and the relationship between sites, CROs and sponsors (Lamberti et al., 2011), the focus is invariably how to improve functionality, efficiency, and productivity in clinical trials and rarely looks at the broader implications. Trial integrity, subject safety and other research ethics considerations are typically addressed only as they pertain to bottom line considerations. For example, industry surveys indicate that communication problems and delays, poorly trained monitors, high staff turnover, site payment issues and protocol design are common sources of frustration reported by sites in relation to CROs—and to a lesser extent, sponsors (Harper, 1997; Korieth & Anderson, 2011; Lamberti et al., 2011; Pierre, 2013). Such challenges can negatively impact recruitment, lead to slower trials and poorer data quality—all of which of course have important cost and profit implications. However, these issues also clearly have


101 A major obstacle to such literature and research is cost. While brief synopses of some reports may be made public in some instances-mostly by way of a hook to entice potential buyers- the details often come with a hefty price tag. For example, a 2012 CRO quality benchmarking report published by Insight Pharma Reports is available for $6800. More affordable are survey results published by CentreWatch, a company that collects and provides global clinical trials information. For example, CentreWatch publishes the results of an annual survey wherein sites rate their preferred CROs. These results are available to those with a subscription to their monthly publication ($400/year) or one can purchase the relevant issue for $60.
important ethical implications and it is not surprising that many of these issues are also key concerns in the more limited academic literature in this area, including the present study.

As alluded to above, while still relatively limited, academic scrutiny of CROs and their broader implications for the ethical conduct of clinical trials has been building in recent years. Much of this focus has been in the context of emerging clinical trial markets (Petryna, 2009; Schipper et al., 2011), but there has also been important work done in the more traditional or established markets (Fisher, 2009). Given the focus of this dissertation, the literature relating to the established markets is most relevant although many of the same problems arise in both contexts. Chapter 2 of this dissertation outlined some of the key drivers of outsourcing of clinical trials to CROs, but the basic idea is faster, cheaper trials. It is to be expected, then, that many of the issues associated with CROs have been described as arising from “trade-offs between costs, speed and quality of clinical trials” (Schipper et al., 2011) and that these issues arise in both the emerging and traditional markets. For example, issues associated with poorly trained and overworked CRO staff (including monitors), high staff turnover, poor communication with sites (slow response rates to site queries; duplication of requests; lack of clearly established lines of communication) and generally increased workload for investigative sites related to these and other challenges are prominent in the research and literature arising out of both contexts (Fisher, 2009; Petryna, 2009; Schipper et al., 2011).

What is perhaps more surprising are the similarities across emerging and established markets in relation to fracturing of accountability and lack of regulatory oversight of clinical trials. This is described as a major area of concern in relation to outsourced clinical trials conducted offshore (e.g., taking place in emerging markets), (Adobor, 2012; Petryna, 2009; Schipper et al., 2011), and one that has potentially profound ethical and safety implications, especially given a wide range of factors that tend to increase the vulnerability of the populations

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102 Key emerging markets in this context are Latin America, India, China, Eastern Europe and Russia (Schipper et al., 2011).
103 Traditional or established markets tend to be largely defined as Western Europe and North America (Schipper et al., 2011).
104 While not directly on point, it is also worth mentioning that another source of academic scrutiny of the CRO has been the work of Pierre Azoulay (2003; et al., 2010), that provides in depth analysis of why the sponsor-CRO outsourcing relationship has remained relatively difficult as compared to outsourcing in other industries.
in question. Because offshoring is—at least in part—done as another way of decreasing the cost of clinical trials, the receiving countries tend to be low-middle income countries with less developed infrastructure and regulatory oversight whose populations tend to be less educated and less well-off financially as compared to more established clinical trial markets (U.S., Canada & Western Europe for example) (Adobor, 2010; Schipper et al., 2011). However, while the challenges may be particularly acute in these regions, lack of regulatory oversight of clinical trials and uncertain accountabilities are not challenges isolated to emerging markets. Recent literature suggests that (1) even in the most well established of markets (i.e., the United States) there is an overreliance by regulators on sponsors to ensure the ethics, safety and quality of clinical trials-and (2) that sponsors have not been doing enough in this regard (Getz, 2010; Halloran, 2012). The findings of the present study confirm views expressed by other scholars (Flood and Dyke, 2012; Herder, 2012) that these concerns are also valid in the Canadian context and that a number of factors (including, for example, a lack of express regulatory jurisdiction over parties other than the sponsor) may further exacerbate the problems.

Why Now?

In addition to the relatively unexplored implications of CROs as a dominant force in industry-initiated clinical trials (beyond those considered by industry) and the apparently limited oversight and accountability of CROs under Canada’s clinical trial governance structures, there is a third factor that suggests this as a timely and important area of study. As described in Chapter 2, Canada is currently losing ground in terms of its share of industry dollars for clinical trials. There is significant pressure within Canada to protect and grow our role in the clinical trial business—i.e., to access more of the increasingly rare industry CT dollars. This push to at once stop the slide and promote growth of the industry in Canada is explicitly stated by a range of institutions—including federal and provincial regulators, public research sponsors, research institutions and hospitals, private sector research organizations (e.g., CROs and other auxiliary service providers), as well as individual medical and research professionals and their professional organizations. The combination of these three factors raised a number of questions

105 While cost is probably the key factor, offshoring is also described as having other important advantages for pharmaceutical sponsors and CROs, including a way of accessing treatment naïve populations.
for me. One in particular (drawing on my background in law and research ethics), was the extent to which our current research oversight framework was attuned to the current pressures and realities of clinical drug trials and—to the extent it is or is not—how well does the current framework protect the interests of the human subjects and public as future consumers of drugs from these trials? Such considerations seemed particularly pertinent and important given the major focus from all levels on attracting additional clinical trials to Canada on the one hand, and the recognized lack of regulatory oversight of clinical trials on the other.

3.3 Research Study: Design And Methodology

In order to understand how well Canada’s framework for clinical trial oversight addresses current research realities, I decided to conduct a two-part study. The first part consists of a qualitative interview study with a focus on the interface between CRO and site. This was done to start uncovering, from the perspective of those people working at the frontlines of clinical trials in Canada, what the pressures and challenges were that arose between the CRO and the site and how these compared to trials where there was no CRO (that is, where the site interacted directly with the sponsor). The second part is a critical ethical and legal analysis of the laws and policies relating to clinical trials in Canada. A key rationale for this two-part approach that combines empirical and normative elements is the idea that an examination of the rules and guidelines can only provide insight into how things are supposed to unfold. Ultimately, it is only by going to the front lines and speaking with those directly involved that we can determine whether and to what extent what is supposed to happen is actually what is happening, and how the inevitable complexities of real life change and affect how the rules and regulations are implemented. Each of these components will now be described in turn.

3.4 Qualitative Interview Study

This research includes a qualitative, interview based study approved by the University of British Columbia’s Behavioural Research Ethics Board. A qualitative methodology is appropriate where there is little known about the topic area, and where the researcher seeks to describe what is going on. Morse and Richards (2002) list a number of instances in which qualitative methods may be the best or only way of proceeding, including forays into areas about which little is known. As they note, “if you don’t know what you are likely to find, your project requires methods that will allow you to learn what the question is from the data” (p.28). These
authors observe that qualitative research is also indicated where “the purpose is to make sense of complex situations, multicontext data, and changing and shifting phenomena…Qualitative methods are highly appropriate for questions where preemptive reduction of the data will prevent discovery” (p.28). As noted earlier, my research explores the under-examined interface between the CRO and investigative site and the challenges and pressures that arise thereat.

My choice to adopt a qualitative method was also guided by Ronald Chenail’s advice that:

It is important for researchers to establish a research posture (i.e., the relationship a researcher wants to have with…her subject or other) (Wolcott, 1992) and making subsequent methodological choices in which all cohere and are consistent with the ascribed posture. By keeping things plumb in this manner, researchers can greatly increase the chances that their projects will be internally coherent and imminently more do-able than those studies which grow out of alignment. (2000)

In discussing the researcher’s posture in more detail, Chenail (2000) outlines seven possible relationships a researcher may have with the “subject or other”, and states that “it is very important for researchers to be aware of these postures and to carry out a research method which is fitting with such a stance.” The first posture outlined, and the one most relevant to my proposed study, is that of ‘Curiosity’. This posture is characterized by a desire “to know more about the particulars of a subject” where what is known about the subject area is limited. In such arenas, qualitative methods with “their emphasis on open-mindedness and curiosity” are particularly appropriate. As I have suggested above, this posture seems particularly appropriate for my intended area of study.

In terms of specific strategies, for this study I adopt a qualitative descriptive approach as described by Sandelowski (2000). Such an approach is well suited to provide a rich, comprehensive description of the phenomenon, event, or subject under study (Sandelowski, 2000). The qualitative descriptive approach does not bring with it a predetermined set of techniques, but instead is characterized by and allows for a “reasonable combination of sampling, data collection, analysis and re-presentation techniques” (Sandelowski, 2000). For example, in this study my primary concern was to make inquiries into a relatively underexplored area and to make sense of what emerged from the data without prematurely imposing preconceived ideas or theories. In so doing, I adopted a variety of strategies for sampling and analysis to allow key categories and themes to emerge from the data. While my goal was not to
develop a theory, I borrow some of the strategies from Grounded Theory methodology (Charmaz, 2006) in order to systematically code my data and develop a rich account of investigative sites and their interactions with CROs. The Grounded Theory informed approach means I do not force predetermined ideas onto the data—but instead allow the key codes and themes to emerge from the data as analysis proceeds through the constant comparative approach to coding. Charmaz & Bryant (2008) explain that grounded theory is “a systematic, inductive, comparative, and interactive approach to inquiry with several key strategies for conducting inquiry”. There are many variations of this methodology, and as others have noted, there are “conflicting opinions and unresolved issues regarding its nature and process…” (Cutliffe, 2000, p.1476); however, certain grounded theory strategies are well established, and I have adopted a number of them in this study including:

- Simultaneous involvement in data collection and analysis;
- Constructing analytic codes and categories from data, not from preconceived logically deduced hypotheses;
- Using the constant comparative method, which involves making comparisons during each stage of the analysis; [and]
- Memo writing to elaborate categories, specify their properties, define relationships between categories, and identify gaps.106

The specific techniques employed in the current study are described in further detail below.

3.4.1 Sampling And Recruitment

Sampling

I initially adopted a purposive approach to sampling in order to further my understanding of the field under study—namely, the CRO/Investigative site interface. As such, I sought to recruit participants with maximum experiential knowledge of the frontline interactions between Site and the CRO. My review of the literature suggested that key roles in this regard were the research coordinator at the site and the clinical research associate or monitor at the CRO. However, I was also interested in understanding the broader contextual pressures that could affect the CRO-Site interface and so wanted to recruit individuals working with pharmaceutical companies who hired the CROs to manage their clinical trials, as well as those in more administrative or management roles at each of the sponsors, CROs and sites. I anticipated that

106 These are a subset of the Grounded Theory strategies described by Charmaz (2006).
research sites would likely be somewhat more open to my inquiries than CROs and sponsors, and so expected that while it would be critical to interview participants from these other categories, the dominant perspective presented in this study would be that of the site.

In relation to the investigative site, then, I also focus more specifically on the perspective of the research coordinators and staff, rather than the researcher. This is for a variety of reasons. The literature (both industry and limited academic literature) highlights that it is typically the research coordinator—not the researcher—who is the face of the site to the CRO (Fisher, 2006; Fisher, 2009), as well as to the human subjects, incidentally (Davis et al., 2002). Despite this, and while there is a growing literature on the importance of the coordinator’s role in clinical research and some of the professional challenges they face (Fisher, 2006; Gwede et al., 2005; Habermann et al., 2010; Hill & MacArthur, 2006; Mueller, 2001; Raja-Jones, 2002; Speicher et al., 2012) there is less academic empirical literature examining this role specifically in the context of the relationship between CROs and sites and the issues that arise therein.

The coordinator perspective relating to the pressures and realities of dealing with the CRO is made even more relevant given the suggestion in both the industry and academic literatures that in many cases coordinators work with very little oversight or support from investigators, even though under the relevant rules and regulations (e.g. ICH-GCP) the latter are required to provide sufficient oversight and guidance, and are ultimately responsible for the conduct of the research at their site. Because of this fact, how coordinators perceive, interpret and respond to the realities and pressures of working with the CRO is particularly important.

In addition to the importance of the coordinator perspective in its own right, the decision to focus on coordinators instead of investigators at the site level was also made for a logistical reason. Early on in the recruitment process, it became clear to me that accessing investigators was going to be extremely difficult and that if I wanted to interview physicians an important point of contact would be through the coordinator. While I did initially consider this approach, I

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107 This is also a consideration that helped inform my decision to focus on what I expected would be the more accessible interface between Sites and CROs—as opposed to the CRO-sponsor interface, for example.

108 In contrast, this might not have been so critical or interesting in situations where the investigator controlled or had a great deal of influence in how the interactions occurred. In such cases, the investigator perspective would have been much more important to include.
ultimately chose not to pursue it. This was because as the data collection process unfolded, I realized that coordinators were being quite frank with me about some of the challenges they were experiencing within their own site. Instead of jeopardizing this frankness with a request to speak to their investigator, I decided to focus solely on the coordinator and staff perspectives.

Recruitment

As an outsider to this field, I had no pre-existing networks to draw upon to facilitate initial recruitment efforts and was initially concerned that access—particularly to CRO and sponsor based participants—might prove difficult. My initial efforts included attending a variety of industry conferences in both Toronto and Vancouver. Through these conferences I was able to speak informally with a variety of people, many of whom were employed by pharmaceutical sponsors and CROs across Canada, as well as a number of independent consultants working in a variety of related areas including auditing, regulatory affairs, and project management consulting. Such informal conversations frequently led to people agreeing to participate in my study. I provided them with my recruitment materials and then followed up with them by email and was able to schedule a number of interviews in this way. A number of individuals I met at these conferences also passed along my information to other colleagues, who in turn contacted me expressing interest in my study. These efforts and resulting snowball sampling generated interviews with individuals working for sponsors and CROs as well as with a couple of industry consultants with expertise in areas such as auditing and regulatory affairs, and project management. However, and perhaps interestingly, I did not meet any site-based participants at these conferences. This is not to say coordinators and researchers or site administrators may not have been in attendance, but I did not encounter them or have the opportunity to speak with them.

In order to gain access to investigative sites, then, I needed to adopt a different strategy. During my PhD studies, I was fortunate to be a research assistant on a separate three phase CIHR funded study entitled Centring the Human Subject in Health Research: Understanding the Meaning and Experience of Research Participation (CHS Study)\textsuperscript{109}. At the time I was looking to recruit participants for my dissertation research, I had the opportunity to co-present findings

\textsuperscript{109} See for example McDonald et al., (2008) for a description of this research project.
from phase I of the CHS study to groups of research professionals (researchers and research workers) that I expected included individuals who worked with CROs in the course of clinical drug trials. In the course of these presentations I was able to briefly introduce my study on site-CRO interactions, and then follow up when interested individuals later approached me for more details. This process provided me with a number of participants, both directly through the attendees at the presentations, but also indirectly through attendees passing on my contact information to their interested colleagues. This, in turn, yielded important recruitment opportunities as I received invitations to briefly introduce my study at a number of different meetings, including a research symposium hosted by one of the B.C. health regions outside of Vancouver, as well as a monthly networking meeting for an organization for research professionals. This organization provides networking and professional development opportunities for clinical research professionals working in a variety of positions across both industry and grant funded clinical research. Following the latter presentation, the organizer kindly invited me to post my recruitment materials on their website, which also generated further participants for my study. Most of the participants recruited through these efforts were site based—generally either research coordinators or research administrators—and were largely (though not exclusively) at public or academically affiliated hospital based sites, as opposed to private research clinics. While all but one of my site based participants were working at investigative sites in British Columbia at the time of the interview, some of them had previous work experience at sites located in other parts of Canada and/or abroad.

In total, I conducted a total of 24 interviews for this study, with participants stratified by place of employment and role across four broad categories, namely: Site, CRO, Sponsor and Consultant, as outlined in Table 3.1.110 While I have categorized participants based on the role they held at the time of the interview, many of the participants had held previous positions in one or more of the other categories and so brought this experience and insight into their interview as well (Table 3.2). As indicated in Table 3.1, 12 of the participants were working as research coordinators, managers or staff at investigative sites at the time of the interview. Interviews

110 Given my recruitment methods and the different groups I was targeting, it is very difficult to estimate even in very rough terms, the total number of potential participants my recruitment efforts might have reached.
were semi structured, and typically lasted between 1-1.5 hours. In addition to the 12 site interviews conducted for this study, an additional two interviews with physician investigators at academic investigative sites were also conducted. While these interviews were conducted as part of phase II of the CHS study and have not been included in the total count of 24 interviews for this study, they contained questions probing the site’s relationship with CROs. Approval to incorporate relevant interview data into the current study was obtained in advance from both the REB and affected research participants.

Table 3.1: Distribution of Participants, based on role at time of interview (Total: 24)

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Coord/staff</td>
<td>Mgr</td>
<td>Exec</td>
<td>PM</td>
</tr>
<tr>
<td>6(C)/2 (staff)</td>
<td>4</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

*Includes: 1 Coordinator at community hospital site, and one site manager at a community research unit. Terminology: Coordinator includes people who also have management positions over other staff members. “Mgr” refers to people who do not interact with patient subjects at all, but deal only with research staff (and in some community sites, the interactions between the site and CRO or sponsor).
Table 3.2: Distribution of full range of experience of participants

<table>
<thead>
<tr>
<th>Interview # and role</th>
<th>Date dd/mm/yr</th>
<th>Site</th>
<th>CRO</th>
<th>Sponsor</th>
<th>Consultant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site</td>
<td>Mgr</td>
<td>Coord</td>
<td>Staff</td>
<td>Exec</td>
<td>PM</td>
</tr>
<tr>
<td>1. Consultant</td>
<td>3/06/10</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>2. CRO</td>
<td>3/08/10</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>3. Sponsor</td>
<td>13/08/10</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>4. CRO</td>
<td>16/08/10</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>5. Consultant</td>
<td>25/08/10</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>6. Site</td>
<td>30/08/10</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Sponsor</td>
<td>2/09/10</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>8. CRO</td>
<td>13/09/10</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>9. Sponsor</td>
<td>28/09/10</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>10. Site</td>
<td>19/10/10</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. CRO</td>
<td>19/10/10</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>12. Site</td>
<td>21/10/10</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13. Site (2)</td>
<td>21/10/10</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>14. Site</td>
<td>22/10/10</td>
<td>X(P)</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>15. Site</td>
<td>26/10/10</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>16. Site</td>
<td>2/11/10</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>17. Site</td>
<td>12/11/10</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>18. Site (2)</td>
<td>12/11/10</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>19. Site</td>
<td>16/11/10</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20. Consultant</td>
<td>17/11/10</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>21. Site</td>
<td>18/11/10</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22. Site</td>
<td>22/11/10</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>23. Sponsor</td>
<td>13/01/11</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>24. Sponsor</td>
<td>13/01/11</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

*Colour coding for participants are based on the role occupied at the time of the interview. While the vast majority of site participants worked at academic or public sites- one worked at a private site, and two others described their previous experience in private sites. I have highlighted that here (P). Where nothing is indicated, the participant in question is describing their experience in a public or academic site.
3.4.2 Data Collection

I interviewed participants across each of the categories in my study using broad, open-ended questions about their knowledge, perceptions and experiences of interactions between contract research organizations and sites, as well as what tended to go well and what tended to not go well with these interactions. In addition, a few more specific areas or issues were probed. For example, I asked participants in all categories whether they thought the involvement of a CRO to manage or coordinate the trial brought increased or different pressures to sites compared to trials in which sites worked directly with the sponsor. As the data collection process proceeded, I made revisions to the interview protocols to reflect emerging issues or if I noticed that questions were not effective. As one illustration, I noticed that sponsor oversight of the CRO-Site relationship was alluded to by some early participants and realized that while I asked about this indirectly through some of my original questions it was sufficiently important to address in a direct question. Finally, I also specifically asked participants whether they had ever encountered ethical challenges or issues in their work. The wording of this question in particular evolved over time as I tried to strike a balance between leaving it very open and giving participants the opportunity to identify and raise what they deemed to be ethical challenges on the one hand, and causing confusion or even a defensive response on the other. That this is somewhat challenging is likely related to the fact that “ethics” tends to be viewed as a specialized term naming an area of regulatory concern, and not as naming less formalized and regulated areas of social interaction. Hence, while this question ran through each interview, the way it was framed or asked evolved. It is worth noting that many of the issues and themes described in this report emerged both in response to the direct questions, but also indirectly as participants discussed their day to day dealings and interactions in the clinical trials context. Interview protocols (sites, sponsors, CROs & consultant) are attached as Appendix A to this dissertation, with changes from the original indicated by italics.

With the permission of my participants, interviews were digitally recorded and then transcribed. While most of the interviews took place in person, three took place over the phone either for scheduling reasons or because the participants were located out of province and there was no opportunity (such as a conference etc) wherein we could arrange a face to face interview. Transcription was done by a professional transcriptionist who signed a confidentiality agreement.
As I received each transcript, I compared it to the recorded interview both to check for accuracy and as a way of becoming more familiar with the data. While field notes were taken immediately following each interview, I also used this transcript review time to add any other notes or reflections that occurred to me about the details of that specific interview to the original field notes (with date added indicated). To protect the anonymity of participants, transcripts were also stripped of all identifiers and labeled according to role and date of interview (e.g. Research Coordinator, dd/mm/yr).

3.4.3 Data Analysis

As described above, and as informed by Grounded Theory (Charmaz, 2006), data collection and preliminary analysis occurred simultaneously which allowed me to revise my interview protocols and ensure areas of interest that emerged in earlier interviews were probed for in later interviews. This iterative process also made it easier to be sensitive to questions that were not working well and needed to be revised or honed. In addition, as some of my preliminary coding and categories developed I was able to adopt a theoretical approach to sampling to address identified gaps or new areas of interest that emerged. As one scholar commented, “theoretical sampling is purposeful sampling but it’s purposeful sampling according to categories that one develops from one’s analysis and these categories are not based upon quotas; they’re based on theoretical concerns” (Jane Hood, as cited by Charmaz 2006 at p. 101). As I checked each interview transcript and stripped them of identifiers, I entered them into NVIVO and started an open coding process. My approach to coding was largely an inductive one, allowing the main issues or topics to emerge from the data generated by broad open-ended questions in the semi-structured interviews. In addition, and as previously explained, I also had some more targeted questions that probed specific areas of interest that arose either from my own reflections, from the literature or both (such as whether the CRO brought additional or different pressures to bear on the site, as compared with the sponsor). In the coding process, I carefully read through each of the transcripts and broke the data down into incidents or codes while “staying open to all possible theoretical directions indicated by [my] readings of the data” (Charmaz, 2006, p.46). I initially worked through eight interviews, selecting interviews from each category that I considered particularly informative or insightful. By the end of this process I had a list of 60 codes and subcodes (Appendix B). In order to refine this list, I went back into
each code and reviewed the incidents (or data) I had coded under it. As a result of this process, some codes were discarded as being too broad or too general to be helpful or interesting, others were merged and refined.

Once I had refined and reduced my list of codes, I decided to adopt a somewhat different approach. I wanted to delve into each group of participants separately to see how the cross cutting list of codes I had created fit each group and make sure I wasn’t losing any nuance particular to each group of participants. I decided to create four separate word documents (one for each group of participants) and then finish the coding process by going through the remaining transcripts by participant group, starting with sites. This allowed me at once to fully immerse myself in each group of participants and make sure I wasn’t missing anything important in my coding, and also facilitated searching the data by enabling me to use key word searches within each group of participants. I started with sites because they ultimately emerged as the largest single category of participant with the richest data set. This, in combination with the fact that from the outset I have been interested in understanding the effect of the CRO on the investigative site and the research that takes place thereat, led me to adopt the site perspective as the primary lens through which to explore the data. In other words, while the other perspectives (CRO, sponsor, consultant) are of course important and bring added depth to the exploration and description of the topics discussed in this dissertation the primary perspective presented—and therefore through which the others are filtered to a certain extent—is that of the site. It is worth noting here, too, that by adopting the site as the key perspective I am also acknowledging one of their most pronounced concerns; that is, that they did not have a sufficient voice by which to make their views heard by the sponsors (and in some cases CROs) who ultimately make key decisions (budget, protocol etc) with profound implications for them. This isn’t necessarily a deciding reason why I chose to approach my data this way—but it is a benefit of this decision.

Through ongoing refinement of codes, this process generated a list of 34 categories. Having generated this list of categories, I needed to then return to the data to ensure I understood whether and how each of the categories applied to each of the key groups of participants (CRO, site, sponsor), and where there were areas of overlap and divergence in how they applied to each group. In order to facilitate this process, I created a Venn diagram where I listed each of the main categories that were discussed within and across groups of participants that pertained to the
relationship between CRO and site (Appendix C), as well as key quotes illustrating the range of views on the category in question. This helped me flesh out and develop the dimensions of the categories by drawing on the range of perspectives across all groups of participants, and also allowed me to start to gain a better understanding of where and how the various categories related to each other. As I worked through the issues in this way, I kept going back into the complete data set and scanning for words, concepts ideas that would be relevant to the issue I was exploring to try to ensure that it was developed as fully as possible.

Once I had worked through each of the categories, I consolidated my thoughts and reflections into two extensive draft papers that reflected how I had come to characterizing the data. The above process had focused my attention on two areas: first were those issues that arose as between the CRO and the site—which had been the intended primary area of exploration for this dissertation. A total of 18 categories and subcategories were relevant to this paper. These were divided into two broad areas. On the one hand were issues that my participants identified as ethical (*fraud; undue pressure; privacy; & protocol concerns*) and on the other were issues that were less acute perhaps and more systemic in nature, but which also had profound implications (ethical and otherwise) for the parties involved. These included: *internal organizational issues* (subcategories: CRO; Sponsor; Site); *Middle Man* (subcategories: Disruption of Sponsor-Site relationship; Undercutting the Middleman; Cutting Corners; Not their Baby; Payment) and *Training and Staff Issues* (subcategories: Training; Turnover). However, what also emerged prominently from the data were issues identified by investigative sites that were internal to the site, but which also seemed to have (at least potentially) profound implications not only for the site personnel but also for the clinical trials being conducted at the site and for the site’s relationship with external others, including the CRO and the sponsor. Four main categories were particularly relevant, namely: investigator training, investigator involvement, staff training and institutional support. Ultimately, it became clear that these issues would be most effectively discussed in two chapters, and so I addressed investigator training in one chapter (Chapter 4) and the remaining topics in a second chapter (Chapter 5). While the dominant perspective in these two chapters is by definition that of the investigative site, I do incorporate the views from other categories wherever possible so as to provide as rich and complex an account as possible on these issues.
Hence, the three data driven chapters in this dissertation address a range of issues both internal to the investigative site and those between the site and the CRO. The next component of the study involved a detailed examination of the legal and policy frameworks that govern clinical trials in Canada, with attention to whether and to what extent the issues and concerns raised by my participants at the frontlines are addressed.

3.5 Critical Legal And Policy Analysis

I started this process with a close review of key primary documents, namely the *Food and Drugs Act*, and its *Division 5 Regulations*; the *ICH GCP Guidelines* and the *Tri Council Policy Statement 2*. I also reviewed a number of guidance documents issued by Health Canada, including, for example, the *Guidance Document for Clinical Trial Sponsors: Clinical Trial Applications*[^111], finalized in May 2013, which provides additional detail to sponsors across both industry and investigator-initiated trials on the substantive and procedural requirements for clinical trial applications. Reviewing these documents helped me to get a clear understanding of the roles and responsibilities of the multiple parties involved, but also made it clear that Canada relies on a complex patchwork of formal regulations and less formal guidance documents (including the *GCP Guidelines* and *TCPS2*) in the governance and oversight of clinical trials. This was made even more clear when I compared the Canadian approach with that adopted by the U.S. FDA. A key difference between these two approaches is in relation to the clarity of jurisdiction over each of the parties involved in clinical trials. Pursuant to the *Division 5 Regulations* under the *Food and Drugs Act*, Health Canada’s direct jurisdiction is limited to the sponsor. The roles and responsibilities of the other parties (REB, investigator, CRO, Monitor) are not mentioned, and in fact one has to look to the *GCP Guidelines*—whose legal status is less than clear (Lemmens, 2005) for this information. In contrast, the U.S. regulations incorporate the *GCP Guidelines* directly and as such the FDA has clear authority over each individual party. The implications of Canada’s approach are discussed in more detail in Chapter 7. The point here is simply to highlight some of the issues that emerged through the review of the primary source legal documents.

While a review of the above documents provided part of the picture, it was also important to understand how the responsibilities and obligations are enforced. Health Canada’s Health Products and Food Branch Inspectorate is the federal body responsible for inspecting clinical trials in Canada. A review of their inspection strategy, as well as the reports of their findings was interesting in itself, but also in terms of what was not included. For example, and again-as will be discussed in much more detail in Chapter 7, the inspection reports include the findings of the less than 2% of clinical trials inspected by the Inspectorate every year—but do not include (and nor are they otherwise available) the results of compliance verifications—or complaint driven inspections.\textsuperscript{112} Issues and concerns associated with the inspection process were also highlighted in the 2011 Fall Report of the Auditor General of Canada (OAG, 2011). Among the problems noted by the Auditor General was that Health Canada does not regularly collect the information necessary to implement their risk based inspection strategy. A review of the legal literature highlighted additional issues, including among others a lack of transparency and accountability (illustrated, for example, by Health Canada’s failure to have or enforce a meaningful registration system for clinical trials) (Herder, 2012; Lexchin, 2009; Lexchin, 2011). Another important resource that provided additional insights into the oversight of clinical trials in Canada were the transcripts of the Standing Senate Committee on Social Affairs, Science and Technology Hearings exploring the regulation of clinical trials in Canada, as well as the report of its findings issued in November 2012. A number of experts from government, industry, and academia took part and explored a wide range of critically important issues. Other resources and articles were found by searching a number of legal databases including Quicklaw, CanLii and LexisNexis.

Following the close exploration of the oversight framework for clinical trials in Chapter 7, Chapter 8 explores issues of liability and exposure of some of the key parties involved in clinical trials. This involved examining key sources of potential liability, including breach of statute, breach of contract, negligence (tort), as well as the potential for fiduciary obligations. Such considerations are important as they provide additional insights into the complex relationships within the clinical trials industry, and are also likely to inform how parties fulfill

their respective roles. In addition to the literature, I also used Quicklaw and CanLii databases to search for relevant Canadian case law—particularly cases involving investigators and/or contract research organizations. I also searched the publically available summaries of decisions by the provincial colleges of physicians and surgeons of B.C. and Ontario on the chance that some of the cases may have involved physician misconduct in the research context. However, given that these searches ultimately yielded very little, most of the case law I draw on in my discussion is American which, while informative in terms of theories and trends, obviously carries very little weight in terms of precedent in this country.

3.6 Situating The Researcher

Starting with an interest in research ethics, I came to this topic with a background in health law\textsuperscript{113} and bioethics\textsuperscript{114}. I have not, however, worked in the area of clinical trials management and largely viewed the area through an academic lens. This had both positive and negative aspects. On the positive side, I could view the situation from the outside critically. On the negative side, I lacked the insider's knowledge and familiarity with the area which presented a number of challenges, not the least of which included navigating variability of terminology in relation to organizations and roles within the industry, and gaining access to potential participant populations.\textsuperscript{115}


\textsuperscript{114} I obtained my MSc(Bioethics) from the University of Calgary in 2004 and have pursued my PhD through the CIHR funded Ethics of Health Research and Policy Training Program at the University of British Columbia at the Centre for Applied Ethics.

\textsuperscript{115} For example, the term CRO itself can be thought of more as an umbrella term that covers a wide variety of organizations of different sizes, offering different kinds of services etc. It became clear early on that it was not sufficient for me to ask about CROs; instead, I needed to be more specific about the kind of CRO I was particularly interested in. Likewise, there is great variability in role description. Coordinator, study coordinator, Research Coordinator, research nurse, Nurse Coordinator are all terms that are loosely used to describe a similar position, but are not necessarily interchangeable. For example, a research nurse may be a member of the research team but may or may not have the administrative or management responsibilities associated with a research coordinator. Likewise, while many coordinators have nursing backgrounds, this is not always the case.
As it turned out, it also meant I came to the area with a number of assumptions that were called into question by my inquiries, with some needing to be significantly revised and others discounted completely as my awareness and understanding of the field evolved and grew. For example, my initial expectation was that my site-based participants would have a number of concerns related to industry-initiated trials and particularly those involving CROs. In fact, this assumption underpinned and shaped the focus and structure of my research, the goal of which was to understand the issues that arose as between sites and CROs in order to provide some Canadian insights on this issue, and to use this as a starting point to determine how well Canada’s clinical trial oversight framework addressed research realities at the frontlines of clinical trials. This assumption was based largely on my preliminary readings of both the academic and industry literatures that, as noted previously, identified a number of problems between sites and CROs. This assumption was not mistaken in itself and indeed, as will be seen, many of the concerns and frustrations identified in both industry and academic literatures were echoed and described in more nuanced detail by my participants.

What I did underestimate and fail to anticipate at the outset was the importance of internal site challenges for my participants, although these are already fairly well described in the literature. For example, among other issues, insufficient training of research investigators and their staff (Anderson, 2008; Brody, 2007; Dodsworth, 2012; Fisher, 2006; Fisher, 2009; Getz, 2005; Goldhamer et al., 2009; Halloran, 2012; Pierce, 2004; Speicher et al., 2012), insufficient investigator involvement (Davis et al., 2002; Fisher, 2006; Gamache, 2002; Speicher et al., 2012;), and lack of institutional support (Baer et al., 2011; Hill & MacArthur, 2006; Khan et al., 2007; Spilsbury, 2008), have all been identified to varying degrees as important problems for investigative sites. However, and as will be discussed in detail in Chapters 4 and 5 of this dissertation, increased training opportunities and increased pressure on investigators to provide greater oversight (by both sponsors and regulators) are among the recent initiatives that have been undertaken by a variety of stakeholders across the industry to address some of these concerns. Given these initiatives, as well as an underlying preconception I held that researchers affiliated with large research institutions would be well acquainted with their research responsibilities, and the fact that what I was interested in was the external site-CRO relationship, I did not ask specifically about internal difficulties.
As my data collection and analysis processes unfolded however, two things became apparent. First, while participants working at investigative sites were very interested in talking about the challenges of working with CROs, they also very frequently raised challenges they faced within their own site, most often unprompted and often by way of comparing their experiences working across both industry and investigator-initiated clinical trials. Interestingly, the problems identified (and particularly the lack of investigator training in GCP and other regulatory requirements) seemed more pronounced in the context of investigator-initiated trials where there was no industry sponsor or CRO involved. This suggested a troubling training gap amongst academic investigators that I had not anticipated. It also suggested that despite the various initiatives and improvements to date, there is more work to be done to address these issues that continue to be a major source of concern—at least for some Canadian sites. The second thing that occurred to me as I proceeded with the data collection and analysis processes was that, at least to some extent, it seemed that the internal site challenges had implications for the site-CRO relationship, and that the site’s relationship with the CRO had implications for its internal dynamics.

These realizations have had a profound impact on how I think about and present the findings of this study. It would have been reasonable to focus on the findings associated with the CRO-Site interface (external findings) as the main findings, and characterize the site based findings (internal findings) as incidental findings falling outside the initial scope of inquiry. However, a number of factors suggested a different approach and one that would present the internal and external findings on more equal footing. First, given the exploratory nature of this study into a relatively unexamined area (at least from an academic perspective), the idea of “incidental findings” perhaps suggested too much certainty around anticipated findings and as such seemed somewhat misleading. Second, and as noted above, was the importance of the internal issues to my site based participants and the fact that for many, the internal issues raised garnered a similar level of concern to the issues relating to CROs. Third was the idea that insights gleaned from a close examination of site internal dynamics would not only contribute fresh Canadian data in this regard, but could also yield a more nuanced understanding of the site-CRO interactions by providing a more thorough understanding of one of the two parties involved.
In light of these considerations, the remainder of this dissertation is organized as follows. **Chapters 4 and 5** together present the findings relating to the challenges site participants reported facing within their own workplace with the key areas pertaining to investigator training and involvement, staff training and institutional support. In **Chapter 6**, the dissertation shifts its focus to the CRO-site interface and the challenges encountered therein, and also provides some initial reflection on how internal site dynamics may affect, and be affected by, the site’s external relationships. Shifting somewhat away from the strictly data driven chapters, **Chapter 7** provides a detailed examination of the legal landscape that shapes how clinical trials in Canada are conducted and informs how those involved in clinical trials understand and define their roles and responsibilities, and then in turn how those responsibilities are enforced. In addition, potential gaps or weaknesses in the legal and policy frameworks that pertain to the key issues raised by participants in earlier chapters, are highlighted. Specific questions around liability and legal exposure are described in **Chapter 8**. Finally, **Chapter 9** revisits the key findings in the report, makes some recommendations to address key areas of concern identified in those findings, and also discusses some of the limitations of this study and suggests areas for future research.
Chapter 4: Examining Investigative Sites And Their Internal Challenges:
Investigator Training

As explained in Chapter 3, while the initial focus of this dissertation was on the relationship between investigative sites and CROs, this evolved and broadened through the data collection and analysis processes. The result is that the investigative site is both a focal point of the research and the lens through which the site-CRO relationship (the other focal point) is examined. A number of factors informed this evolution. First, and despite similar recruitment efforts across all categories, the majority of my participants (11/24)\textsuperscript{116} were coordinators and research staff working in public sites affiliated with large academic institutions. Consequently, the site perspective emerged as the dominant one in the data. Second, even though the interview questions developed for the qualitative portion of this study asked almost exclusively about the site’s relationship with CROs (see Appendix A), many of my site based participants spoke at length about concerns they had, not in relation to CROs or sponsors, but about challenges arising within their own investigative site. These were not interpersonal or commonplace workplace grievances, but concerns with serious implications at many levels. For example, some of the issues translated into heavy workload and lack of oversight for staff, which in turn resulted in things “falling through the cracks”. Such consequences not only created significant stress for site staff but also had implications, not surprisingly, for the relationship between the site and the CRO or sponsor, not to mention for the overall safety and quality of the trials being conducted.

Four major categories of concerns were reported:
1. Insufficient investigator training;
2. Lack of investigator involvement;
3. Insufficiently trained coordinator or research staff; and
4. Lack of institutional support.

While each one of these is important in its own right and contributes to or at the very least exacerbates what I will argue are systemic gaps in our human subjects protection and trial

\textsuperscript{116} As described in more detail in Chapter 3, one additional site participant was a research director/manager in a private research institution. Moreover, a number of my participants both in the site category and the other categories (CRO, Sponsor, Consultant) also had experience working in both private and public sites.
integrity oversight structures, the primary focus in this chapter is on investigator training issues. The other three areas of concern, and the implications they have for the broader systemic blind spot I describe herein, will be explored in the next chapter.

4.1 Context

As described in more detail in Chapter 2, the level of academic involvement in industry funded clinical trials has dropped dramatically since the mid 1990s, with some figures indicating that 70% of all clinical trials in Canada are now being done in the community and only 30% done in academically affiliated sites (Ogilvie, 2012). In examining the industry/academic interface in terms of clinical trials it is important to recall the distinction (described in Chapter 2) between two broad categories of clinical trials: industry-initiated and investigator-initiated. In industry-initiated trials, the pharmaceutical company initiates and finances the clinical trial and retains control of all aspects of the trial, including design, development, and analysis. In such situations the company is the sponsor of the study and as such—under the Food and Drugs Act, Division 5 Regulations and GCP Guidelines that have been adopted by Health Canada—has a number of clearly defined responsibilities. These include: the filing and maintenance of the Clinical Trial Application (CTA), ensuring supplies for the clinical trial are manufactured and controlled as per established Good Manufacturing Practices (GMPs), and that the trial is conducted in accordance with Good Clinical Practices (GCPs) (Sedgeworth & Derewlany, 2006). While sponsors frequently hire CROs to assume all or some of the clinical trial process for industry-initiated trials, they retain ultimate responsibility for the quality and integrity of the clinical trial data. Such trials may or may not involve academic sites and/or investigators. Where an industry-initiated trial does involve academic physicians, it may be in a variety of ways; for example, they may be the qualified or sub-investigator at the investigative site, or they may be in a more advisory or consulting role—for example on an advisory committee or as QI for the entire trial.

Investigator-initiated clinical trials, in contrast, are designed by the qualified investigator who in turn retains control of and responsibility for all aspects of the trial. Such trials may be supported and funded by a wide range and combination of funders, including industry, government, non-profit organizations etc. While investigator-initiated trials can involve products that have not been authorized for sale in Canada, they tend more frequently to involve drugs that
have been previously approved for market. Perhaps because of this and a confusion or conflation with phase IV trials, there has been some confusion—including among investigators themselves—that physician-initiated clinical trials involving a marketed drug do not require a Clinical Trial Application to be filed with Health Canada (Arbit & Paller, 2006; Sedgeworth & Derewlany, 2006). As will be discussed in this chapter, the data from this study suggest that this problem persists. Regardless of whether an investigator-initiated trial involves testing a new, unauthorized drug or taking a previously approved drug beyond the limits of its authorization, regulations are clear that the clinical trial must be filed with Health Canada, and the investigator (or the investigator’s institution as the case may be) is deemed to be the sponsor. Sponsor-investigators must meet both investigator and sponsor responsibilities under GCP and associated regulations.

Investigator-initiated clinical research has been called “the cornerstone in the evaluation of new drugs and interventions”, and identified as an important source of innovation as well as of reliable, affordable and clinically relevant information (Bergmann et al., 2010; Johnston & Vohra, 2006; Swank et al., 2011). Investigator-initiated clinical trials are typically regarded as more impartial, and as avoiding many of the trappings of conflict of interest that are associated with industry-initiated research (Brown, 2002; Lewis et al., 2001). As noted by Lewis et al. (2001),

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117 Phase IV, or so-called post-marketing trials, include all studies performed after the drug has been approved by the regulator for the market, and that are related to the approved indication. Such trials do not require filing with Health Canada.

118 In a guidance note discussing investigator-initiated trials (http://www.hc-sc.gc.ca/dhp-mpc/prodpharma/applic-demande/guide-ld/clini/cta_for_sponsors-eng.php), Health Canada specifies that,

- the institution/investigator is considered to be the sponsor of the trial for studies that involve:
  - the use of a product that is not authorized for sale in Canada
  - a product marketed in Canada, where the use of the product in the clinical trial is outside the parameters of the NOC and/or DIN, i.e. one or more of the following is different:
    - indication(s) and clinical use
    - target patient population(s)
    - route(s) of administration
    - dosage regimen(s)
In its best form, academic participation in drug-related science both spurs innovation and, through the disinterest and skepticism that are hallmarks of the academic mission, provides a check on the premature enthusiasms of industry… The duty of universities is to seek truth. The duty of pharmaceutical companies is to make money for their shareholders. Drug companies that fail to do so go out of business. Universities that subordinate the disinterested search for truth to other ends lose credibility and their claim to a privileged status in society. If either abandons its fundamental mission, it ultimately fails.

While there is an extensive literature detailing the critical limitations and caveats to the claim of academic objectivity that have arisen with the commercialization of academic research (Brown, 2002; Brown, 2006; Krimsky, 2003; Lemmens, 2004; Lewis et al., 2001) there is perhaps a need to more explicitly recognize these dangers in the specific context of investigator-initiated research—even if only to bring increased awareness around the funding arrangements of such research. As others have noted,

Further evaluation of differential bias between investigator and industry-initiated contracts for clinical trials within academic medical centres is needed. Of particular note in this respect is the fact that some investigator-initiated trials are funded entirely by industry… (Johnston & Vohra, 2006).

Although the issues and concerns associated with conflicts of interest are profound¹¹⁹, the present discussion focuses on a different set of challenges that seem to be less well documented. More specifically, these are problems relating to investigator training in, and knowledge of, their research responsibilities under relevant regulations and Good Clinical Practices (GCP)¹²⁰ and the implications these have for the integrity, quality and safety of the research being conducted. While there are also important questions about the extent to which the regulations and guidelines are effective in achieving their aim (Lexchin, 2011)¹²¹, these are being put aside here and instead

¹¹⁹ I have written with Dr. Michael McDonald elsewhere about conflicts of interest in this context. Please see McDonald and Preto, (2011).
¹²⁰ *ICH-GCP* is an international standard for quality of clinical trials. As noted by Haeusler (2006) and defined in the document itself, *GCP* covers “the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials’ with the objective of having ‘assurance that the data and reported results are credible and accurate and that the rights, integrity and confidentiality of trials subjects are protected.’”
¹²¹ See also, “ICH: An exclusive club of drug regulatory agencies and drug companies imposing its rules on the rest of the world,” Prescrire International 2010, 108. 183-186
I am proceeding with the discussion from the starting point that the regulations and guidelines—particularly those associated with GCP—are relevant in key areas.

4.2 A Cause For Concern: Investigator Training

The Division 5 Regulations under the Food and Drugs Act, and the ICH GCP Guidelines stipulate that for any clinical trial, there must be one qualified investigator (QI) at each clinical trial site. The QI must be a licensed physician (or dentist if appropriate), and is responsible for the medical decisions and care provided to clinical trial subjects. The QI must sign the Qualified Investigator Undertaking that stipulates he/she will conduct the trial according to Good Clinical Practices. These requirements apply to both industry-initiated and investigator-initiated studies. While the QI may delegate many aspects of the conduct of the trial to appropriately qualified staff, the regulations and guidance documents clearly state that “the investigator should be aware of, and should comply with, GCP and the applicable regulatory requirements.”

4.3 Knowledge Gaps

He didn't really see the difference, and I was trying to explain...but he doesn't know GCP. He said, "GC who? ICH?" (Research Coordinator, 18/11/10)

Despite the clear requirements outlined above, one of the concerns raised most frequently by my participants was that the investigators they worked with were not sufficiently aware of their research responsibilities as established by GCP Guidelines and other applicable regulations. As one coordinator put it,

I would say that the major problem is the lack of GCP training and just… on the part of the investigators. I mean, they do studies and they think they know but there’s actually rules and they depend on us and you really have to keep reminding them that ultimately it’s their responsibility…And they…they don’t get it. (Research Coordinator, 16/11/10)

http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/efficac/e6-eng.php#a4.0 Investigator-initiated research commonly takes place within an academic institution or affiliated hospital. As is discussed in the discussions section of this chapter, this means that investigators would need to also comply with the provisions of the Tri Council Policy Statement (2010), even if the particular research in question is not receiving any funding from CIHR (or SSHRC or NSERC).
Many of the specific areas of concern for coordinators related to study documentation and consent. One coordinator described her frustration when she tried to address some concerns with a PI relating to the way in which he was consenting subjects,

I have a huge issue currently with consent. That's what Health Canada and the FDA usually find being done incorrectly...because there's no SOP in place so not everyone is doing it the same way. According to our ethics application, the doctor goes in first to introduce the study. Well, I've seen doctors go in and say, "You should sign up for this study." And I called [one of them] on it...I said may I suggest that we introduce the study in a different way?" and he said “I consent...subjects each week (for therapeutic purposes). I know how to do it." I said, "Well, research is a different sort of area and that should be presented in a different way." … He didn't really see the difference, and I was trying to explain, "Yes, you're dealing with a different kind of consent than I am." We discussed it. It was a bit of an exchange for like an hour, but he doesn't know GCP. He said, "GC who? ICH? (Research Coordinator, 18/11/10)

Another coordinator echoed these concerns generally, and then also specified that investigator-initiated studies are particularly problematic:

They [PIs] are not aware of *GCP Guidelines*. They're not aware -- like I think a lot of it is documentation. A lot of it -- some of it is informed consent process...It's huge actually the work that you have to do to document your study...and I think that’s where a lot of the investigator-driven studies are really lacking... (Research Coordinator, 22/11/10)

The above illustrations are from a variety of coordinators working across a number of research areas within academic affiliated research sites. Each of the coordinators has worked extensively on both industry and investigator-initiated trials. While coordinators raised concerns about investigator training in both of these contexts, an important difference was also highlighted—namely the mitigating factor of industry oversight in the industry-initiated trials. In other words, coordinators were far more concerned about the investigator training deficits where there was no industry sponsor checking up on whether the investigator was meeting all his/her responsibilities than those in which there was industry sponsorship. As one coordinator reflected, such concern was further exacerbated by a perception that REBs tended to pay somewhat less scrutiny to investigator-initiated studies,

I mean that’s the one thing about sponsor driven studies is there is so much oversight already that I often say to the REB, “You should be putting these through expedited because they’ve already been through so much oversight and you should be looking more carefully at at these grant funded, physician initiated –mickey mouse-studies-because there’s no oversight and those guys are pulling the wool over your eyes. (Research Coordinator, 16/11/10)
This underlying reliance on industry also prompted an interesting comment from this same coordinator. She observed that perhaps if investigators were “babysat” less by sponsors in those industry-initiated trials, they would have a better appreciation of their research responsibilities in both industry and investigator-initiated trials,

I think we should be babysat less [by sponsors/CROs] because that would...I think that would also turn it around and maybe make the PIs realize that they are responsible...And they don’t. They don’t remember that...So if you took that babysitting role out, and this is the same thing I tell...the PIs on their own [PI initiated] studies...they must run that study just like a sponsor runs a study, because guess what, they are the sponsor...[but] people don’t think about...So when you tell them that...you tell these guys that are doing these grant funded, “You are the sponsor. This is what you’re responsible for...” “I don’t have time for that.” And they’re right; they don’t have time because...those grants do not give them money to hire somebody to be able to...you’re finding out. You’re doing a study and, guess what, you’re chief cook and bottle washer, right? (Research Coordinator, 16/11/10)

That investigator knowledge of GCP and research requirements is a problem at academic sites across both investigator and industry-initiated trials was underlined by comments made by other participants as well. For example, this participant who had previously worked for a CRO recalled a conversation she had had with one academic coordinator who worked on both industry and physician initiated trials,

I would say the vast majority of such [academic] sites have some, but not total information. One of the coordinators [I know]...she's like, "I'm the only person with GCP certification in my damn group." And she freaks out about that, because if she's gone, there's nobody certified, and then nobody who knows the rules, the regs and the operations. (CRO, 13/09/10)

In another example, a sponsor provides a good illustration of the kinds of challenges that can result from a failure to follow ICH-GCP—in this case, an investigator at an academic site making an unauthorized change to a protocol without sponsor’s agreement that may have resulted in patient safety issues:

…one of the main things we always have to be aware of [are] physicians who have not as much experience...They’re a principal investigator, they have patients on a study, and

123 My participants are typically categorized by role at the time of their interview. However, two participants were not working—or not working in clinical trials—at the time of the interview. I have categorized these participants by the category based on their most recent relevant position.
they’ll make dose changes or drug changes without referring to a protocol. So that’s what just happened to me yesterday [at an academic site]... we want to educate that PI to if he wants to make a change in study drug or in a conmed\(^\text{124}\), first of all, consult the protocol...because that patient is on a protocol. If he doesn’t, it could be a protocol deviation, which is, again, could lead to patient safety issues. So and those are audit findings – like, those are pretty severe....[The coordinator] agreed....She was just shaking her head that he didn’t do this. He just sort of sent [the coordinator] an e-mail and said, “I did this.” And it’s, like, wow. She said he didn’t even, like, sort of check to see if it was okay. (Sponsor, 02/09/10)

This example also highlights that investigators will often act independently and without the knowledge of their research coordinator—which in turn underlines the importance of both the investigator and the coordinator knowing and understanding their respective responsibilities and obligations as well as working within the parameters of the protocol.

As suggested by the above illustrations, and as has been described elsewhere in relation to community sites (Fisher, 2009) this lack of knowledge in relation to some of their research obligations on the part of investigators puts coordinators in an interesting position—they are at once in a subordinate position to investigators, but in some sense charged with ensuring investigators meet their responsibilities. When one considers the already extremely busy position of coordinators—some have identified up to 128 different activities that they are responsible for (Davis et al., 2002)—and the fact that the investigator is free to act without advising the coordinator, relying on coordinators to “supervise their supervisors” seems at the very least arguably problematic if not downright ill advised.

4.4 Training Opportunities\(^\text{125}\)

While I did not interview investigators as part of this study\(^\text{126}\), I did speak to research staff, sponsors, CROs, and consultants about the availability of training opportunities for both

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\(^{124}\) This is a concomitant medication, which means a drug that the patient may be on, but which is not part of the clinical trial.

\(^{125}\) Note, these are the training opportunities explicitly discussed by my site based participants. It is important to note that these do not present an exhaustive discussion of all available options. For example, and as discussed further in the discussion section of this chapter, the FDA and NIH have both developed their own investigator training programs. While these government programs were alluded to briefly by participants in other categories, they were not mentioned by my site based participants—likely because they are among the rare initiatives that primarily target investigators and my site participants were almost exclusively coordinators and research staff.
investigators and staff. Pursuant to the *GCP Guidelines* adopted by Health Canada\(^{127}\), “the investigator should be aware of, and should comply with, GCP and the applicable regulatory requirements.” However, there is no guidance about how this assertion is to be realized or any established standards to this effect. In light of this lack of detail, it is perhaps not surprising that there are a wide variety of initiatives in this regard and that such initiatives are undertaken by everyone from industry sponsors, CROs, research professional associations (e.g., ACRP), and private consultants among others. It is also worth noting at the outset of this discussion that with very few exceptions (most notably, the recently developed FDA investigator training course and the very recently accredited ACRP CPI exam) available training sessions tend to jointly target clinical investigators and their staff. As such, while I am discussing this in the context of PI, overview of available training opportunities applies also to coordinators (which group I will discuss in a separate chapter).

### 4.4.1 Medical School

Physicians do not emerge from medical school trained in how to conduct research. As one of my participating research coordinator explained, “as a physician, you go through med school, you go through all your fellowships and your rounds and you’re taught how to operate. You're not taught how to do research” (Research Coordinator, 18/11/10). This coordinator’s perception that training received in medical school typically fails to prepare students to conduct research-and more specifically, clinical trials is also supported in the literature (Fisher, 2008) and by the recent initiatives to try to address this in medical school curricula.\(^{128}\) Conducting clinical

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\(^{126}\) As mentioned in Chapter 3, I did interview two investigators under the auspices of another study and received REB approval and their permission to answer some questions relevant for this study; however, such questions were relatively limited and training was not covered.


\(^{128}\) See for example, the description of the Comprehensive Research Experience for Medical Students (CREMS) program out of the University of Toronto ([http://www.md.utoronto.ca/program/research/crems/students.htm](http://www.md.utoronto.ca/program/research/crems/students.htm)). While UBC states research as part of its goals “to offer an educational program that facilitates and enhances research opportunities for students and faculty” and “to develop an adequate number of ‘physician-scientists’ with training in knowledge translation between scientific/clinical and patient/population treatment settings”, a review of the medical school curriculum does not reflect this research focus. For a good discussion of the improvements in this regard in the U.S., please
trials is a complex matter that requires knowledge across a number of different areas that go far beyond the clinical focus of most medical schools. These include, among many others, research methodologies, biostatistics, business and logistic components of clinical trials, as well as knowledge of the ethical and legal requirements (Fisher, 2008). A review of current Canadian medical school curricula, goals and objectives suggests that this may be changing, with a number of schools creating research opportunities and optional research training programs alongside the basic medical school requirements, as well as graduate training programs in clinical research. While these are encouraging initiatives, the extent to which these changes are incorporated into the mainstream medical school curriculum and lead to better trained physician investigators remains to be seen—and even where they are effective, it is likely that there will be some lag time before their results are felt at the front lines of research.

4.4.2 Sponsor & CRO Initiatives

Given the high stakes involved in clinical trial research, it is not surprising that industry sponsors make some attempt to ensure that investigators are at least somewhat familiar with their obligations under applicable guidelines and legislation—especially in relation to certain GCP requirements. Participants across all categories discussed these initiatives. For example, one sponsor described the efforts made by her company to bring investigators up to speed on their GCP responsibilities,

So we do provide a lot of training for sites on clinical research...we have this program, it’s called the investigator training program – it’s ITP. And basically that’s a one-day course that [we] offer free to sites and their investigators on good clinical practice...It’s a good program. It’s just a quick – not quick – it’s a full-day overview on good clinical practice...a lot of the times they have either worked with [our company] in the past, or intend on working with [us] in the future. But...it’s very generic. So anybody could come to it. (Sponsor, 02/09/10)

In addition to the above optional, more extensive course set-up, sponsors also tend to provide brief GCP refresher sessions at the investigator’s meeting that takes place prior to the

see Teo, (2009). As noted by Ken Getz in Nelen (2009), the various initiatives in the United States to improve investigator training was likely in large part “a result of the very highly publicized and tragic patient deaths in the late 90s that led to a whole host of reform...and efforts to create a higher level of accountability.”

129 See footnote immediately above.
commencement of the trial, as well as at the site initiation visit\textsuperscript{130}. One coordinator explained, “usually the CROs or sponsors provide \textit{[GCP training]} at investigator meetings…They might provide a half an hour….It is a lot to cover and it's all pretty dry material” [Research Coordinator, 18/11/10]. While it is doubtful that such brief sessions are sufficient to ensure investigators are aware of the full range of their responsibilities and how to meet them, their benefit and effectiveness is eroded even more by the fact that investigators often send their coordinators to these meetings in their stead. This same coordinator observed that in her experience PI attendance at such meetings is pretty rare, “it depends… you hope it is a PI and a coordinator, [but] most of the time, it's the coordinator”.

Sponsors and/or CROs may also provide individual sites with some \textit{GCP} refresher material during the site initiation meetings, though again these sessions are one part of a very busy meeting that focuses more on the specific protocol and study requirements, and makes sure the site has everything it needs to begin the trial. As one participant who had previous experience working for a CRO observed, however, while such site-based training might be conducted by the CRO, such sessions are invariably driven by the sponsor,

\textit{[GCP training for sites] is a sponsor driven behaviour. CRO's don’t give a shit. The sponsor will have education at the site initiation visit. They'll send their monitor in to do maybe more GCP training if the monitor sees that there's constant GCP violations in place. (CRO, 13/09/10)}

4.4.3 Professional Organizations And Other For-Profit Offerings

In addition to courses being developed by academic institutions and the initiatives undertaken by sponsors (though sometimes carried out by CROs), there are a number of

\textsuperscript{130} As described in this article by Stone, J.(2010) “On most trials, the sponsors host investigator meetings and mandate attendance for the principal investigator and coordinator. …Topics that are typically reviewed at investigator meetings include the protocol, especially the inclusion and exclusion criteria for enrollment, any unusual procedures, the safety issues, the regulatory or \textit{GCP} (Good Clinical Practice) issues, and the procedure for case report form submissions. Sometimes, the protocol is still in draft form, and investigators can make substantive input. Most of the time, the meetings are an unnecessary duplication of activities that will have to be repeated at the [site specific] study initiation meeting and are therefore quite wasteful, but they can foster a “bonding” experience between the site and the sponsor. Investigator meetings are particularly valuable for less-experienced investigators and coordinators, as they provide excellent opportunities for networking and exchanging tips.” \url{https://www.ctnbestpractices.org/second-opinions/investigator-meetings2014perk-or-problem}
professional organizations and private companies working to address what the FDA has identified as a “chronic shortage of well-trained, experienced clinical investigators committed to performing clinical trials over the long haul”\textsuperscript{131}. Courses offered by such groups range from in depth day long or multi day classroom sessions to online modules. While the cost, content, style and quality of these courses can vary significantly, they seem to typically focus on GCP and regulatory requirements and some hold different levels of accreditation so that they count towards CME or CNE requirements for example.\textsuperscript{132} Participants in my study discussed these initiatives, and particularly those offered by professional organizations (e.g., SoCRA, ACRP and DIA), which typically offer courses jointly to investigators, coordinators and monitors, as generally “really good, but prohibitively expensive”. For example, this CRO based participant observed,

Holy cow, they are very expensive....And they have their one meeting a year and sometimes they have GCP courses and GCP testing. But again, it's like, "Oh here, in March we'll be in San Francisco. And in May we'll be New York, and those are your options." (CRO, 13/09/10)

Of particular note is that as of October 2012, the Association of Clinical Research Professionals (ACRP) became the only certification exam for PIs to be accredited by the


\textsuperscript{132}By way of a few examples, ClinfoSource provides online GCP training that is accredited for both CME and CNE credits. A basic GCP course takes approximately 10 hours to complete (1 hour for each topic) and costs $455 USD. An advanced course costs $655 USD, and takes roughly 14 hours. Online GCP courses offered by Infonetica Research Solutions cost $125 USD, and take approximately 9 hours to complete. Their GCP course has been accredited for Continuing Professional Development credits by the Faculty of Pharmaceutical Medicine, Royal Holloway, University of London. A two hour web based seminar on GCP offered by Barnett Educational Services costs $795.00 (http://www.barnettinternational.com/EducationalServices/Webinars.aspx). A three day in person course in GCP offered by the Centre for Professional Innovation and Education cost $2450.00 per person. While the topics covered seem very similar to the online courses, they advertise the course as an opportunity for participants to work through “several real life situations such as reviewing pre-study documents and informed consent form for completeness and compliance; conducting drug accountability; reviewing case report form for accuracy and adherence to protocol and performing source document verification.” http://www.cfpie.com/gcp_training.htm
National Commission for Certifying Agencies (NCCA), the accreditation body of the Institute for Credentialing Excellence (U.S.). This exam tests investigator “knowledge of ICH and GCP in the conduct of [their] duties and responsibilities”, and highlights *ICH Guidelines* E2A, E6, E8, E9\(^{133}\) as well as the *Declaration of Helsinki* as the key documents for review.\(^{134}\) ACRP also offers a variety of courses for those working in clinical research (including investigators) that focus largely on *GCP* requirements and how to put these into practice. For example, ACRP’s *Fundamentals of Clinical Research* is a two day course that among other things provides its participants an overview of the differences between pharmaceutical products, devices and biologics, explains the different roles and responsibilities of clinical research professionals conducting clinical trials, describes how to apply *GCP* in their daily functions and reviews main relevant regulations. In October 2012, this two-day course cost $990 for members and $1170 for non-members.

An important initiative in the Canadian context in terms of training of research professionals is the Network of Networks (N2). As indicated on their website, N2 is a not-for-profit incorporated organization and an alliance of Canadian research networks and organizations working to enhance national clinical research capability and capacity. Bringing together trialists and clinical research professionals from across the country, N2 provides a common platform for sharing best practices, resources and research-related content to ensure efficient and high-quality research, integrity of clinical practices and accountability.

Through their partnership with the Collaborative Institutional Training Initiative (CITI) at the University of Miami, N2 provides free access to their member institutions to CITI course content (modified for the Canadian research context). One of the main courses offered is a 12 module

\(^{133}\) In order, these are the guidelines pertaining to: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting; Good Clinical Practice; General Considerations for Clinical Trials; and Statistical Principles for Clinical Trials.

\(^{134}\) While the ACRP CPI exam was accredited in 2012, its roots can be traced back to 2001, when ACRP first offered PI certification exams. Between 2001 and October 2012, ACRP certified nearly 900 PIs. In comparison, it is interesting to note that ACRP has been offering certification for coordinators since 1992 and for monitors since 1995. These certification programs both received accreditation by NCCA in 2010. ACRP has certified more than 17,000 coordinators and more than 9,000 monitors.  
[http://www.acrpnets.org/PDF/CPI_Accreditation.pdf](http://www.acrpnets.org/PDF/CPI_Accreditation.pdf)  
The costs for sitting each of the certification exams are (member/non-member): PI ($594/$944); CRA (498/698); CRC (462/662).
GCP training program. The N2 site also indicates that they provide limited access to the course content to individual non-members for a nominal (unstated) fee.\textsuperscript{135} Many of the major academic research institutions and/or their affiliated hospitals in Canada are members of N2; however, it is relevant to note here while two participants did mention institutions were “getting better” at offering training, no one mentioned the N2 (or CITI, the American collaborator) initiatives by name or really even by description. This suggests that what may be needed, at least in part, are increased efforts to promote awareness of such offerings.

4.5 A Matter Of Priorities

Interestingly, at least on the surface, site participants had somewhat different views on availability of training\textsuperscript{136}. Some expressed significant concern that GCP training was either hard to find or prohibitively expensive, whereas others indicated that “there's a lot of training opportunities [in GCP and regulatory requirements] happening now here at [our institution]. Certainly a lot more than when I started” (Research Coordinator, 22/11/10). Another coordinator also commented that GCP training

is readily available…it’s free. I mean, most of the time you can just find it anywhere. And certainly, the…a lot of the companies are starting to actually….Abbott for example has got a training session in their eCRF that you have to do before you can even start the study. (Research Coordinator, 16/11/10)

Returning to the wide range of training options described earlier in this section, this discrepancy in views can likely be largely explained as a difference in interpretation of what counts as “training”. For example, quick and dirty overviews of GCP appear to be quite readily available; however, more in depth training seems much less accessible both in terms of offerings and cost. This again raises the issue of what is, or ought to be, considered sufficient training and suggests the need for some standardization in this regard.

However, availability of training is not the only challenge described by participants. There was also a sense that many investigators simply did not make training in this area a priority. For example, one coordinator observed that just because training is available does not mean it is being accessed by investigators and suggested a potential solution,

\textsuperscript{135} For more information please see: http://n2canada.ca/education-and-training/
\textsuperscript{136} As noted earlier, while this is largely from the coordinator perspective, the training opportunities being discussed encompass both coordinators and PIs.
…but the problem is always…that the people that go to these training sessions—the people who go to do them online—are the people who already know about it. So my view is if you want to change one thing, you should have to do GCP training within [the university system for research ethics review] before you get your ethics approval. They have it for TCPS. [PIs] should have to do it for GCP…But they’re not going to do it if you just tell them to do it…. (Research Coordinator, 16/11/10)

This last point highlights that standardization of training, while an important step, is not going to be effective unless such training is actually undertaken by investigators—that is, unless it is made mandatory. While an examination of how best to realize these twin goals is well beyond the scope of this paper, the suggestion made by this participant—to incorporate this as a pre requisite to ethics approval—is an intriguing suggestion. As she alludes, such a move would be quite simple to incorporate at least in the academic context we are focused on here, as investigators already need to complete TCPS2 training in a similar fashion. The effectiveness of this simple but insightful suggestion would admittedly be limited to the academic context, however, as there is no such precedent or pre-existing infrastructure for community based sites involved in privately funded trials. Moreover, and as has been an issue with the TCPS2 tutorial, care would need to be taken to ensure the training module was effective. This, among other things, requires finding a balance between meaningful coverage of the material and sufficient brevity to make it a worthwhile, feasible task for busy investigators.

4.6 Discussion

The U.S. Food and Drug Administration has observed that “adherence to the principles of good clinical practices (GCPs), including adequate human subject protection…is universally recognized as a critical requirement to the conduct of research involving human subjects.” In Canada, investigators must adhere to the GCP Guidelines (which have been adopted by Health Canada), and in investigator-initiated trials will also have responsibilities as sponsors under the Division 5 Regulations of the Food and Drugs Act. Though not without some controversy, the GCP Guidelines apply both to industry and investigator-initiated trials, across both academic and non-academic investigative sites. Their recognized (though not unquestioned) purpose is to

137 http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm
138 There is some suggestion in the literature that requiring academic physicians to comply with GCP standards is wrong headed and is having and will continue to have negative implications
improve the quality and safety of clinical trials (Vulcano, 2012; Lexchin, 2011; Yusuf, 2010; Haeusler, 2009). It is also important to note that in addition to the GCP Guidelines and requirements under the Food and Drugs Regulations, investigators conducting clinical trials funded by CIHR or who are working within an institution that receives funding from one or more of the three Canadian federal funding agencies (CIHR, NSERC, SSHRC) must also adhere to the requirements and standards established by the Tri Counsel Policy Statement 2 (TCPS2). In addition to the generally applicable principles, the TCPS2 also has a specific chapter on clinical trials. This chapter outlines a number of ethical issues that investigators need to take into consideration from design issues (e.g., equipoise, placebo) to consent related issues (including for example issues related to the dual role of physician-researchers and therapeutic misconception), to safety monitoring and reporting requirements as well as clinical trial registration, among others. While the TCPS 2 is generally compatible with ICH Guidelines, areas of tension (for example, use of placebo) do arguably exist that must be navigated by investigators, REBs, CROs and sponsors. Whereas ICH Guideline E10 takes a permissive stance towards the use of placebo, TCPS 2 is more restrictive (Sampson et al., 2009). This illustrates some of the tensions and sources of confusion that could plague researchers and their staff conducting clinical trials in the academic sector.

for investigator-initiated trials because there will be less investigator-initiated research (Bergmann et al., 2010; Swank et al., 2011; Tyndall, 2008; Morice, 2003). These discussions seem to be mostly emerging from the European context.


For a related discussion, though as between FDA and Declaration of Helsinki, see Kimmelman et al., 2009.

TCPS 2 was only rarely mentioned by name by my participants, and never directly in relation to a specific issue. However, it is interesting that a couple of participants raised inappropriate use of placebo as a relatively frequent cause for concern. Site participants would be at least peripherally familiar with the TCPS 2, as they are all required to take a tutorial on this document prior to commencing research involving human subjects.
The findings of this study suggest that it is not at all clear that physician investigators are sufficiently familiar with their obligations in this regard. The concerns raised in this study are supported by limited regulatory data and in the literature. For example, while regulatory oversight of clinical trials is extremely limited (only 1.3% of clinical trial sites in Canada are inspected annually), the findings of such audits are troubling. The vast majority of deficiencies observed by Health Canada between 2004-2011\textsuperscript{144} were breaches of GCP standards (64.5%)\textsuperscript{145}. These included, for example, lack of quality assurance systems or failure to implement existing systems (26.7%), protocol deviations (9.7%); inadequate training and qualifications of personnel (8.9%); deficiencies in the informed consent process (6%), failure to ensure that medical care and medical decisions relating to the trial were under the supervision of the qualified investigator (4.2%), and failure to obtain REB approval prior to starting the study(0.9%).\textsuperscript{146} Similarly, for FDA inspections conducted between 1996 and 2010 (inclusive) the majority of findings involved failure of investigators to follow protocol, maintain appropriate records and problems with the consent process and documentation—again all of which are covered in clinical trials regulations and GCP standards (Talele & Bowalekar, 2012).\textsuperscript{147} While these numbers represent only a very small percentage of active sites, the prevalence of GCP and regulatory breaches among the

\footnotesize{\textsuperscript{144} During this timeframe, there were 329 inspections conducted across sponsors (27), CROs (14) and investigative sites (288). There is no indication of whether inspected sites were in the academic or community setting.\textsuperscript{145} It is worth noting that whereas under the \textit{GCP Guidelines} record retention and maintenance is part of \textit{GCP}, this is identified as a separate heading under the \textit{Division 5 Regulations}, and so is reported separately in the audit report. However, it constitutes 25.4\% of all observed breaches.\textsuperscript{146} Other significant breaches of \textit{GCP} that were identified included breaches of Good Manufacturing Practices (5.4\%), lack scientific soundness and/or failure to have a protocol (.3\%). Please see Health Products and Food Branch Inspectorate (2012). Summary Report of Inspections of Clinical Trials Conducted from April 2004 to March 2011, for more details. It is worth noting, contextually, that the report states a number of times that of the 329 inspections “92\% were assigned an overall compliant (“C”) rating while the remaining 8\% were assigned a non-compliant (“NC”) rating.”\textsuperscript{147} It is important to note that the report being discussed analyzes both device and drug trials. The point here is simply to highlight the similarity between the breaches and problems identified in the two countries. For more detailed discussion of the findings, please see the report available at: http://www.appliedclinicaltrialsonline.com/appliedclinicaltrials/article/articleDetail.jsp?id=792938&pageID=3}
violations observed at investigative sites strongly suggests that the investigators responsible for the research at those sites are not sufficiently aware of their responsibilities. Another recent illustration of this is provided by a warning letter issued to an investigator in 2013 for failing to follow protocol, which violations compromised the integrity and validity of the study in question (Gaffney, 2013).  

This concern is echoed in the literature. Pierce (2004) for example, discussing both academic and non-academic sites states, “alarmingly, investigators rarely do know what they are responsible for knowing.” Inadequate training, as well as unrealistic expectations of the level of commitment required, increasing liability considerations and mounting pressures within the clinical trials industry have all been identified as factors limiting the number of community-based physicians willing to become involved in research (Brody, 2007; Fisher, 2009; Getz, 2005). As industry analysts have been observing for some time, a shortfall of well-trained investigators combined with high turnover rates puts pressure on the capacity to conduct clinical trials (Getz, 2005; Taylor, 2011). Again, given the roles and responsibilities of these investigators in relation to both subject safety and research integrity issues, this is an area of significant concern.  

While fairly widely discussed in the context of the shift of clinical trials from academic to community sites, lack of investigator knowledge of GCP Guidelines and regulatory requirements is less prominently discussed in the academic context. When it is discussed, it tends to be primarily in the context of investigator-initiated clinical trials wherein the investigator typically

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148 Letter to Dr. Frazer available at: [http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2013/ucm366762.htm](http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2013/ucm366762.htm)


150 It is worth noting that my study participants across the other categories (CROs, Sponsors & Consultants) were fairly ambivalent about whether site training (jointly in terms of staff and investigators) was more of an issue in the community or academic contexts. As will be seen further in Chapters 5 and 6, some felt particularly strongly that community sites did a far better job in relation to training and generally being prepared to run a clinical trial; others felt far more confident working with academic sites. However, there was general agreement that it really depended on the individuals and that there were good and bad sites in either domain.

151 Instead, individual and institutional conflicts of interest have tended to dominate the literature exploring academia, the pharmaceutical industry and clinical trials.
assumes the dual role of sponsor-investigator (Lad & Dahl, 2013). What this seems to suggest is that academic investigators are familiar with their investigator responsibilities, just not the added sponsor responsibilities that become an issue in investigator-initiated trials.\footnote{While not exactly in line with my data—which suggests that lack of investigator knowledge is a problem in both industry and investigator-initiated trials across both investigator and sponsor responsibilities—at the end of the day, there is agreement that investigator-initiated studies present the most concern.} In one of the only papers on point in the Canadian context, for example, Sedgeworth & Derewlany (2006) observed that “investigators (in investigator-initiated studies) may not be aware of all of the regulatory requirements that they are obliged to meet.” Similarly, in his description of a University of Minnesota initiative (a program to assist investigators with IND submissions), Arbit & Paller (2006) noted that “complying with the FDA’s regulations (which incorporate GCP) can be daunting and an overwhelming burden to faculty researchers who are rarely familiar with their obligations as sponsors...” (Arbit & Paller, 2006). Explaining why their institutional quality assurance program targets investigator-initiated research in audits (even over industry sponsored trials), Lad & Dahl (2013) highlight that many investigators who undertake investigator-initiated studies “are unfamiliar with FDA regulations as they apply to clinical trials when they function in the role as sponsors.” More generally, Tyndall (2008) observed that “academic investigators, although experts in their field, often lack knowledge of the complex and evolving area of the clinical trial process...”. Interestingly, while Tyndall acknowledges that GCP requirements are important in purely commercial trials because of conflicts of interest, he ultimately suggests that they are less necessary and in fact present significant obstacles for investigator-initiated research wherein “commercial conflicts of interest are mostly not an issue.” This position, which seems to be a minority view\footnote{There is some suggestion in the literature that requiring academic physicians to comply with GCP standards is wrong headed and is having and will continue to have negative implications for investigator-initiated trials because there will be less investigator-initiated research (Bergmann et al., 2010; Swank et al., 2011; Tyndall, 2008; Morice, 2003). These discussions seem to be mostly emerging from the European context.}, overlooks the fact not only that there are other kinds of interests that can compromise professional judgment (Davenport, 2010; IOM, 2009; Levinsky, 2002) but also that in many instances investigator-initiated research is in fact funded in whole or in part by industry albeit with safeguards in place to try to limit industry influence. The extent to which
such safeguards are effective has been identified as an area in need of further research (Johnston & Vohra, 2006).

Although lack of investigator knowledge of GCP and regulatory requirements is undoubtedly problematic across the board, a couple of factors make the prevalence of this concern in investigator-initiated research particularly troubling. First, given the lack of regulatory oversight it is clear that many clinical trials in both the community and academia go uninspected every year, and that many sites would likely not get inspected by Health Canada over the course of any given clinical trial. However, investigative sites in industry sponsored clinical trials are subject to scrutiny and audits not only by the regulator but also by their industry sponsor who is ultimately responsible for the conduct of the clinical trial and the integrity of the data it generates, as well as by the CROs working to meet their sponsor client expectations. While admittedly not ideal given the conflict of interest inherent to such oversight (discussed elsewhere in this dissertation), the sponsor is highly motivated to ensure that the data submitted in support of their New Drug Submission (NDS) or amendment thereof\textsuperscript{154} is accepted, and so will tend to hold their sites and CROs to high standards. As such, this industry-based oversight arguably picks up some of the regulatory slack. However, industry—even if providing some or all of the funding—does not have responsibility for investigator-initiated trials and so such trials are not subject to this extra layer of oversight. In such circumstances the institution, through the auspices of the research ethics board, becomes particularly important in ensuring regulatory compliance. Lad & Dahl (2013) also emphasize the role of an institutional quality assurance program as critical in this regard, but recognize a dearth of available information in the literature about how institutions should go about developing and implementing such programs, including what the role of REBs should be in this regard. The possibility then, suggested by some participants in this study, that REBs tend to review industry-initiated research with more scrutiny than investigator-initiated studies, becomes particularly problematic. Klitzman (2013) identifies a variety of attitudes on REBs towards industry funded research, and concludes an important question is

\textsuperscript{154} New Drug Submission (NDS) is the Canadian equivalent to the U.S. New Drug Application (NDA). In both cases, these constitute the process of submitting clinical trial data and other information to the regulator in order to have a drug approved for sale in that country.
…whether IRBs should be more cautious with industry studies than with other protocols, and if so, how much, when, and why. Further debate and research about these issues is vital to optimize beneficence and justice. (p.16)

In the absence of such research, the combination of minimal regulatory oversight, (possibly) limited REB scrutiny, no oversight from industry, and a lack of knowledge and training of investigators creates a perfect storm that at the very least raises the potential for serious quality and safety concerns in relation to investigator-initiated trials.

The second reason that investigator-initiated trials are a particular source of concern is simply the imprimatur of quality that is commonly associated with academic research. There is literature and evidence to suggest that some scepticism and caution in regards to industry sponsored trials is warranted. For example, there are numerous studies (including a recent Cochrane Review) demonstrating that industry funded trials tend to have more positive results in relation to the drug (or device) being tested than do trials with other sources of funding (Lundh, Sismondo, Lexchin, et al., 2012. See also Bekelman et al., 2003; Davidson, 1986; Friedberg et al., 1999; Stelfox et al., 1998).155 There is also literature and data indicating that stakeholders from investigators to the lay public to regulators do tend to have more confidence in the results of academic research than in industry funded research (Davenport, 2010; Flier, 2009; Lemmens, 2004; McDonald et al., 2008). Together, these factors arguably make it even more important for investigator-initiated research to meet the standards established to ensure safety and quality, as the processes, findings and results of such research may not be subjected to the same level of critical scrutiny as industry affiliated research—especially when those responsible for research oversight at all levels (regulator, REBs) face serious resource constraints and prioritize their activities based on perceived risk.156

155 As mentioned above, the extent to which such findings also apply to investigator-initiated studies funded in whole or in part by industry—as opposed to purely commercial clinical trials—is an interesting and under-examined question.

156 For example, and as indicated by Health Canada, the selection of a site for inspection “is based on a variety of criteria, but ultimately, the Inspectorate takes risk factors into consideration…The status of a study (open/closed to enrollment), the number of subjects enrolled, the therapeutic area and study population, the level of clinical trial activity at a centre and the compliance and inspection history of a site are some of the factors that may be taken into account.” http://www.hc-sc.gc.ca/dhp-mps/compli-conform/clini-pract-prat/docs/insp_strat-
As has been eloquently and compellingly argued elsewhere, …the state and doctor-researcher have independent trust based obligations to protect the interests of patient-subjects. As the state relies on the volunteerism of patient-subjects to further the public good of medical knowledge, it operates under an obligation to protect the interests of patient-subjects. The [research ethics committee (“REC”)] fulfills this obligation on behalf of the state when it reviews research prospectively…The scope of REC review however, has inherent limits and attention to these limits emphasizes the doctor-researcher’s independent obligation to protect the interests of the patient-subject. (Miller and Weijer, 2006, p.546)

If Miller & Weijer are correct in their assertion that both researchers and the state have trust based obligations in regard to research subjects, then this may have some profound implications in terms of both their legal and ethical responsibilities. It may well be the case, for example, that such relationships (or at the very least, obligations) are found to be fiduciary in nature, meaning that the state and researchers would be held to the highest standards in the discharge of their responsibilities. This possibility, and its associated implications, is discussed albeit briefly elsewhere in this dissertation. For present purposes, it is sufficient to recognize that Health Canada, academic institutions and investigators all have important roles to play in ensuring the quality and safety of clinical trials, and that reasonable steps should be taken to fulfill those obligations even in the face of limited resources and other challenges. It seems almost trite to say that such reasonable steps should include ensuring that those responsible for the conduct of the research at the individual sites-namely the investigators-are well trained in the regulations and standards recognized as critical for the quality and safety of clinical trials. And yet, such trite statements appear necessary. One need not even rely solely on common sense for the claim that such training would improve the current situation as there is growing evidence supporting the important role that investigator training has in this regard (Haeusler, 2009; Vulcano, 2012). While this leaves open a number of important questions and logistical challenges\textsuperscript{157}, replacing the optional, patchwork approach to investigator training with a recognized mandatory course in regulatory and GCP requirements would make a good start.

\textsuperscript{157} This list of factors is not exhaustive and other factors perceived to increase the risks associated with a given study could of course also be taken into account.

For example, who should establish training requirements? Are current GCP standards and regulations, if followed, sufficient to ensure safe, ethical clinical trials that will generate high quality data?
In relation to this last point, it is interesting to compare the approaches of American and Canadian regulators. Both the FDA and NIH have developed courses for investigators, from brief sessions to three day intensive training courses covering “new safety concerns, adverse event monitoring, compliance with legal and ethical aspects of clinical research, and acceptable scientific and analytic standards in clinical study design and conduct”158. In contrast, Health Canada has not developed any investigator training modules—as noted above, it reiterates the requirement to demonstrate investigator qualification. A Health Canada administrative document entitled *Frequently Asked Questions at the GCP Information Sessions (2010)*159, clarifies that Health Canada neither provides nor endorses any specific GCP resources or investigator training courses, but indicates that such training may vary significantly in structure and level of formality. In terms of guidance, Health Canada simply notes that courses should include information on the legislated regulatory requirements under the *Food and Drugs Act* and *Division 5 Regulations*, as well as relevant supporting guidance, including, but not limited to, *ICH-Good Clinical Practice Guidelines*. Health Canada also states “the frequency of this training should be commensurate with the level of research activity at the site, and be of sufficient regularity to ensure that new

158 For example, the FDA has developed a “3-day course [that] covers new safety concerns, adverse event monitoring, compliance with legal and ethical aspects of clinical research, and acceptable scientific and analytic standards in clinical study design and conduct. The course is presented by senior FDA experts and guest lecturers from industry and academia.” The session in November 2012 marks the fourth annual offering of the course, and when the website was checked on November 7, 2012 the session was full and a wait list was in place. NIH also offers courses for investigators running NIH funded studies. For more information, please see http://pharma.about.com/gi/o.htm?zi=1/XJ&zTi=1&sdn=pharma&cdn=b2b&tm=2107&gps=843_610_1676_877&f=00&tt=2&bt=0&bts=0&zu=http%3A//www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/SpotlightonCPIProjects/ucm201459.htm, retrieved June 3rd, 2012.

159 In November 2010, Health Canada traveled across the country hosting a number of GCP information sessions. As described in the HC presentation, these sessions were to: “describe the role that Health Canada plays in clinical research in Canada; provide an overview of the GCP compliance monitoring program in Canada; explain the process by which clinical trial inspections are conducted in Canada; and to provide a summary of findings from inspections conducted since 2002”. The administrative document referred to here was generated as part of these sessions. http://umanitoba.ca/research/orec/media/GCP_Compliance_Program_Part_1_EN.PDF (accessed October 31st, 2012)
clinical research personnel are promptly trained and existing personnel maintain familiarity with the requirements.”

While one can perhaps understand why the regulator would avoid endorsing specific GCP programs, this creates the challenge for future investigators and their staff to know what constitutes sufficient training in this regard. As the body responsible for setting medical education standards and for supporting lifelong learning for physicians, the Royal College of Physicians and Surgeons of Canada for example may be well situated to develop or promote a course in GCP for physician investigators. This would at once seem to be within their mandate and be a means of establishing a course with a reasonable degree of credibility and objectivity. In any event, this is not yet the case in Canada; instead, while Health Canada reiterates the requirement to demonstrate qualifications and training, it appears that the current bar for doing so lacks serious definition and may be reached with minimal effort or training.

Whatever level of duty and obligation the regulator owes to research participants (i.e., fiduciary or not), the fact that Health Canada has to date taken no steps to establish clear training requirements or guidelines, let alone develop its own courses or initiatives in this regard (where other regulators have in recent years) suggests they may not be being adequately fulfilled. As others have noted, while standardized training and requiring certification may not be a panacea, it “will improve the protection of humans involved in research across the global community, which will make research safer and go a long way to improve, preserve and justify the public’s confidence and trust in research” (Pierce, 2004).
Chapter 5: Examining Investigative Sites And Their Internal Challenges: Investigator Involvement, Staff Training And Institutional Support

As explained in the previous two chapters, participants discussed a number of issues that had important implications for the internal functioning of the investigative site, as well as for the site’s relationship with CROs and sponsors. Investigator training, investigator involvement, staff training and institutional support all emerged as issues that presented important challenges or areas of concern particularly for my site based participants—though other categories of participants also expressed similar concerns.

At the outset of this chapter, it is worth reiterating a few points about the data collection process in relation to these issues. First, none of these issues were initially part of the interview schedules, which asked much more general questions focused on the relationship between CRO and sites (Appendix A). However, as the data collection process evolved it became clear that these issues were areas of concern across all categories—albeit to varying degrees. Second, because of the way the recruitment for this study happened, most of my site-based interviews took place after I had interviewed numerous participants in other categories. Investigator training, investigator oversight, and research staff training and experience were all raised in these earlier interviews, mostly in the context of factors that tended to cause frustration or concern in the relationships between sites and CROs/sponsors.

Third, how my site-based participants came to talk about these issues varied. In some cases, participants were responding to general questions and they raised the issues spontaneously. For example, problems with investigator training and familiarity with GCP requirements were raised by two site participants in response to the question “what would you describe as some of the ethical challenges you face in your position?”. Three other site participants first brought up the differences between investigator-initiated trials and industry-initiated trials during the course of the interview and then raised both investigator training and oversight as part of that discussion. In other instances, I asked about the issues more directly. For example, in two interviews where the coordinators in question had experience working in

160 For example—my first site based interview was interview #6, and I did not have another site based interview until #10, which is when I interviewed the first research coordinator (#6 was a site manager).
both community and academic sites I asked them to compare their experiences in this regard, and I did probe the issue of training specifically in that context. Generally speaking, however, the participants tended to raise the issues spontaneously and then I followed up, asking them to tell me more about the concern or issue they had noted.

Finally, and as alluded to above, most of these issues were raised not only by sites but also by participants in other categories, often as factors that frustrated their relationships with sites. While I have included data from these other interviews, this has been done simply to highlight whether and to what extent the concerns raised by sites were shared by those interacting with them. As already explained in Chapters 3 and 4, the focus of these first two data Chapters (Chapters 4 and 5) is first and foremost on issues within the site itself, and more specifically how the issues identified affect the research coordinators and staff working at those sites.

### 5.1 Context

As outlined in more detail in the previous chapter, while there has been a large drop in academia’s share of industry sponsored clinical trials, there is still a substantial amount of industry-initiated clinical trial activity that takes place at universities and their affiliated hospitals. In addition, there are also clinical trials designed and run by investigators. While such investigator-initiated trials may receive some or all of their funding from industry sponsors, responsibility for all aspects of the trial remains with the investigator. There is no sharp demarcation between industry-initiated and investigator-initiated trials, either in terms of the individuals involved or the rules that apply. For example, many of the coordinators and research staff that I interviewed worked with one or more investigators across both industry and investigator-initiated trials. Moreover, the same regulations and guidelines apply in both contexts.\(^{161}\) One important distinction that is particularly relevant to the present discussion, however, is that investigators who undertake investigator-initiated studies assume a dual role of sponsor investigator—thereby assuming all investigator and sponsor responsibilities under GCP

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\(^{161}\) These include, first and foremost, Canada’s *Food and Drugs Act* and *Division 5 Regulations*; the *ICH-GCP Guidelines* and (for all research funded by 3 federal funding agencies or taking place at an institution that receives such funding) the *TCPS2*. 

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(which have in turn been adopted by Canada) and other applicable regulations. The implications of this are (at least) twofold. First, investigators have many more responsibilities and obligations in investigator-initiated trials than they do in industry sponsor trials—a fact which both this data (Chapter 4) and the literature suggest is often missed by those same investigators (Arbit & Paller, 2006; Lad & Dahl, 2013; Sedgeworth & Derewlany, 2006; Tyndall, 2008). A second point, related to the first, is that whereas industry sponsors tend to closely oversee the conduct of their clinical trials, either directly or indirectly through CROs (or both), lack of investigator oversight is a well documented problem (Davis et al., 2002; Fisher, 2009; Gamache, 2002; Lad & Dahl, 2013; Speicher et al., 2012). Moreover, while budgets have certainly become tighter in recent years as sponsors expect far more for far less from both the CROs and sites working on their trials (Alsumidaie, 2013; Neuer, 2012), industry-initiated studies still tend to be better resourced than their investigator-initiated counterparts (Lad & Dahl, 2013). As will be discussed in more detail in the discussion section, these and other factors make it at the very least arguable that while the challenges identified in these two chapters do not arise exclusively in relation to investigator-initiated trials, the associated consequences may be more troubling in this domain. Whereas issues associated with gaps in investigator training were described in the previous chapter, the focus here is on investigator involvement, staff training, and institutional support. Each of these areas will now be explored in turn.

5.2 Investigator Involvement

Investigator involvement, and the implications of varying levels thereof, was discussed in some way by essentially all of the site-based staff (as well as by many participants in other categories). The theme of Investigator Involvement actually has two distinct sub themes: Early Engagement of the Research Team (in selecting and planning for the study) and Providing Oversight (of the actual study). While the first category could be characterized as laying the strategic groundwork for the ultimate success of a trial at a given site, the second provides the necessary ongoing support to help maintain proper lines of accountability and responsibility, and to ensure the potential for success is realized. Although certainly related, each of these sub themes has its own issues and implications.
5.2.1 Early Engagement Of The Research Team

Engaging the research team in key decisions early in the process—including for example whether to take on a specific study or how best to design—or request certain changes in multi site studies can have a profound impact on the level of staff satisfaction and trial success at the site. This emerged from the data as important both in the negative (i.e., through examples and accounts of when this didn’t happen) as well as in the positive (i.e., by participants describing processes or situations where such engagement did happen). By contrasting these experiences, it became clear that such engagement—while perhaps not decisive, had important implications for sites, particularly in relation to workload and overall fit between study and site.

5.2.1.1 Workload

The data suggested that investigators who were less connected to the research team and/or clinical frontlines were more likely to overload site staff by taking on too many studies. One coordinator, for example, described the process by which her site chooses to bring on more studies. In describing her experience with an investigator who was under-involved with the research staff and rarely on site, she said

I hope it [the decision to bring on more studies] involves communication between the CRC and the PI…I would hope there's better communication, but I know what happened to me. "Oh, you can do one more study." "No, actually, I'm already working nine hours a day. I don't want to work weekends."… Well, it [the study] gets tacked on and you do the best you can. But then you can imagine if you have nine different studies and different phases and different indications, things can fall between the cracks because of the heavy workload….(Research Coordinator, 18/11/10)

This correlation between investigator remoteness (both in terms of geography and involvement) and workload was also described by a site manager working as a liaison between academic investigators on both industry and investigator-initiated trials and clinical sites. She observed a common challenge, particularly where the PI is “an academic, who isn’t actually on the floor” or at the clinical frontlines, was

overwhelming a location with research projects. Because each researcher only has two to seven projects that they are thinking of but they don’t understand that one unit could then potentially have 70 projects that come at them to run; and you physically can’t run that many projects and provide clinical care. (Site Manager, 2/11/10)
Interestingly, even in situations where coordinators reported a close working relationship with a PI or group of PIs, there was an underlying sense of needing to rein in the tendency of PIs to take on too many trials. However, investigators who worked more closely with their coordinators and research staff tended to seek their input on which trials to take on, and were thereby less likely to overload their research teams. As this coordinator who worked as part of a dedicated research team explained,

Well, we [the coordinators] certainly have something to say about manpower because they always want to take on stuff and...take on the world and we can’t do that...[So] the response from the coordinators mostly has to do with whether we think we can recruit and a little bit who’s running the study... And then it’s a matter of does it compete with anything else and do we have staff that can take on something new. (Research Coordinator, 21/10/10)

This level of engagement and input in the logistical ability of the site to take on a given trial was illustrated by other participants-including this coordinator who reported having an active role when her site considers potential trials. As an example, she described a situation in which she had told the investigator she would not take on a particular study,

In some cases the CRO will contact us directly because they picked us up out of a listing, and I’ll look at it...[For example] We’d just finished a study [for indication x] and another one came across our desk and it was the same initial criteria as the first one. I went back to the PI and I said, “I’m sorry, I’m not willing to take this on...because the recruitment for the other study didn’t succeed until they lowered the percentage. (Research Coordinator, 12/11/10)

What starts to emerge from the data is that staff engagement is facilitated not only by individual investigator styles of involvement with the research team—but also by having a system that consciously makes space for staff input. In relation to this latter point, examples would include having clear criteria that coordinators assess as part of the decision making process (as alluded to in the preceding quote), having regular meetings, or by making the coordinator an entry point by which prospective trials are submitted to the site so that an initial review and logistical assessment can be done (as is suggested by the last quote above). Whatever the systemic mechanism for engagement, a key element seems to be avoiding a system where investigators
simply make the decision to accept a trial in isolation from the key staff who will be involved.\textsuperscript{162} The data suggests that where there is no such mechanism in place, staff are more likely to experience excessive workloads—which in turn appears to contribute to a sense of frustration and dissatisfaction in the workplace.

5.2.1.2 \textbf{Fit And Design Issues}

In some instances, participants raised concerns about the study itself—for example, worries about the design or even in some cases about what is driving or motivating the study sponsors. Again, the data seemed to suggest that the degree to which there was a team relationship between the investigator and study staff impacted the extent to which staff felt they could bring such concerns forward directly to the investigator—which in turn had important implications for staff satisfaction and buy in for a given study—and even in some cases for the success of a study.

For example, this site manager highlighted that where investigators are more removed from the clinical frontlines there is more likely to be a disconnect between the protocol design and clinical practice, which in turn can negatively impact staff and patient uptake. She then observed further that this is compounded by the fact that the remoteness of the investigator can also make it more difficult for the staff to bring such concerns forward:

\begin{quote}
I think that sometimes there is the ability to request changes but again, it is very relationship based which makes it very difficult if you have a PI that doesn’t really have a good relationship or has kind of parachuted into a place. It is much less likely that you are…that you feel empowered enough to ask for those design changes. (Site Manager, 2/11/10)
\end{quote}

Another senior coordinator who had been with the same investigator for 4 years described the extent to which she had influence over what studies were taken on by the site,

\begin{quote}
Well I usually just talk about [any concerns] with [my investigator]. I can just say, okay, we shouldn’t be doing this if this is the -- this is the feeling I'm getting. And if that’s really what's going on, I don’t want to be enrolling people in it and stuff like that. And then he might not listen to me right away, but he will. Yes. Let's just think about what your doing, who you're getting involved with. Like the mom, right? That’s kind of what I am. (Research Coordinator, 22/11/10)
\end{quote}

\textsuperscript{162} The importance of staff engagement in this regard has also been suggested in the literature. For example, Poston & Buescher (2010) emphasize the critical role that research coordinators have to play from the time the protocol is assessed to the completion of the trial.
While important, the connection between relationship and ability to raise concerns is not really surprising. However, what is more revealing are the measures participants described adopting when they were otherwise unable to get their concerns heard or adequately addressed by the investigator. For example, one site manager with prior coordinating experience described a variety of ways staff “get around” studies they have concerns about:

That is also, in the front line area when someone has pre-designed and dropped you something that you don’t like. You are looking for the, ‘How do I get around this?’…. So also, there are the clinical trials or different studies that I hear about where the uptake was very poor… people can promote a study very negatively like, ‘Oh there is this thing, you just might want to read it’ versus, ‘Hey there is this great study—do you want to be a part of it?’ So I think that that is one of the ways of when people don’t like a designed study, they work to—consciously or subconsciously—to do what I call tank the study.

And later,

And when it is multi-centered, international…there won’t be contextualising, there won’t be anything. And that’s where, again, the standard deviation forms or deviation from protocol becomes maybe your friend-though I definitely would never promote that, but I mean there was a point where I just felt that was the only way I could get through the study ethically. So I did it…Yeah and [also] I mean staff will quit; you know a study is going poorly when your staff is all quitting and leaving…(Site Manager, 2/11/10)

The above suggests a range of means-from unenthusiastic recruitment to the use of deviation forms, and even quitting by which staff may try to address concerns they have in relation to a specific study that is underway. Where a study is not yet running and has yet to receive ethics approval, the REB may also prove useful in this regard. As one research coordinator reported, specifically in the context of investigator-initiated trials that did not have the benefit of added sponsor oversight:

I’m probably one of the few coordinators that will phone the REB and say, “I don’t think you should put this study through,” or “I have these concerns about this,” or “Maybe you should be looking at this a little more carefully.” And they’ll make a note to do that & I’m right most of the time…. (Research Coordinator, 16/11/10)

In adopting this approach, this coordinator highlighted the importance of the relationship she had developed over the years with the REB. For example, she stressed that while such an approach “can get you into trouble with the PI”, the REB knew her and “knew that she wouldn’t say anything unless [she] felt really strongly about it” and so the REB “was very careful about how
they handled it” in order to protect her anonymity. She went on to explain that such circumstances tended to arise outside of her usual working relationships,

The guys I report to are great. The guys I regularly work with are great because they appreciate the experience that I have. But there are some people who think that they know what they’re doing… I’ve worked with people in the past who go, “Oh, just put down five cc’s of blood. If we don’t use it all, we’ll have some and use it for something else.” You know?!

The above suggests both that such a pro-active appeal to the REB can be effective for research staff who do not feel their concerns are being adequately addressed, but also highlights the potentially serious risks they are taking. In particular, the staff member must rely heavily on the REB to navigate what could clearly be tricky terrain-addressing the concerns without identifying the individual who brought the concerns forward.

This use of the REB to help research staff and coordinators have their concerns about a given study addressed by the investigator was mentioned more passively as well. For example, this coordinator was working with an investigator she had not worked with before and was unable to convince him of specific regulatory requirements. As such, she had to rely on the REB to catch what was admittedly a relatively obvious problem,163

right now actually I’m working with a…doctor and although I told him, you know, you need Health Canada NOL… they’ll ask you for it. He said, “Well, I’m using—I’m just comparing two drugs that were approved twenty years ago.” I said, “Well, whatever you’re putting into patient’s body, have to go through, first full board.” He was thinking, oh no, we don’t need because it just—you know, comparison. I said, “Okay, but you’ll see.” And of course they (the REB) are asking for Health Canada approval because it’s a drug. (Research Coordinator, 19/10/10)

The above examples show the coordinators falling back on the higher authority of the REB to support them in addressing study related concerns when the investigator fails to do so sufficiently. Interestingly, these coordinators emphasized that such problems were far more likely to arise in the context of investigator-initiated studies than in industry-initiated trials, and both suggested this was because of a lack of knowledge and familiarity with relevant

163 It is worth noting that this participant was content to let this go to the REB without her bringing it to their attention directly (as was done in the previous example). However, what is unclear is whether she would have felt as comfortable relying on the REB without giving them a heads up for something more subtle.
requirements.\textsuperscript{164} The challenges associated with the lack of training and awareness of sponsor-investigator responsibilities are discussed in more detail in the previous chapter (Chapter 4.)

5.2.2 Providing Ongoing Oversight

In addition to early engagement with the research team, another aspect of investigator involvement that emerged as important from the data was continuing oversight. Despite the requirement under the \textit{GCP Guidelines} that the investigator provide appropriate oversight of the research for which they are responsible as PI, it was clear from the data that in many cases this was not happening. As described by one coordinator, while

there are some that are quite open and friendly… others you don't see. They're just PI in name only. And you leave the lab results or you leave paperwork in their mailbox to sign. There's that environment too. They've got to be engaged and they need to have the time to do that. (Research Coordinator, 18/11/10)

Another senior research coordinator expressed concern about lack of investigator oversight both generally, but particularly in relation to inexperienced or inadequately trained staff:

Well, [PIs] still rely on the coordinator but…which is fine. There has to be a delegation of duty, but within that delegation there always has to be the remembering that you [the PI] are ultimately responsible….And they don’t remember that. They just presume that you (the coordinator) are going to do your job right. They don’t ask questions about what you do, they just sign on the dotted line when you tell them to sign. And it’s okay when it’s somebody who has a lot of experience. It’s not okay…it’s never okay actually…. (Interviewer: And they’re still…they have the same attitude with a green coordinator?) Yeah. It’s huge. It’s a huge problem.” (Research Coordinator, 16/11/10)

In contrast, others described working environments wherein such oversight and support was achieved and provided examples of how that was done,

We meet with our PIs once a week. We keep them informed with any little thing or a big thing that goes on, whether it be via email or at our weekly meetings. Yeah, we let them know. (Research Coordinator (2), 21/10/10)

\textsuperscript{164} It is of note that a couple of coordinators also described appealing to the REB with some success in the context of industry-initiated studies when CROs or sponsors were not sufficiently responsive to the concerns they were raising. In those cases, it was the coordinator’s role (as opposed to the investigators’) to interact and resolve such disagreements with the CRO. Whether the CROs would have been more responsive if the investigator had raised the issue with them directly is unknown. This is discussed in more detail in Chapter 6.
Still another site participant commented more explicitly about the positive impact of strong investigator involvement for the overall morale of the research team:

You get that that the investigator is really supportive of the team…I think that’s what keeps you together… I think that’s really, really valuable. They’re tremendously busy people but it’s all about building relationships… It is keeping…relationships keep you together through really challenging times in the study. Sometimes you just get running around like a chicken with your head cut off and what do I have to do…check, check, check. Read the protocol again...It can be a little harrowing and I think that support [from PI] goes a long way. That appreciation goes a long way as well, having an open contact with your investigator is important. (Research Worker, 26/10/10)

Despite the clear importance of such oversight (and the fact that it seemed to be occurring in many sites), there were a number of indications across all groups of participants that insufficient investigator involvement is still a major challenge in many instances. As one participant observed,

The FDA has brought out some new guidelines on investigator responsibilities and they’re really, they’re really up on investigator oversight of clinical trials and trying to work to promote and enforce that more, so that investigators aren’t sloughing everything off to the coordinator, which we know happens. (Sponsor, 13/08/10)

Another participant with extensive auditing and consulting experience reiterated this concern,

That’s a huge issue of the actual investigator involvement in the study…I'd say it's still probably the number one area of concern…I mean, you get them signing up for studies and it's quite frankly the RN or the coordinator that’s doing all the work.

In response to a probe around whether she felt this was more of an issue for institutional or community based sites, she also noted

Surprisingly, the community sites are -- it's so new for them that they're usually way more active [than the academic investigators]…You get some [academic PIs] that are outstanding. But you get the ones that are wearing a lot of hats as they have academic responsibilities… They have teaching responsibilities. They have clinical responsibilities. They have department responsibilities. And they have this research going on and they count on the coordinator to run it. And that’s the area where there's some very, very good coordinators. But there's boundaries. And you see [the coordinator] overstepping…and not to say that they want to necessarily. But they get in a position where this needs to be done. And it has to be done. And they know what to do. They're well educated, smart, but it's not their role to do it…Because ultimately the PI signed the contract-so that person has responsibility. And the investigator has the responsibility to review that data and sign off on that data, and not the sub investigator, the investigator. (Consultant, 17/11/10)
While described in somewhat different terms, another participant who had significant experience not only as a coordinator and site manager, but also previous CRO project manager experience, commented specifically on the importance of having an engaged PI—both for the site, but also for the relationship between site and CRO. When asked about key factors that led to a good relationship between site and CRO, she explained:

I think it’s just that you both want the trial to succeed. Really that’s what it is. A lot of it is PI driven, the site PI. How much time, effort you want to put in that’s what I think it is...I find that if the PI is enthusiastic, your trial is way more successful...How excited is your PI? If your PI is kind of like “Eh whatever” and you’re the coordinator. . .I mean often with a lot of these institutional coordinators you have so many trials, so if you don’t spend time on that trial, you don’t recruit. You don’t enrol, you don’t recruit and then they (the CRO) go “How come you’re not...?” (Research Coordinator (2), 12/11/10)

The impact of investigator involvement on the CRO-Site relationship was echoed by other CRO based participants as well. This CRO executive listed a number of critical obstacles to effective site-CRO relationships, including “lack of supervision, lack of support feeding into that chain of lack of communication-lack of principal investigator involvement.” She also shared the opinion that lack of investigator involvement was more typically a problem with academic sites than with community sites because community sites “are in business to make money to create a successful business and to serve the community. [Those PIs] accept the conditions, the requirements really, for their presence and their involvement.” (CRO, 16/08/10)

Taken together, these two categories of investigator involvement (early engagement and ongoing oversight) have profound implications for how a study will unfold at a given site. For example, an investigator who engages the site staff in deciding what studies to take on stands to have a much clearer idea about existing workload, ongoing or recently completed studies that could negatively affect recruitment, and how well the study design will fit with the clinical realities at the site. By helping to ensure reasonable work loads, avoiding overtaxing potential subject populations and facilitating conduct of research at the site, such informed decisions help promote both subject safety and trial success. Such critical goals are further supported by investigators who are present at the site, who oversee the conduct of the trial in a meaningful way, and who foster effective communication with their staff (for example, through weekly meetings and generally being receptive to concerns and questions). Lack of investigator involvement—particularly in relation to ongoing oversight has certainly long been identified as a
problem in academic (Davis et al., 2002; Fisher, 2009; Speicher et al., 2012) and industry literature (Gamache, 2002) as well as by regulatory authorities.\textsuperscript{165} For example, the FDA has long recognized this as an area of concern. In 2001 more than 37% of investigators receiving warning letters were cited for failing to properly supervise their trials. In 2009 the FDA released a guidance document “Guidance for Industry: Investigator Responsibilities—Protecting the Rights, Safety, and Welfare of Study Subjects” (2009) that highlighted the role and responsibilities of investigators. Despite this, and as evidenced by recent citings in FDA warning letters, lack of oversight continues to be a very real problem (Anderson et al., 2011; Speicher et al., 2012).

While much of the attention around investigator involvement seems to focus on the supervisory aspect of ongoing trials, the data in the present study support observations (Baer et al., 2011) that it is critically important to pay attention and promote both initial engagement and ongoing oversight. Finally, while the lack of investigator involvement is concerning in both investigator and industry-initiated research, it at least arguably takes on added import in the former wherein there is no extra layer of sponsor oversight (albeit with all its own shortcomings).

5.3 Staff Training

In addition to the investigator-associated challenges that have been described to date (gaps in training, insufficient early engagement and ongoing oversight), my site based participants also identified insufficient training of research staff as an area of concern. Given the heavy load carried by investigators who are typically balancing clinical and in many cases academic responsibilities with their research responsibilities, it is not at all surprising or concerning that they rely heavily on their staff and delegate many of their responsibilities. In fact, this is explicitly provided for in the GCP Guidelines. Where this practice arguably becomes a matter of significant concern is when investigators lose sight of the fact that they are ultimately responsible for all trial activity at the site, and for ensuring the wellbeing of the subject and the integrity of the data. In order to fulfill these obligations and responsibilities, it has been observed by others that the investigator must, among other things, ensure that those to whom s/he is delegating are sufficiently trained to competently and safely accomplish the tasks they are being

\textsuperscript{165} As evidenced by regular citation in U.S. FDA warning letters to investigators and guidance documents issued specifically to address this issue and clarify investigator responsibilities.
delegated (Speicher et al., 2012). However, as alluded to in some of the quotes in the previous section, it is not at all clear that this is standard practice.

The investigator’s task in this regard is made more difficult than it otherwise would be by a lack of mandatory professional standards for coordinators. As noted by one senior coordinator,

Yeah, and some kind of secretaries, administrative secretaries [function as coordinators], there are no requirements to do—to be a coordinator, like profession...and I think that’s horrible. It’s not good, it’s not good for the whole field. [There should be] more standards, yes! (Research Coordinator, 19/10/10)

The lack of mandatory professional standards or training requirements leads to significant variation in the levels of training, experience and expertise of research coordinators, and of research staff more generally. This same coordinator bemoaned the practice she had frequently encountered wherein residents or even medical students are hired as research coordinators,

Investigators hire their colleagues as research coordinators...because these people see this coordinating position just as a transition from one point to another. And usually they are not involved at all...For me and some of my colleagues, it’s our career and our life...[But] most of the time the PI thinks anybody can do coordinator work. It’s not true. It’s not true and it’s bad for business.

A number of my site level participants expressed concern that many in their field were not sufficiently trained. As one coordinator observed,

some of them (PIs) don't have a research department. They might have one contract research assistant. They don't know the research process, so they're basing everything on that person. Well, that person might not be trained.(Research Coordinator, 18/11/10)

Another participant, a research staff member at a large academically affiliated hospital site, noted:

It’s just that a lot of people are not trained in research and that’s the big problem. People don’t come from research backgrounds and go into the clinical world. What usually happens is people are in the clinical world by fate or they were a nurse or they have a friend of a doctor and they need somebody to help them coordinate all these challenging things and that’s how you get in... I feel that that sometimes is when you miss that boat. Clinical care is all about really the safety and you want to make sure that people are safe. Coming from a clinical background, sometimes you take it for granted I think that what the data is and that sometimes to them is secondary but it can’t be secondary. This data impacts the development of this drug, it impacts if the regulatory bodies were to come in and say there’s no integrity to this data, you might limit that product availability to other patients that can benefit from it globally. You really have to keep the whole picture in
your head and say that we need this data. It needs to be right. It needs to be done right because this affects lives. (Research Worker, 26/10/10)

As noted previously, most of my site based participants were, at least in their current position, working in large academically affiliated (i.e., universities or their affiliated teaching hospitals) sites. That being said, this problem was also alluded to by one participant who worked in a community site,

A lot of community investigators are starting out there, they’ve got one coordinator, who might not either pick up on a problem or if they do, they might not address it in the same way just because they haven’t been doing it that long. There’s a lot of different sizes and shapes and forms of clinical research sites out there. (Site Manager, 22/10/10)

Another participant highlighted the important role of mentoring in gaining knowledge and developing skills required to be a good coordinator, even over more formal (course based) training. She observed,

I'll tell you I’ve done SoCRA exam and stuff like that, but I know other people that have done it, and they haven't any experience and it doesn’t make them any better coordinator…You know what, you need a mentor. You need somebody. And that’s how I learned. And unfortunately that isn't a priority. (Research Coordinator, 22/11/10)

The above suggests that additional training or education opportunities, while perhaps not a panacea, might be an important aspect of addressing these concerns. Interestingly, and as was discussed in more detail in the previous chapter on investigator training, there was some disagreement amongst my participants as to the availability and accessibility of training. Some were of the view that training was very limited in terms of availability and prohibitively expensive. These participants tended to refer to the courses run by professional organizations (SoCRA and ACRP), as well as some for profit private companies as prime examples. Others indicated that the situation was improving, and pointed to training being more frequently offered by sponsors as part of their site initiation process and with increased efforts also being made by local research organizations and health authorities. While the divergence of these views is

As noted in the previous chapter on investigator training, available site training sessions/initiatives tend to jointly target clinical investigators and their staff. As such, while I will briefly discuss availability of training opportunities for research coordinators and staff in this chapter, this section should be read in conjunction with the relevant sections in the investigator training chapter.
interesting, what is arguably most important is that the data suggests that despite ongoing initiatives and efforts to improve training (as described in the previous chapter), many of those whom such efforts would be targeting did not seem to be aware of them.

If educational opportunities are not sufficiently well advertised, this may in part be because of a lack of established networking mechanisms for study sites by which to share information and distribute such announcements. This point was raised directly and indirectly by a number of site staff. For example, as one coordinator explained,

I'd just like to reiterate if there was more communication, more opportunities for training—there's a huge community [in this city] of people doing clinical research...I went to that Health Canada workshop yesterday – there were probably a good 200 people there. But you find out about things by word of mouth. It's not necessarily advertised, so my co-worker didn't know that it was free and she could have gone yesterday. I think there are educational opportunities out there, but people don't necessarily go out and seek them or don't know where to find them…(Research Coordinator, 18/11/10)

Another senior coordinator echoed this concern, and indicated a need for a site focused networking group or organization,

We have a limited network of Coordinators here….and there’s a limited number of people that you talk to and share information with…No [real networks exist] that I’m aware of. I mean there’s only so much you can share on LinkedIn, that’s more networking broad overall career networking as opposed to issue networking. Yes, there’s not really a lot. We did have [regional] Coordinator meetings here on and off for a couple years, but that’s basically gone by the wayside…[But] there’s definite value to that….one local institution] plays an overall role….but specific issue addressing [for sites], not so much. Those (SoCRA, ACRP) organizations have a very, very broad research community. You’re not just looking at sites, you are looking at CRAs and sponsors and regulatory professionals. You are looking at people participating from the local laboratories who may be participating as a contracted resource. So I think the scope of those organizations is far too broad to cover [site specific issues]. (Research Coordinator, 12/11/10)

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Key among these would be, for example, the N2 initiative that offers extensive courses in GCP and other topics to its member institutions free of charge. This is described in the previous chapter; however, it is relevant to note here that many of the major universities in Canada and/or their affiliated hospitals are members. This suggests that what may be needed (at least in part) are increased efforts to promote awareness of such offerings. In this regard, it is interesting to note that while two participants did mention institutions were getting better at offering training, no one mentioned the N2 (or CITI—the American collaborator) initiatives by name or really even by description.
While in a somewhat different context, this site participant also indicated that there could perhaps be more done to foster discussion between sites and even offered a suggestion in this regard,

I think some of them [sites] do [talk]. I think they do in their own little groups and I think it’s all ad hoc. I think a clinical research symposium could really benefit from an hour plenary where you walk around and see peoples’ posters or see what their research is. Just say ‘what kind of trial do you do?’ and when you see what kind of trial, like ‘oh, do you run into an issue with this?’ It’s dialogue and having access to your professional bodies that’s so important I think…. This is a complicated thing and I say it always to other young people who are trying to go in (to clinical trials). I say the most important thing is to start networking because it is so complicated….It can be very isolating. It’s really hard. (Research Worker, 26/10/10)

On the one hand, then, the data suggests at the very least a lack of consistency in training and expertise among research professionals, made worse by isolation and lack of professional networking opportunities for those working at the front lines of clinical research—even within large research based institutions. On the other, the data also suggests that the research professionals cited above are passionate about what they do and are looking for ways to improve both their own levels of expertise and that of others in their field.

Finally, while the data certainly suggests that lack of training and training opportunities for study staff is a major concern for those at the site level, data from other participants in this study makes it clear that a lack of study staff training and expertise is also a major concern for those looking to enroll sites in studies. However, there were mixed views on whether training issues were more of a problem in the academic or community contexts. For example, and in supporting her preference of working with academic sites this sponsor based participant explained,

I don’t think the community sites necessarily have the training and the staffing to be able to conduct trials to the degree that the academic sites have—or the support…(Sponsor, 13/08/10)

In contrast, and specifically in relation to academic sites, this CRO based participant expressed significant frustration at the lack of effort put into training research staff,

[A]cademic sites…should be ashamed of themselves the lack of support they give for training and education to their site personnel. It’s despicable, truly. Sponsors have taken on the cost and the burden of educating site personnel frequently on a very fast turnover
basis because job satisfaction can be extraordinarily low. It’s the very centres that provide professional training and learning opportunities that are not choosing to be accountable for teaching their own. (CRO, 16/08/10)

This frustration has not gone unnoticed by those wanting to ensure that industry sponsored trials continue to come to Canada. As one individual involved with a provincial initiative to attract industry sponsored clinical trials discussed, work is underway to address this gap:

There’s a training committee that’s working on training initiatives for sites…There’s a quality systems initiative that’ll work on developing this certification program, so sites would have to meet certain criteria in order to become certified. Certain SOPs, they’d have to have training systems on those SOPs, you know, all this kind of stuff. And then they would be promoted as being a certified site, which would presumably attract more business to those sites. That would be more appealing to pharma, and I think more appealing for site staff as well. (Sponsor, 13/08/10)

Hence, and not surprisingly, training issues—while a cause for concern and a challenge identified by the site staff themselves—were also very much on the radar of those working with the sites on industry-initiated trials. As was discussed in the previous chapter, and as will be discussed further in the discussion section of this chapter, while a widely shared concern, such issues are arguably of particular concern in the context of investigator-initiated studies. In such trials, the lack of industry oversight combined with the general lack of regulatory oversight, and as seen above, a lack of investigator oversight could make it more likely that issues that do arise as a result of inexperienced or poorly trained staff may not be identified or addressed.

5.4 Institutional Support

In addition to investigator training, levels of investigator involvement and oversight, and problems associated with staff training and experience, many site staff working at academic health centres discussed challenges associated with a lack of organizational support (from the research institution and the health region) that made their work more difficult.

Academic sites are complex entities with multiple departments with diverse cultures and systems. One of the many challenges raised by my participants at the site level was how to navigate this and harness the potential of the site. For example, the following quote from a coordinator discussing conducting research at a large academic hospital highlights a variety of issues:

I say “I’m trying to save a patient a poke, can I piggyback off of you?” Then you get the person that is doing it at the lab and often they’ll go “Well it’s not part of my job”
description, I won’t do it.” But then you’re supposed to be a great research hospital…and the [institution will] say “Yup research is our goal, blah, blah, blah. Completely, again remember I was saying your mission don’t match with what your description is? That could be it…. It’s like some people can’t seem to, I don’t know, they just can’t think beyond that [their job description]. Or, just logistically if I want to set up something in the lab or if I want to set up downstairs in ultrasound or whatever, there’s a lot more hoopla going on. Well you can’t be here and you can’t be here, don’t come and step on my turf, that kind of thing. That, I think a lot of the CROs don’t understand… You almost need like a little, I don’t know if it’s a liaison department, but just to realize that research is part of your operation. (Research Coordinator, 12/11/10)

This quote points to a wide range of challenges that appear to be characteristic or common when working with an academic site—but also points out that such obstacles are not necessarily clearly understood by CROs. As has been reported by others (Baer et al., 2011; Hill & MacArthur, 2006; Raja-Jones, 2002; Spilsbury, 2008) challenges emerge when study staff need to interact with or draw upon hospital staff—from doctors and nurses, to lab technicians and others not affiliated with the research—to facilitate the conduct of the research. This can create a sense of isolation and erode coordinator motivation and job satisfaction, which is only compounded by the lack of networking opportunities and isolation described earlier (Fisher, 2009; Khan et al., 2007).

In the present study, such tensions are reported by participants both in relation to physician initiated studies and industry sponsored studies, but with there being somewhat more suspicion around industry sponsored trials. As one site participant observed,

if the sponsor is a drug company or something-from the health care side—a lot of people have mistrust automatically then of the research trial as well. So that is something which I encounter a lot of. (Site Manager, 2/11/10)

Another coordinator described resistance received from nursing staff in relation to an investigator-initiated study,

Maybe nurses are extremely protective. I know there was one study we were doing and boy it was really, really difficult. The nurses really put up a lot of opposition. And it's just not really understanding. And the whole thing is you can't make care better in these settings….I know they [the patients] have got…problems...But you know we can't -- you know, you can't make things better if you don’t do the research. (Research Coordinator, 22/11/10)
Interestingly, there were also concerns expressed from the other side of the issue. I had the opportunity to speak with a few research managers at academically affiliated hospitals who reported tensions from the staff who were not associated with studies. As one manager put it, our strategic plan has research as one of the cross-cutting mandated themes, so people really feel pushed into ‘you've got to do the research and support the research’... I mean, if your manager approved the study going on because management thought it was a nice idea-- but you are the staff member who is not comfortable and you don’t really want to present that study (to patients)—it is really hard to back out...So that is when you go, ‘Oh, I am really busy with these client scenarios and I have had no chance to present it’ and that is where the individual...there is no opt out mechanism for an individual....It would be nice (if there was)...[but] we have a healthcare shortage in general. So we can’t pull people just because they don’t like to do research. It might be that we don’t ask them to participate, eventually. You know, you find the staff who are more interested and really just work with them and that is what we are asking. (Site Manager, 2/11/10)

On a related, but somewhat different level, another coordinator identified a lack of support for research not so much by the institution, but by the health region that negatively impacted the site’s ability to negotiate with sponsors and CROs,

If [the health region] took this on as a big organization….but basically they say they’re keen on research, but they give you no support. So until you get that support…even with CROs, even with budgets, even with everything, if [the region] took a firm stand and said, “We cannot do a study unless we are paid X,” and depending on what...there would have to be some standard fees for this, this and this so that you’d have a standard fee. And you always have to remember in the back of your mind that they’ll easily threaten you with this too-- that they can do studies a hell of a lot cheaper in India. And not only that, but everybody there is trained in GCP… (Research Coordinator, 16/11/10)

Not surprisingly, this participant observed that this problem is becoming more pronounced as budgets are continuously reduced and sites are being expected to do more with less on a regular basis. All site-based participants shared the view that the days of lucrative industry studies that could help support investigator-initiated research were essentially gone. In many cases, industry sponsored research is not only no longer really profitable, it is approaching being unsustainable as sites more frequently risk running industry sponsored trials at a loss.168 Particularly in relation
to this last point, however, it seems at least reasonable to expect that in light of all of the initiatives currently underway both in B.C. and across the country to develop infrastructure and attract clinical trials (described in Chapter 2), this lack of regional and provincial support is in the process of being addressed.

5.5 Discussion

The challenges and areas of concern raised by site participants (and in many instances corroborated by participants in other categories) described in these two chapters have been discussed in varying levels of detail in the literature and acknowledged by regulatory authorities. Some of the key areas of concern in relation to investigators failing to meet their responsibilities that have been described in the academic and industry literature relate to protocol adherence (Fisher, 2006; Vulcano, 2012) and the extent to which they provide oversight and support to their study staff (Baer et al., 2011; Davis et al., 2002; Fisher, 2006; Fisher, 2009; Gamache, 2002; Kellen et al., 1994; Mueller & Mamo, 2002; Roberts et al., 2006; Speicher et al., 2012). Fisher, 2009, for example highlights that lack of investigator oversight also has implications for workload, because such investigators tend to be less aware of the demands of the studies that are ongoing at the site and tend to overcommit their staff. Others identify “unavailability of investigator” as a major impediment to coordinators and research staff being able to fulfill their responsibilities (Kellen et al., 1994; Mueller & Mamo, 2002; Roberts et al., 2006). Many of these references also address insufficient availability of training for staff. More specifically on this latter topic, it has been observed that research coordinators—despite their critical role in relation to subject safety and data integrity (Poston & Buescher, 2010)—often lack training in research ethics and research integrity (Anderson, 2008). Some have suggested that this lack of training could have dire consequences for both subject safety and trial integrity, particularly in the face of investigator misconduct (Anderson, 2008; Broome, 2003; Habermann et al., 2010; Pryor et al., 2007). Finally, a lack of institutional support and resistance from other hospital staff is discussed for example by Roberts et al. (2006).

Regulatory authorities too have addressed some key issues. For example, a number of U.S. FDA warning letters have been issued to investigators who have failed to provide adequate

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168 This is also discussed in the literature. See for example, Shawn, R. (2010) Academic site pressures. Modern Healthcare. 40(4), 14.
supervision and oversight to their staff (Halloran, 2012; Shah, 2011), and both the FDA and Health Canada require investigators to sign undertakings that they will (inter alia) follow GCP and provide appropriate oversight of the trials for which they are responsible.169

As such, the findings reported in these two chapters do not constitute categorically new insights. However, they are still interesting and important for two reasons. First, they do constitute fresh illustrations of these problems in a Canadian context, as well as provide verification that these are still issues and areas of concern despite ongoing efforts and initiatives that have been undertaken—mostly in the name of attracting additional clinical trial business to Canada. Second, and more importantly, I would argue that the findings in this study suggest that it may be past time to bring renewed attention and scrutiny to bear on investigator-initiated trials. For the last 20+ years in particular, the critical literature from bioethics and health law relating to clinical trials and academic institutions has been dominated by literature identifying, analyzing, debating, addressing and assessing the dangers associated with conflicts of interest (individual and institutional level) that arise in the context of commercialized clinical trials (Blumenthal, 2002; DeAngelis, 2000; IOM, 2009; Krimsky, 2003; Labonte & Torgerson, 2005; Lemmens, 2004; Lemmens & Waring, 2006; McDonald & Preto, 2011; Neuman, 2011; Thompson, Baird & Downie, 2001). While no doubt critically important and worthy of ongoing attention—it could be argued that this intense focus on conflicts of interest has resulted in other issues, including those discussed here, being somewhat ignored in bioethics and health law, and in the policies that have been informed by debates in these areas.

While many of the problems identified by participants in this study arise in both industry and investigator-initiated trials, they tended to be discussed by participants most in relation to investigator-initiated studies. This was particularly true for those issues associated with lack of investigator training and involvement and insufficient staff training. Lack of sponsor oversight (including inspections, GCP training and monitoring), and the perception that REBs tended to pay less attention to investigator-initiated trials were among the key factors identified by participants in describing their concerns.

169 Though it should be noted that the U.S. FDA form 1572 is far more explicit and detailed in what it asks of its investigators.
Investigator-initiated studies do not have the benefit of a highly motivated sponsor to ensure standards and regulatory requirements are met. As is described further in Chapter 7, regulatory oversight of clinical trials is essentially non-existent and sponsors are charged with ensuring that their clinical trials meet established standards in terms of safety and integrity. While not perfect, industry sponsors are highly motivated to ensure returns on the huge investments they make in developing and testing their drug. The assumption is that industry sponsors will go to great pains to ensure the quality and integrity of their data so that their new drug submissions succeed. It should be noted however that the U.S. FDA seems to be reevaluating its assumptions in this regard, with renewed attention and initiatives being undertaken in relation to sponsor oversight of clinical trials (Getz, 2012; Halloran, 2012; Kasper, 2012). Some of these, such as the potential for additional scrutiny and regulation of the sponsor-CRO relationship are being met with concern by the industry (Getz, 2012; Halloran, 2012). Others, such as the recently approved FDA initiative for risk based, centralized monitoring, are being greeted with cautious optimism (Panzitta, 2013).

In contrast, and despite the above noted shortcomings, while the stakes in investigator-initiated research are no doubt high (investigator’s reputation, funding, not to mention the therapeutic benefits that stand to be gained by the research) they do not seem to yield the same results in terms of motivation (or resources) for sponsor-investigator oversight as the prospect of losing billions and billions of dollars has for industry sponsors. The data and literature described in Chapters 4 and 5 of this dissertation point to ongoing problems with investigator oversight and awareness of sponsor-investigator responsibilities. Moreover, this lack of sponsor-investigator oversight may be further compounded if investigator-initiated trials are subject to less scrutiny by other oversight mechanisms as well—namely the REB and the regulator. For example, and as will be discussed in more detail in Chapter 7, a recent Senate Committee report suggests that under Health Canada Inspectorate’s risk based selection process, more industry sponsored trials are singled out for inspections than are investigator-initiated trials (Ogilvie, 2012). In terms of REB review, given their limited resources and proportional approach to review (and the heightened perception that industry sponsored research is more risky) it seems reasonable to expect that industry sponsored research will tend to receive greater scrutiny than investigator-initiated trials. Such expectation is also supported by a recent reminder issued by FDA to IRBs to
make sure that they subject investigator-initiated trials to appropriate levels of scrutiny.\textsuperscript{170} While Klitzman (2013) and Lad & Dahl (2013) present evidence to the contrary, suggesting that some REBs may actually scrutinize investigator-initiated studies more than industry-initiated trials, Klitzman (2013) acknowledges that this is an area that needs further research and debate. When combined with the key findings presented in these two chapters on intra site challenges, including:

1 that investigators are often insufficiently aware of their responsibilities—particularly where they act both as sponsor and investigator (i.e., in investigator-initiated trials);

2 that there is an ongoing and serious lack of investigator involvement in the trials they take on and this materializes both in failure to engage the research team early on in a way that would foster informed decision making around (e.g.,) trial selection and design issues as well as ongoing oversight and support; and

3 that the staff that are charged with most of the day to day running of the clinical trial as well as an ever growing list of other research responsibilities, may be insufficiently trained or experienced to take on the tasks delegated to them by the investigator; it does not seem unreasonable to conclude that there may well be serious cause for concern and that additional steps may be needed to ensure the trust and confidence that is generally enjoyed by investigator-initiated studies is in fact merited.

In considering what some of those steps might be, some insightful suggestions were offered by my participants. For example, one way to start improving investigator knowledge and awareness of their research related responsibilities would be to institute a GCP tutorial requirement, along the same lines that is required for the TCPS2. While this would certainly not address all of the concerns, and while the effectiveness of this proposal would depend on a number of factors including the substance and quality of the tutorial itself, it is a very practical and likely relatively cost effective solution. Hopefully, greater appreciation of their responsibilities, including oversight, would in turn start to address some of the problems

participants identified in relation to lack of investigator involvement. Improving levels of staff engagement and developing mechanisms to ensure that sites incorporate insights and expertise from the immediate and extended research team to help ensure staff satisfaction and trial success is also important (Baer et al. 2011). Suggestions by participants to develop and promote networking opportunities for research coordinators and staff, and to create a forum for discussion of site specific issues could be one part of the solution to address issues associated with gaps in staff training and experience. Such steps would also likely serve to empower conscientious research staff and reduce moral distress by providing them with opportunities to share their experiences with those in similar roles and learn from the experiences of others. Developing mentoring programs was another suggestion that could be helpful in this regard—particularly to help new research coordinators develop the more nuanced skills necessary to effectively balance the many complexities of what has been described elsewhere as a very multi faceted role (Davis et al., 2002; Fisher, 2009; Poston & Buescher, 2010).

While each of these suggestions would no doubt be part of an effective solution—it may also be reasonable to suggest that given the challenges identified, investigator-initiated trials should be subjected to the same level of scrutiny and review by REBs and Health Canada as their industry sponsored counterparts. The extent to which this is or is not happening, and how to ensure such research is subjected to appropriate scrutiny has very recently been identified as an important area for more research and debate (Klitzman, 2013). Given the concerns raised by my participants, it is clear that whatever the level of scrutiny such oversight must be done with sensitivity by REBs or it could risk undermining the efforts of those bona fide whistleblowers compelled by lack of other alternatives to bring their concerns forward. At the very least, it would seem wise to clearly recognize and acknowledge the areas of concern described above so that all investigator-initiated research is not unquestioningly assumed to be higher in terms of quality, integrity and safety than it actually is.
Chapter 6: Challenges Reported By Sites Working With CROs

The previous two chapters (Chapters 4 and 5) provide some close scrutiny of investigative sites—mostly in the context of large academic health centres, with a focus on understanding some of the on-site obstacles staff encounter in their day to day conduct of clinical trials. These challenges include issues associated with lack of investigator training and involvement, problems with staff training, and gaps in institutional support. While these chapters primarily focus on the effects such issues create for site staff, they also to a more limited extent draw on interviews with non-site participants to highlight some clear implications such “internal” issues have for the relationships sites have with others—including CROs and sponsors.

This chapter (Chapter 6) builds on the insights gained in Chapters 4 and 5, but shifts from an internal focus to explicitly examine the relationship sites have with CROs. More specifically, while the findings in this chapter draw on data from across all participant categories, the dominant perspective is still that of the site that serves as the lens through which the data is filtered and analyzed.

6.1 Context

Since the mid-1990s, contract research organizations (CROs) have taken on an ever increasing and central role in conducting clinical trials, as industry sponsors look for ways to maximize profits and minimize costs. Because they are often responsible for recruiting sites, monitoring and managing all aspects of data generation and collection, CROs tend to become the face of the sponsor for investigative sites and have an important role to play in ensuring subject safety and data integrity among other things. CROs and their relationships with sponsors and sites have been explored in the industry literature, including a more recent focus on how CROs affect the site-sponsor relationship. However, such articles tend to focus primarily on the logistical challenges, obstacles and proposed solutions to maximizing efficiency and speed of trial conduct, without considering the broader implications (Lamberti et al., 2011; Pierre, 2013)\textsuperscript{171}. In contrast, there seems to be relatively little academic literature (empirical or

\textsuperscript{171} For example, such literature tends to address how to maximize the efficiency of monitoring site visits, or how to improve communication between coordinators and monitors. There are also
otherwise) exploring or discussing the broader implications (e.g., legal, ethical) that can follow from CRO-site interactions, although the literature on this seems to be expanding particularly in relation to the use of CROs in emerging markets in less developed countries (Adobor, 2012; Petryna, 2009; Schipper et al., 2011).\textsuperscript{172} The work by Jill Fisher (2006; 2008; 2009) represents an extremely important contribution in this area in the context of the more traditional, established markets and her work has certainly informed the present study\textsuperscript{173}. Despite this growing literature, it is still fair to say that given the central role of CROs in clinical trials they have not received the attention or scrutiny they deserve.

As explained above, this chapter reports the key findings from the present study on the complex relationship between site and CRO. What emerges from the data is a description of a complex multifaceted relationship between sites that conduct clinical trials, the CROs who are involved in management, monitoring and many other aspects, and the sponsors who fund (and typically design) the trials. While there are many challenges and issues reported that tend to erode the site’s satisfaction in this three-way relationship, it is not always clear whether sites perceive the sponsor or the CRO to be at the root of their concerns. Some of these challenges (a very narrow subset) are discussed in explicitly ethical terms (privacy related concerns, for example), others are described more as practical or operational problems with many related to the CROs position of middleman between sponsor and site and the logistical problems and frustrations this creates for sites. As will be described further below, participants also explicitly

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articles discussing, for example, the importance of hiring an experienced coordinator if you are a new community based PI and the logistical challenges that can arise when a PI takes on too many research studies without ensuring adequate staff or infrastructure.
\textsuperscript{172} For example, the study published by SOMO (Centre for Research on Multinational Corporations), Salud y Farmacos & CSER (Centre for Studies in Ethics and Rights) in 2011, is entitled \textit{Putting Contract Research Organisations on the Radar: An exploratory study on the outsourcing of clinical trials by pharmaceutical companies to contract research organisations in non-traditional trial regions}. As the name suggests this study focuses on the role of CROs in developing trial regions; however, it also provides a limited discussion of challenges with CROs in the more established clinical trial market.
\textsuperscript{173} Jill A. Fisher’s work, including that published in her book \textit{Medical Research for Hire: The Political Economy of Pharmaceutical Clinical Trials} (2009), explores CROs in the American context, but does not pay a great deal of attention to the academic research organizations or academic investigative sites. A few others include Mirowski & Van Horne (2005) and Shuchman, (2007)..
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reflect on whether CROs bring new or increased pressures to sites over and above what they would experience if working with sponsors directly. The remainder of this chapter will review and illustrate these findings and argue that while the CRO may have a critical role to play in making clinical trials possible and profitable for sponsors in today’s global economic and regulatory climates, they also exacerbate existing (and may even create new) ethical tensions or concerns in their interactions with sites which must be addressed in order to ensure the safety and integrity of clinical trials in Canada. A summary of the main issues, including whether and how these are discussed by each of the four categories (site, CRO, sponsor and consultant) is provided in Appendix D.

6.2 Do CROs Exert More Pressure On Sites Than Sponsors?

As described in Chapter 2, clinical trials are a high stakes, high pressure industry. In an effort to reduce timelines, minimize costs and maximize profits industry sponsors often rely on contract research organizations for a wide range of tasks associated with clinical trials—from recruiting sites to managing trials and monitoring the data generation and collection process—among many others. The literature supports the findings in this study that most site-sponsor relationships are in some way and to varying degrees (often entirely) mediated through the CRO (Getz, 2012; Glass, 2010). An important question, then, is whether and to what extent this changes the kinds and degree of pressures that sites are under to perform.

CROs are the primary auxiliary service provider supporting industry sponsors in the fiercely competitive and high stakes clinical trials industry (Fisher, 2009; Getz 2012). As with any service provider, the CRO must meet and even exceed the sponsor client’s expectations while at the same time doing things as economically as possible in order to maximize their potential profits and remain competitive. Contract research organizations are hired by pharmaceutical companies for a variety of reasons, but an underlying rationale is that they will be able to complete the tasks they are assigned more quickly and economically than the sponsor itself. As well, hiring CROs allows sponsors to downsize through outsourcing various tasks as well as increasing flexibility (a sponsor can replace or threaten to replace a given CRO with another CRO). Where the outsourced tasks involve managing and monitoring investigative sites and data generation, it is foreseeable that the CROs may exert more pressures on the sites than the sponsors themselves would because of the need to meet and or exceed their clients’
expectations to help secure future contracts and build their competitive reputation. Interestingly, while there has been a good deal of research done around site preferences and how to improve sponsor-site relationships (Glass, 2010; 2009; Harper and Neuer, 2008; Lamberti et al., 2011) this has largely been done by industry and there has been little empirical research done to explore whether and to what extent CROs bring additional pressures to bear on sites over those associated with sponsors or what the implications of those pressures might be.174 This is despite a recognition that many of the concerns associated with the outsourcing of clinical trials relate to “tradeoffs between costs, speed and quality of clinical trials” (Schipper et al., 2011). The present study examines this specific question, among others, across all 4 categories of participants (Sites, CROs, Sponsors and Consultants).

Interestingly, while there was general agreement among site participants that CROs created more work for sites (discussed later), there was less consensus within this category as to whether CROs actually exerted new or added pressures on them (to work faster, for example) as compared to working directly with sponsors. On the one hand, some participants felt that the involvement of a CRO made no difference in regard to the intensity of the pressure on the site to perform their study tasks,

because any pressure from the CRO is pressure from a sponsor. I mean, it’s all about milestones and timelines. I have the same amount of pressure working directly with [Big Pharmaceutical company A]on a study that I do working with [CRO X], who is contracted to [Big Pharmaceutical company B]. (Research Coordinator, 12/11/10)

In contrast, other sites were of the view that the CROs exerted more pressure on sites generally to perform tasks faster in order to make themselves look good for their sponsor clients. As one participant described,

the CRO, to make themselves look good, want to perform for the sponsor as well. They want to pretty much do better than what the sponsor may have been able to do on their own resources and so...there is a little bit more pressure on the site. There is definitely that...when a CRO gets involved they really want to take out all the bells, whistles and gongs and they want your attention and they want to get results...They want things happening fast and they want those results. (Research Worker, 26/10/10)

174 Fisher (2009) does talk about CRO monitors creating more work and making more demands on sites than sponsors—but there is more nuance and detail in my participants’ discussions on this point.
This was echoed by another participant who had worked as a CRO project manager, but was working as a site coordinator at the time of the interview,

CRO pressures are usually deadline oriented because [CROs] are only given so much money from the sponsor...[the CRO] is only given so much money, timelines are tight. I can tell you, let’s say…you [CRO] are supposed to be able to build a database from the protocol in eight weeks. Well often the sponsor wants it by five or six. So you [CRO] then put on the pressure on the sites because somehow you have to line up all the dates and stuff and then, okay, you do all of that and all of a sudden the sites – oh, we’re supposed to recruit now. Nothing is happening. Then also I think a lot of the sites don’t realize that when you don’t recruit the CROs may not get paid….So yes, it is always more pressure]……Yes, they will pressure the sites…to meet their criteria so they can get the next contract, oh yeah. (Research Coordinator 2, 12/11/10)

Others described that this extra pressure can result in the site feeling hounded by the CRO,

there's more pressure [than if you were working with a sponsor directly] to get up and running faster…they [the CRO] can really be on you. Every week, they'll be calling for a recruitment update...because they have to prove themselves to the sponsor…(Research Coordinator, 18/11/10).

A third view reported by sites was more ambivalent, that it wasn’t something they could speculate on as they really didn’t know whether CROs exerted more pressure on sites that sponsors would directly,

that could be happening but it’s very hard to prove... because I don’t know what their [CRO] motivations are sometimes in terms of, we need this now or whatever… I don’t know what’s happening, back there [behind the scenes with the CRO]. In some cases I’d speculate but I don’t have any proof….to tell you the truth I can’t identify any real differences in that respect because the whole industry, CROs are—they’re in a challenging position but they’re basically faced with the same pressures in assuming the subset of the sponsor’s responsibilities under GCP that they do, that the sponsor has anyway. So sponsors can inflict the same thing—either they’re well organized etc or they have a high turnover of staff or they—or that type of thing. That funnels down on a site as well. (Site Manager, 22/10/10)

The above indicates ambivalence around whether CROs exert more pressure on sites than a sponsor does directly. However, and as will be discussed further later in this chapter, it also supports data (both from this study and industry research) suggesting sites acknowledge problems can arise working with both CROs and sponsors and that their primary concern is not who they work with (CRO or sponsor) but whether who they work with is organized and effective (Glass, 2009; Lamberti et al., 2011; TTC, 2010).
Although sites varied in their views on the relative pressure brought to bear on them by CROs and sponsors, there was recognition across all categories of the real motivation for CROs to exert increased pressures on sites and an acknowledgement that this likely materialized not infrequently. One CRO executive, for example, observed that CROs would be inclined to increase pressure on sites,

in instances where the sponsor expectations of the CRO are far greater than they were of their own delivery of services. So the criteria can become quite prohibitive, quite rigid, and expectations unrealistic between the sponsor and the CRO and so when that happens then the CRO really, who are they to pressure for delivery of the results? They have to pressure the sites...[and] sites that are feeling pressured...to deliver to the unrealistic expectations can and do fall into that whole realm of not quite properly followed, not good clinical practice guidelines followed, or not best standards of practice and informed consents may be administered without adherence to all of the respectful guidelines that we try to implement in that whole process. So quality is compromised all across the board...(CRO, 16/08/10)

While the above offers an insider perspective on when and why CROs may exert additional pressure on sites, some sponsors instead pointed to the tendency of CROs to promise more than they could deliver as the cause for concern. Many sponsor participants made comments relevant to this issue when discussing specific tasks, such as participant recruitment. Recruitment is recognized as a major obstacle in the clinical trials industry (Fletcher et al., 2012; Getz, 2008) and provides a good illustration of why and how pressures could be amplified with the involvement of a CRO. It goes without saying that in order for a trial to be a success, it needs subjects—but it also needs subjects to be recruited in a timely fashion in order to remain economically and scientifically sound.\footnote{There are arguably both cost and scientific reasons why it is important to recruit in a timely fashion. While the cost challenges are quite obvious, one participant suggested that the rapidly changing nature of medicine and treatments that subjects may be exposed to over time is also a relevant challenge of delayed recruitment. As she explained, “the other problem too, is that if you have the study goes for too long, like, it’s a very, very prolonged enrollment, well medicine changes so quickly. And the reality is if it takes you two years to enroll, you know, fundamentally the patients you enrolled in the first year could be completely different than the patients you enrolled at the end.” (Consultant, 25/08/10)} Sites are the gateways to patient populations, and as
such subject recruitment is a task that generally falls to sites; however, the recruitment of sites often falls to CROs, who become, as it were, keepers of the keys to the gateways e.g., sites and clinicians with patients in the target population. A critical part of the assessment of a potential site is carefully assessing their recruitment capacity, and as such sponsors “are relying on the CROs evaluation of the site to perform, and they will hold the CRO to the flame to make sure that happens. So, it’s doing what you say you can do.” (Sponsor, 13/08/10) Likewise, sponsors indicated that “non-delivery (on site readiness and subject recruitment) is probably one of the main reasons where you would change the CRO” partway through a study (Sponsor (2), 13/01/11). This not only highlights the importance of these critical timelines to sponsor interests, but also demonstrates that CROs are held accountable for their assessments of site capacity—and therefore indirectly for site performance—by sponsors and risk losing current and future contracts should sites fail to, for example, meet their recruitment targets.

As noted above, an additional, highly relevant factor to the question of pressures exerted on sites by CROs is that CROs are not only interested in meeting client expectations, but also, of course, in generating a profit. As is discussed in more detail in Chapters 2 and 7, there is evidence in both the data and the literature that the current clinical trials climate can be described as one wherein budgets are getting tighter, trials are getting more complex, and regulatory oversight is arguably lacking. As such, conditions are ripe for questionable corner cutting behaviours to emerge and for inappropriate antics to be employed to meet objectives. As one participant with significant expertise in auditing clinical trials commented,

So people know that they [Health Canada] are auditing less than 1 percent of clinical trials. And what is the incentive to comply? …So the CROs which are running tight budgets and trying to make profit, because they’re the middle man, and so they have a tendency to see what they can get away with. If you don’t have a really strong person in quality or regulatory within the [contract research] organization, they can run astray fairly quickly. And what makes them stay compliant? INDUSTRY! Industry requirements are currently much more rigid, far more rigid, ten-fold more rigid than the current regulatory requirements by Health Canada. (Consultant, 17/11/10)

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While it seems that industry plays an important oversight role\textsuperscript{177}, the extent to which sponsors are aware of CRO-site interactions varies significantly and such efforts also tend to decrease during financially tight times. As one sponsor participant explained,

> There's definitely some variation on [sponsor awareness of CRO-site interactions]. I think it depends on the company that you work for and how much they put behind that. From a contract organization point of view, it depends on what the sponsor is willing to pay for also. If they think that they've handed the role of the trial and the running of the trial over to the CRO, and it's gonna cost them more to actually get staff out and going to visit the sites then they probably would leave it to the CRO. But other organizations think well, no, it's a very important part to have the face of the sponsor at the site, so they then tend to encourage [visits]…So it does depend on sort of economics and it depends on accessibility I guess of the sites and things…I think it does help but I think it's also, with current situation and budget cuts and things with travel, I think it's not always easy to be able to realize that. (Sponsor (2), 13/01/11)

As this participant suggests, one of the reasons sponsors hire CROs is exactly to take over the conduct of clinical trials and to minimize sponsor involvement in such matters. Some of this benefit is therefore eroded if sponsors then spend time and resources managing the managers and monitoring the monitors.\textsuperscript{178} However, if it is indeed sponsors who are in practice serving the oversight role (something that is in itself at least arguably very problematic) then this variation in level of scrutiny and the fact that such scrutiny tends to diminish when dollars get tight, is extremely troubling. These concerns are explored more fully in Chapter 7.

Finally, it is also important to highlight that site confusion as to the origins of the pressures and demands they experience is likely exacerbated by competing goals or interests of the sponsor and the way in which these are interpreted by the CRO. As described elsewhere, sponsors have a keen and driving interest in ensuring that trials are completed on time and on budget, and employ CROs to help realize this goal (Getz, 2012). However, sponsors also prioritize strong relationships with the sites that conduct the trials, both as future prescribers of the trial product and as gatekeepers to patient populations for subsequent trials (Lamberti et al., 2011; Harper and Neuer, 2008). Whereas the former is a relatively measurable end point, the

\textsuperscript{177} The limited presence of the regulator in overseeing clinical trials in Canada and the challenges associated with industry filling this role are discussed in detail in Chapter 7.

extent to which a CRO helps or hampers the sponsor-site relationship is somewhat more difficult to assess. An interesting dynamic emerged from the data in this regard. On the one hand some sponsors expressed concern that CROs may compromise the sponsor-site relationship by exerting more pressures on the sites to meet targets/timelines etc, and then blaming the sponsor for this added pressure. As one sponsor stated,

the CRO will always use the sponsor as the stick to beat sites with…If your recruitment’s really slow, ‘the sponsor wants you to do this, the sponsor that.’ It’s always thus, “it’s not us who’s responsible”. And the CRAs as well, it’s like, “Oh the sponsor wants you to answer that DCF (data clarification form) in a certain way.” And when I’ve seen [outsourcing to CROs] work well, it’s only worked well when there’s a team and the sites, the CRO and the sponsor, all one part and we’re all trying to achieve the same thing. (Sponsor, 28/09/10)

CROs in contrast suggested that,

part of the reason that the sponsor hires the CRO [is] because a lot of pressure [often] does need to be applied to the site...And that’s one of the things that a sponsor doesn’t need to do if they have the CRO there. That’s not the sole reason they hire a CRO but that’s one of the things that inevitably they do not need to do.” (CRO, 19/10/10)

The above tension could be interpreted in a variety of ways—from a misunderstanding between sponsor and CRO as to sponsor priorities, to the sponsor trying to ‘have their cake and eat it too’. What it does help illustrate, however, is that sponsors have competing goals and expectations of the CRO, and that the CRO must strike a fine balance between (among other things) supporting the site and ensuring they stay on time and on budget. Importantly, and regardless of where the pressures do in fact originate, the confusion sites feel in this regard could foreseeably make them less inclined to report or address associated concerns which in extreme cases may have important consequences for data integrity and/or subject safety.

Hence, despite the somewhat ambivalent view of sites on this point, the data overall suggests there are a number of factors at play that at the very least make it reasonable to expect that CROs likely exert additional pressures on sites as compared to sponsors. This is something to keep in mind in the following discussion of the specific issues and concerns that are raised by sites. In some instances, such issues are discussed specifically in relation to CROs; however, they are also often discussed referring generally to both sponsors and CROs—i.e., without making a clear distinction as to whether the challenge arises more in relation to one over the
In such instances, the increased pressure that may be exerted by CROs on sites becomes particularly relevant in that even though the problems may exist in relation to both CROs and sponsors, they may be worse or more prevalent in trials involving CROs.

### 6.3 Specific Challenges Described By Site-Based Participants

Participants working at investigative sites described a number of challenges and concerns in relation to their involvement in clinical trials involving CROs. Some of these they identified and discussed in explicitly ethical terms—either spontaneously, or more frequently, in response to questions about whether they encountered ethical challenges in their day to day encounters with CROs. Other issues were described more as logistical, practical, or operational sources of frustration and concern. Not surprisingly, the former category captured a much narrower subset of issues than the latter, even though both clearly have important ethical dimensions. What is perhaps somewhat unexpected is that the issues identified as ethical by participants don’t seem to have been explored much, especially in the limited empirical literature. Although the general areas of concern (privacy issues, access to databases, etc) have of course been previously identified and discussed in detail, significantly less attention seems to have been turned to how these issues actually play out or how they are experienced by site staff. These aspects were discussed in detail by my participants and are explored below.

#### 6.3.1 Ethical Challenges: Privacy And Data Security

Despite a focus and in some instances an almost preoccupation with privacy, this relatively new and evolving area is still not well understood generally, and the clinical trials context is no exception. As one non-site participant who had extensive experience consulting on quality and compliance for sponsors, CROs and sites observed generally with regards to knowledge of privacy requirements across the industry,

…you're dealing with privacy, and you're working in the public realm, and you're also working with studies that have interface in the public and private realm, and there's subtle differences. And there are very few people in Canada who actually have an understanding of those differences at a private and public realm, and in relation to [privacy] requirements across provinces. (Consultant, 17/11/10)

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179 This could be because they don’t know who is pressuring them, or because they experience a given pressure from both sponsors and CROs.

180 The modern era of privacy legislation in Canada arguably only began with the coming into force of The Personal Information Protection and Electronic Documents Act (PIPEDA) in 2000.
Privacy related challenges were key among concerns explicitly discussed as “ethical” by site participants, and were most frequently discussed in relation to recruitment, but also with regards to data monitoring practices.

6.3.1.1 Recruitment

As noted earlier and discussed elsewhere, recruitment of participants is recognized as a major obstacle in the clinical trials industry and one that seems to persist and even worsen despite the ever increasing resources committed by sponsors, CROs and sites (Getz, 2008). Not surprisingly, this was reflected in the data with most participants identifying recruitment as a major challenge and as an area giving rise to intense pressures to perform and meet targets. In relation to privacy, a key concern was the pressure sites felt (from both CROs, and in some cases from sponsors) to proactively ‘prescreen’ physician patient databases to determine those patients who may be eligible to participate in a particular study, and to then provide prescreening logs to the CRO/sponsor and/or target those patients in recruitment activities (such as contacting the patient to see if they would be interested in participating in the study). As one site manager described, many sponsors and CROs seem to assume that all patients under an investigator’s practice are fair game,

The most consistent trend that I’ll see is a lack of understanding of privacy law when it comes to pre-screening. When a study starts, they want to see pre-screening…we’ve even had one come forward and say, ‘we want to see the initials and birth date, the disease diagnosis and the date of diagnosis of any subject that you pre-screened.’ Wait a minute, first of all, to be pre-screened, they already have to allow us to review their information, and they haven’t consented to us releasing anything externally to you. (Site Manager, 22/10/10)

Another coordinator described other ways in which CRO pressures can erode the integrity of the recruitment process,

I had one study where it had kind of gotten known through the grapevine where several sites were going back through previous trial participants and basically getting them on to the study. I have a problem with that, because how do you know that those people have agreed to be contacted in the future? We’re very ethical about that. We don’t contact people unless we have their permission, unless we have a form on file with them. And sometimes I think that recruitment pressure from a CRO could potentially be the cause of that kind of what I consider an ethical breach. (Research Coordinator, 12/11/10)

Another coordinator described the challenge of working with companies from other countries-
The trickiest part is actually about recruitment, because—and especially if you are dealing with U.S. companies. They have a little bit different approach. For example, we are not allowed to phone patients and that’s—okay, so there is a study, are you interested? So it’s completely out of question [in Canada], it’s not considered as ethical. (Research Coordinator, 19/10/10)

This lack of understanding of what is permitted and prohibited under the privacy rules creates a great deal of confusion and uncertainty and is exacerbated by the fact that there are subtle changes under the legislation across the country, as well as important differences between Canada and other countries such as the United States and member states in the European Union. As such, some of the challenges that are reported by sites may be attributable to foreign-based companies who have not acquired sufficient familiarity with Canadian requirements. However, as noted above, there are also many in this country without sufficient knowledge of this relatively new and evolving area.\textsuperscript{181} This can lead to site personnel, for example, unwittingly breaching privacy regulations by responding to inappropriate sponsor/CRO requests, which in turn can lead to an escalation of pressure on other sites to follow suit.

While site-based participants discussed this in relation to their specific investigator patient databases, one of the consultants highlighted that this is a broader problem as well and one that really calls for immediate attention in terms of guidance development,

And the other thing is that in Canada and in B.C. in particular, we have a huge, huge valuable resource information in these databases… There’s [MSP\textsuperscript{182}]…there's these registries that the specialists and – that they’ve been keeping for years and years and years…All kinds of them, all kinds. And they’re in private clinics. They’re all over the place. And they have subject information… And so I think that needs to be – privacy issues and ethical issues surrounding the release of that information need to be looked at. Because it’s a valuable source I think we need to deploy that in a way that can be effective for the betterment of health of Canadians…Because I think they will – if you keep saying no and they know it's there... and it's valuable information, there's going to be nefarious means of access. And I think that that’s starting to happen and I really – I think that’s unfortunate… (Consultant, 17/11/10)

\textsuperscript{181} Research ethics boards and site personnel for example were explicitly identified by a couple of participants as seriously lacking in terms of privacy expertise.

\textsuperscript{182} MSP, or the Medical Services Plan, is the public program that insures medically-required services provided by physicians and supplementary health care practitioners, laboratory services and diagnostic procedures in the province of British Columbia.
This highlights an important tension in research ethics generally, and one that is front and centre in the debates and discussion around privacy in particular—namely how to at once sufficiently protect the interests of subjects while also allowing important research to proceed without undue impediment. Whereas one aspect of the concern is certainly to protect the interests of the people to whom the information pertains, the other concern is that confusion around privacy requirements is actually resulting in more obstacles or restrictions than are actually required by law and which are unnecessarily hampering good research.

6.3.1.2 Data Monitoring Practices

Another area in which privacy concerns, as well as concerns regarding data security, arose was in relation to certain monitoring practices. Clinical Research Associates (CRAs), also referred to as monitors, play a critical role in ensuring the integrity of the data generation and reporting processes at sites, among other things. While monitors will have access to documents containing some patient information, including case report forms and source documents\(^{183}\), they are not supposed to remove such documents from the sites in order to help preserve participant confidentiality.\(^{184}\) However, as reported by this site manager, sites need to maintain a certain amount of vigilance to ensure the interests of their participants are protected in this regard:

> we were asked to fax copies of case report forms and source documents. Of course patient ID was blocked out but the informed consent said, your data will reside at the site. And the sponsor or their designates will come here and review it. So we were told, can you please send this…But I said no because we’ve told our subjects as per the consent, that you’re going to come here and you’re going to review it. That’s it, end of story. However, we did find out that other sites that weren’t on the ball about that went ahead and did it. It’s going to be their fault for violating subject confidentiality because they should know. And that’s what the patient has consented to. (Site Manager, 22/10/10)

Interestingly, another participant who had previous CRO experience recalled a common practice that had caused her significant concern in this regard:

> CRF’s (case report forms) were coming back to the [CRO] office….There were people's names on there. They were -- their health information is on this damn piece of

\(^{183}\) Source documents are essentially the subject’s file. Case report forms collect the data from the source documents that is required for the trial (Fisher, 2009).

\(^{184}\) Protecting the privacy of participants is an integral element of ethical research and established and protected in GCP Guidelines, as well as the TCPS2. Privacy protections are also established through federal and provincial privacy legislation.
paper...So then the question is what the hell was that coordinator doing...A lot of coordinators will double check what the monitor is taking home with them, because they want to know-- you know the monitor can have anonymized stuff if she needs to take it back with her to photocopy for whatever reason. But [monitors] can't take the originals out of their files, so that was a really big problem... (CRO, 13/09/10)

The above highlights the importance of increased awareness by all parties, from sponsors to CROs to site personnel, of privacy and confidentiality requirements. It also suggests that more is needed to ensure that checks and balances are in place to ensure that patient/subject information is being adequately protected in the day to day interactions between these parties.

6.3.1.3 GCP Violations: A Matter Of Interpretation

In addition to the above relatively specific issues identified by participants as ethical concerns they encounter in their interactions with CROs, participants also identified differences in interpretation of standards and guidelines (most frequently, ICH-GCP and privacy legislation) as a cause of some concern. As noted by one of the consultants and echoed by a number of other participants, many of the problems that arise as between CROs and sites often come down to interpretation of legislation and guidelines...And so everybody knows that the regulations are written in the affirmative, but there's no clauses that say, ‘In the case of’, or ‘If this occurs’, so it comes down to a lot of judgment calls (Consultant, 17/11/10).

Such grey areas leave room for interpretation and can contribute to situations wherein site personnel feel that what they are being asked to do by the sponsor or CRO is not in keeping with ethical guidelines or other requirements, even where perhaps technically what is being asked can be supported by a given interpretation.

While discussions of this were understandably somewhat vague in the data, and included descriptions of discomfort and having a general sense of something “not feeling right” there were a couple of clear examples. One manager describes the “grey zone in the interpretation of privacy” where “for example, GCP says you have to keep information confidential etc., but GCP doesn’t go down to the level that privacy law does. And I think overall there’s a grey zone in the interpretation of privacy requirements by the clinical research industry” (Site Manager, 22/10/10). Another coordinator explained it this way:

there are things that we’ve just refused to do...because we don’t believe that it’s in accordance with good clinical practice or good ethical practice, or if it’s contravened what we’ve stated in our ethics application. (Research Coordinator, 12/11/10)
Again, while site participants referred to both CROs and sponsors in this regard, if as argued above CROs do in fact exert increased pressure on sites, there may be reason to expect this would be more of an issue in relation to CRO-site relationships. 185

Interestingly, it is worth noting that site personnel reported that in some such instances they did not feel they were able to have their concerns adequately heard or addressed without drawing on the institutional REB. As one participant explained,

If they insist, I will, for example, and it’s got to go back to REB, I’ll put a note on the… submission…saying, “This is what the sponsor is telling us, we’re not necessarily in agreement with it, we’re going to do what’s best as best we can.” Or one way I got around it one time was, “We would appreciate the [REB]’s comment on this”. And then the [REB] will come back and say, “No, this is the way we want you to do it”, which will be, of course, the way that I want to do it. …Absolutely it has [more authority coming from the REB], because the REB has responsibility for the study. And unless the REB gets the answers that they want…they’re not to going to approve the study and they generally have much more influence. (Research Coordinator, 12/11/10)

While this seems an effective solution or approach in limited circumstances, it raises some concerns. First, relying on the REB in this fashion would likely only be a viable strategy in the academic setting where the REB is associated with the site, the coordinator has some kind of ongoing relationship with the REB that would increase the likelihood of seeking its input in this regard, and the coordinator is directly and heavily involved with the ethics application process. 186

In contrast, community based site staff tend to have less involvement with the ethics application process, because typically the CRO coordinates the review through a private REB of their choosing, and one with whom they tend to work across multiple projects.

While disagreements in interpretation can be difficult to substantiate and address (many of my participants simply described feeling uncomfortable with how the GCP Guidelines were being applied), the main concern this issue presents is that in a high pressure, high stake context

185 An additional factor that may be relevant to consider here too is related to sheer numbers. There is a greater diversity of CROs in operation than there are major sponsors. For example, there are 643 individual CROs working in clinical research in the U.S. (Getz, 2012), and 53 PhRMA member pharmaceutical companies (http://www.phrma.org/about/member-companies). As such, it stands to reason that CRO interpretations of legislative grey areas could be equally diverse.

186 As explained in Chapter 5, these circumstances also allow the coordinator to draw on the REB when the investigator does not sufficiently address issues or concerns.
such as clinical trials, there is strong motivation to adopt interpretations of standards that require the minimum amount of work, investment and/or time. Moreover, where a site disagrees or has concerns about the way in which standards are being interpreted by CRO/sponsor, the fact that the interpretation is technically acceptable can make it even harder for the site to raise their concerns—something that can be difficult even on the clearest of issues.

The above describes the main issues site participants identified when asked about ethical concerns they encountered in their interactions with CROs. However, site participants also identified a number of other challenges at this interface. While many of these may be described as logistical or operational with serious implications for site satisfaction (and therefore potentially serious implications for the site-CRO relationship and even site-sponsor relationship) many also potentially have profound implications for subject safety and data integrity that make them ethically troubling.

6.3.2 CRO As Middleman

While the complaints and concerns regarding CROs were quite varied, the vast majority of them stem from the CRO being positioned between the sponsor and the site. Both CROs and sponsors are hierarchical organizations and by introducing the middleman, most questions or concerns raised by sites must go through many more steps before being answered and resolved. While the specific requirements (and the clarity with which they are outlined) will vary with each contract, it is not unusual for concerns raised by sites with their monitor to be taken in turn to the CRO project manager and then from the project manager to the appropriate contact(s) at the sponsor. This fractured communication process can contribute to a wide range of frustrations for sites, and as one experienced monitor explained, “At the end of the day, really, what it comes down to is that sites like to work directly with the sponsor. They don't want a middleman” (CRO, 3/08/10). The main concerns related to this middleman factor include delayed or frustrated communications, disrupted relationship between sponsor and site, payment woes and an overly results oriented (as opposed to quality or solution based) approach—all of which can among other things increase the workload for sites and decrease overall efficiency.

6.3.2.1 Frustrated Communication And Increased Workload

From the site perspective, one of the key concerns directly related to the “middleman” factor is that the multitude of questions that arise from budget and contract negotiations through
to specific substantive and procedural issues relating to the protocol or clinical trial itself, take much longer to get answered. At the front end of the relationship between sites and sponsors, site participants expressed the view that CRO involvement can mean

a slower process… for budget and contract negotiations…[and what sites] have to end up doing is writing long emails and hoping that that information…goes directly to the sponsor and not a phone call kind of paraphrasing a few things that doesn’t have the full impact of what [sites are] saying through a CRO…So budget and contract negotiation…it’s always better done with the sponsor. (Site Manager, 22/10/10)

The frustration with slow responses and inability to answer questions carried over to the day to day issues and questions that arise in the conduct of clinical trials with many site participants sharing the concern that where,

a CRO [is] involved, I just find that they’re just so administrative in nature and just so, so slow to respond to anything, you know. It doesn’t matter what question or issue I raise, they say, “Oh, I’ll have to talk to the sponsor and get back to you. (Site Manager, 30/08/10)

Another site participant observed that CROs “make things far more complex than they need to be…instead of making one phone call or one email or something, it winds up being a very convoluted process” (Research Coordinator, 21/10/10). There can also be added delays when a CRO misunderstands the details of a site’s question and has to return to the sponsor multiple times with clarifications. As one coordinator explained,

there’s always, always room for interpretation, so you think that’s what you said to them [CRO] and they go back and they relay what they think they heard [to the sponsor]. It’s like the old thing you used to do when you whisper in somebody’s ear and it goes down the line…So yeah, the preference would be to deal with the sponsor always and take the CROs totally out of it. (Research Coordinator, 16/11/10)

In addition to delay, other coordinators also noted that communications involving the CRO created more work and just generally increased procedural complexities,

when you start adding more layers of people, like I said, it's more time-consuming, communication is muddied, there's more paperwork, there's more costs, there's more confusion, there's more chance of audits and retrospective [reviews], like a lot of hands in the pot. (Research Coordinator, 18/11/10).

While clearly such delays and added confusion can be frustrating for the site, the latter quote also identifies that such delays also have real cost implications, both in terms of added effort and time it takes to get answers to questions, but also in terms of the (at least perceived) increased
likelihood of audits or reviews—which also create additional work and costs for sites. Any added costs become particularly difficult in the current climate wherein many sites are struggling financially\textsuperscript{187}. As one participant who had both site and CRO experience lamented,

[CROs] could be such a beneficial thing to have. If only to buffer the effect of the sponsor down to the site to take some of that crap that they deal with, with the paper work and the regs and all that stuff. And minimize the effect on the site, and let the site just focus on the recruitment and the research. That doesn’t often happen unfortunately. (CRO, 13/09/10)

Although most site participants I spoke with certainly echoed these concerns, a minority of participants expressed the view that CROs did succeed in bringing important benefits to the site. One coordinator, for example, conceded that “usually it’s not good just to cut things in such small pieces...because you have to deal with two companies or three...” but was also very firm in her view that

[CRO] impact is very important because they definitely can improve your work. They can help you in recruitment, if you are struggling with recruitment. That can happen very often. They can help you, you know, providing strategies, how to recruit more patients. Or if you—of course if you are doing something wrong...Yes, I think CRO is better solution [than just the sponsor] for this type of reasons. (Research Coordinator, 19/10/10)

Sponsors and CROs themselves were very aware that delays in communication were “a point of frustration for site staff because they can’t get their stuff answered and they’re going through multiple layers to get an answer to their questions,” (Sponsor, 13/08/10) and were able to provide insights into why this was a perpetual problem. Both sponsors and monitors identified two key contributing factors: 1) a lack of longevity and training with the product and process in question, and 2) a lack of decision making authority-so that in some instances, even where monitors had the knowledge to make a decision, they did not have the authority to do so. As one CRO monitor described,

The thing about being either assigned by a CRO to one company or working for a sponsor directly, you get to know the ins and outs of the company, and the company will pull you in and they'll—you're there from the beginning...You get to learn all the innuendos that are going on. “Oh, yeah. I remember that discussion. Yeah, we decided

\textsuperscript{187} The overall financial crunch in the pharmaceutical industry is described in Chapters 2, 7 and 9 of this dissertation. The financial stress of sites in particular is described further later in this chapter.
that we would do it this way because of whatever.” Whereas at the CRO, you don't get any of the background noise, you know. Not often. Sometimes you do, though, when they have meetings, but it's not like being through it.

And later,

working for a CRO, you don't have the liberty of making decisions that you would [if you worked for a sponsor]...And so, therefore, you don't look like you know what's going on...And it doesn't matter if you have years of experience and you've done this before and you know what to do, you can't make any decisions because it's got to go to the sponsor... (CRO, 3/08/10)

Another senior monitor echoed these concerns when discussing what can happen where a CRA isn’t given the information or support from the sponsor that they need to do their work effectively,

Then you can get the scenario where the coordinator says, “I’m going to go directly to the sponsor” and just bypass the CRO. Then we’ve lost credibility and we’ve lost power. And then that’s it. Why be in the position of being the project manager? It’s really not good...(CRO, 19/10/10)

One sponsor based participant who had previous experience as a CRO monitor recalled the frustrations that are often part of that role,

We were privy to only certain information but not privy to some information that we actually needed. So it made things difficult. Like, you sort of felt like you weren’t – like, it was like being left out...you really felt out of the loop. And again, that’s sort of not that great because the sites pick up on that, like, so quickly [when you can’t answer questions]....And you don’t want to feel, like, you know, that you’re not efficient, or effective at your job, so. Yeah, so you kind of have to, you know, kind of fudge it until you can not let them know that. Like, there is that sort of lack of communication between CRO and sponsors.(Sponsor, 2/09/10)

Finally, another sponsor agreed that in terms of decision making authority CRO staff don’t tend to have a lot...which is the difference typically with sponsor CRAs because they’ll be more, I think more engaged in the program because they have more of a vested interest in the success of that program, and it’s their employer who’s doing the study. So, you’ll often see more empowerment at that level with those guys than you will with the CRO staff. (Sponsor, 13/08/10)

Interestingly, one participant also raised the fact that some sponsors will use their Canadian corporate subsidiaries—whether it is the national arm of a global company or a
separate company owned by the sponsor—to act as CRO instead of hiring a real third party CRO. While this individual was speaking of it primarily in negative terms in that it means the site does not get a tax credit for working with a foreign company—she acknowledged that the advantage of this over working with a third party CRO is that “when you’ve got the sponsor or a subsidiary of the sponsor acting as a CRO, you have more of a direct line directly to the Medical Monitors, et cetera” (Research Coordinator, 12/11/10).

### 6.3.2.2 Disrupted Relationship

Another interesting component of sites’ complaints regarding CROs focused more directly on the disruption of the relationship between site and sponsor, and sites feeling alienated from sponsors. One investigator stated that,

> If I could I would really dispense of CROs…They are an impossible block in communication between the sponsor and the investigator. Generally the medical person responsible for the trial belongs to…the sponsor. And it's impossible to contact them. And when you manage to contact them, they always say why didn't you contact us, me, or contact me earlier because I would have liked to discuss this issue with you. And you say, I went through the CRO. (PI2)

This concern was shared by many. One site manager for example described CRO involvement as “plac[ing] a wall between us and the sponsor. So, it just removes us I think…[and] puts some distance between us and really prevents a relationship from developing…and makes it difficult to discuss or resolve issues because we’re not dealing with each other. We’re dealing with this middle person” (Site Manager, 30/08/10). Another site participant echoed this concern, stating that “if a sponsor wants to take on a CRO, it’s really important that they still interact with the site, don’t forget that the site exists. I think that happens” (Research Worker, 26/11/10).

Sites expressed a number of areas in which they felt somewhat alienated by sponsors, and while CRO involvement may not have been identified as a primary cause in each instance, the disruption CROs bring by design to the sponsor-site relationship is a likely contributor. For example, a number of sites expressed frustration with sponsors failing to understand their realities—primarily in terms of resource and economic constraints. One community site manager discussed the ever shrinking budgets that sponsors were expecting sites to work within,

> One day I want to tell the [sponsors] this is a reality faced by a site trying to be competitive. They present us with budgets, they say “well the budget’s really tight, we can’t go any further.” Well, wait a minute, you're leaving off this, this, and this, and we desperately need them-- those things in there because without them, there’s also all the
unspoken things like the problems and the troubleshooting and the inefficient ways of doing this that we have to identify and resolve that never comes to mention when a budget is set. (Site Manager, 22/10/10)

The lack of understanding of site based challenges was reiterated by this coordinator who urged that

…emphasis be put on having the CRO understand sites. And that that information should then be passed on or relayed to the sponsors, understanding the sites. I think that’s very important...Financially, resourcefully...really all we’re looking at is for the two parties to understand that we’ve got the financial constraints. (Research Coordinator (2), 21/10/10)

Another major source of frustration that sites expressed and which they felt they weren’t generally able to raise with remote sponsors related to sponsors making decisions for financial reasons that had major implications for the site. For example, many coordinators described frustrations with electronic data capture systems. Whereas some were “phenomenal” and really facilitated the data collection process at the site level others are really quite poor. Where it’s like there’s no instructions, it’s like a blank page, you’re not even sure you’re at the right website...the sponsor sometimes they are so worried about the financial costs of building the websites they don’t really think about the interface as being an important piece. But, it is, if you want to have the right information coming...but sometimes they want to save money and they don’t. (Research Coordinator(2), 12/11/10)

Echoing this frustration, another coordinator noted, “they never ask me my opinion, if this system is good and the other is better or not good at all. But yeah, definitely I can tell them, well, this program doesn’t work, it’s very inconvenient for us to use it. We have a lot of problems” (Research Coordinator, 19/10/10).

Similarly, and as will be discussed further below, a major bone of contention for sites was their being left to cover costs arising from sponsors changing CROs. One investigator, for example, described the consequence to his site when the sponsor changed the CRO they were working with,

What was frustrating for us at the site ‘cause when the new CRO came in, everything had to be repeated. So in fact that created a cost for us as well because it was twice as much work for the staff. If you only have five patients in a study, that's not too bad. When you have 50 patients in a study, that's a huge amount of work. So that was a big burden on us. (PI1)
Concern at being expected to just swallow costs as part of doing business was echoed by many, and one participant reflected that research would be helpful to know more about the impact of this on the site. As he suggested, this would be a really interesting Masters of Business Administration topic. I think to sit and look at how many more patients does it take [to make it economical for a site] now that if you’ve had a change in CRO and do the real analysis… you probably have to do twice as much… there’s a significant time commitment… I don’t think sponsors account for that. I think they sometimes think that they need to do it [change CROs] for business reasons… but I think that if they want to take that kind of abrupt change, that they really need to sit there and think about the site as well. (Research Worker, 26/10/10)

Finally, the issue of payment itself was a major bone of contention that seemed to be greatly exacerbated by CRO presence. As bemoaned by this site based participant, CROs will sometimes be involved with payment administration…This one time I went right to the sponsor and I said, I don’t want to be paid by them any more—I just want them out of the picture altogether. But this was after lots and lots of efforts to resolve issues and the CRO was just not equipped to manage payments. They were nine to twelve months behind in administering payments. I don’t know what they were doing, or why they were doing it, but it wasn’t acceptable. Because it’s really hard on the cashflow of a site. We’ve got expenses and resources that we need to cover… and that’s important. That’s important, that’s the lifeblood of any business and sites are basically businesses. (Site Manager, 22/10/10)

Interestingly, this problem seems well recognized by sponsors. For example, two participants raised it as among the key obstacles to good sponsor-site relationships, and one that is particularly exacerbated by CROs. As one sponsor explained, Payment is a huge thing with sites. So, in a sponsor CRO relationship, the sponsor pays the CRO, and then the CRO pays the site, so that’s typically how it works. So, because there’s a middleman, there can be a delay with the sites getting their payments, and sites have enough issues trying to get paid by sponsors. That’s a huge enough issue alone. But when you throw a middleman in there, it just becomes all more complex. So, I may have paid my money to the CRO on time, but the CRO may not be distributing the money to the sites on time. Or the sponsor may not have paid the CRO in time, and therefore the CRO can’t pay the sites. So, that becomes a big, big area of concern. (Sponsor, 13/08/10)

This same participant later reiterated the importance of payment and highlighted the profound impact this can have on the sponsor-site relationship, It’s the sites that you want to protect, and it’s that relationship with the site that needs to be maintained… And they need to be paid. So, where the fault lies, you know, it doesn’t really matter. It’s just getting that payment to the site on time. So, some sponsors that
I’ve worked with have demanded that they keep that ability to pay the sites directly, so that they can be assured that that is happening.

Another participant likewise stressed the importance of timely payments for sites,

I always tell my [pharmaceutical clients] that they should find a way to do it [pay sites] themselves…Because that’s the one thing will really upset an investigator – and the CROs tend to only pay investigators after a convoluted process. And they usually wait until the sponsors pay them. And so for this project right now, I mean, 44 sites in, I don’t know, 7 or 8 different countries – we’re [the sponsor] is doing it. Even though it’s a tiny little company. But they – the CRO would have charged about $275,000 to administer the grant payments…Everything’s a profit centre! …And the other thing is, you know, I’m going to pay the sites as soon as I’ve got evidence that that visit has occurred. And we agree that we’ll pay you bi-monthly. Versus the CRO tends to say, “We’ll only pay on monitor data.” Well, why should the site wait for you to get your staff out there? That to me is just – but that’s their playbook. That’s what it says. So no, I never let them – I never – I would do anything to stop a CRO from handling the site payments. (Consultant, 25/08/10)

What emerges from these various examples is that sites are frustrated because they feel they have important input and insights that aren’t being heard by sponsors, but which could help improve both their own local experience, and also potentially the overall conduct of the trial. They are also frustrated because their needs, especially in terms of payment for example, are not being met. Again, while many of the above and related issues may well arise even in situations where sites are interacting directly with sponsors, the presence of the CRO and the distance it creates between sponsor and site appears at the very least to exacerbate the feelings of alienation and disregard that sites can feel from sponsors.

While sponsors do seem to be concerned with the disrupted relationship on some level and even take some steps (in terms of payment for example) to address the issue, it is not always the driving priority. As one sponsor noted,

…the CRAs are the ambassadors for the [sponsor] because they’re the ones that are meeting with the key customers and the future prescribers of the product. So, they do play a very critical role in working with these sites and building the relationships and answering the questions on the product, and so on. So, it’s kind of like early marketing in some ways, and it’s a pretty critical role. You lose that with a CRO, but there are decisions, there are other reasons why companies hire CROs. (Sponsor, 13/08/10)

However, there was also an intelligence gathering aspect that was identified by sponsors as an important aspect of what was lost when sponsors did not nurture a sufficiently close relationship
with sites. As this participant identified, in addition to identifying any problems that may be arising between site and CRO, a close relationship between sponsor and site also has other benefits:

And that’s where if you send your own staff out you hear things. And you hear investigators say, “You know, have you ever thought about using it in this indication?” And, “Have you ever thought about –” And, “Gee, we noticed that –” …And sometimes you also get intelligence about what other drug companies are doing… But the CRA’s never going to tell you this, because that’s not – that’s not on her form. (Consultant, 25/08/10)

Interestingly, this point was recently raised in the industry literature (Smed & Getz, 2013) and highlights a key difference that was identified by both sponsors and sites and discussed earlier-namely, that while the CRO may offer services that are helpful and even necessary for sponsors to successfully realize clinical trials given their ever increasing complexities and global scope, they are still service providers without the same ‘big picture’ interest or commitment to the product being produced. They are rated as successful or not depending in large part on how quickly and economically they can complete whatever tasks have been delegated to them by the sponsor. However, the tension for the sponsor is that “you’re leaving things, you’re leaving your baby in the hands of you know, somebody who doesn’t care about it quite as much as you do because it’s your product.”(Sponsor, 13/08/10) This is described further below.

6.3.3 ‘Ticky Box’ Police Approach

Both sites and sponsors raised the concern that CROs bring a narrow, results-oriented focus to their interactions with sites. Participants worried that CROs tend to be more like “ticky box police”, focusing more on form than on substance, and are not inclined to critically assess and resolve challenges when they arise. As one investigator observed,

So yes, CROs are, uh, ‘fun’ to work with 'cause they don't necessarily have a passion for the drug. Or the study. It's a job for them, as opposed to their baby…they don't know the drug as well, they don't know the rationale for the study as well, they just know the cookbook approach to what needs to be done. (PI 1)

Another participant working at a different site explained,

I find with the CROs…they know their job very well and they focus on THAT, whereas if I’m dealing with a sponsor, because they understand the whole scenario, that it’s more like their baby and I’m not saying the CROs don’t make it their project, but there is more
that [problem solving] approach from the sponsor if they’re our primary contacts...(Research Coordinator (2), 21/10/10)

This concern was also echoed by sponsors who described a tendency of CROs to be less driven than the sponsor to ensure sites were working as well and as effectively as they could be, and to address any challenges early. As one participant observed,

I think that the challenge is that I think the sponsors are usually more motivated to figure out what’s wrong. And the CRO just goes to the default they turn up the volume on the number of e-mails to the site or those kinds of things. So I think there’s a nuance there. (Consultant, 25/08/10)

Such a narrow, results-oriented attitude suggests CROs may be more concerned with ensuring that there are data in each of the boxes than with the process and mechanisms that generated those data. This arguably increases the likelihood that problems with study design, protocol procedure or site application will go unidentified and/or unaddressed, which also raises subject safety and data integrity concerns. Such an approach supports the perception voiced by both sites and sponsors that regardless of the level of competence and skill that a CRO brings to a study, the trial or product simply “is not in their DNA the way it is if you were actually in that [sponsor] organization.” (Consultant, 25/08/10)

6.3.4 Training And Staff Issues

CRO staff training, both in terms of overall levels of competency as well as protocol specific issues, was a major concern for sites and sponsors and even for CRO personnel. 188

6.3.4.1 General Competency Levels

One coordinator in comparing her experiences working with both sponsors and CROs noted generally that, “there is a lack of training and lack of qualification at the CRO level, [and]

188 While most of the comments around training made in the data pertain to CRO and sponsor based monitors, there were also some limited references to CRO project managers and independent monitors. By and large, the views expressed were that CRO project managers were far less well trained than sponsor project managers. Independent monitors received mix reviews, with some indicating that some of the best monitors they had worked with were independent contractors who had moved away from CRO and/or sponsor employment because they had more professional freedom and greater earning capacity. However, others indicated that such monitors were the last category they would hire based on their negative experiences.
it does come through and it does show” (Research Coordinator, 12/11/10). Another site participant stated that CROs tend to hire inexperienced staff and observed that,

it seems there are just a lot of people who are trying to get in the business of clinical research and when [CROs] all of a sudden get that proposal and get that funding, they need to recruit staff, I have a funny feeling that they just recruit whoever they can. It’s just good timing for the people who are getting hired but it’s still unfortunate for some of the sites. (Research Worker, 26/10/10)

This perception was in turn supported by a starkly candid admission by a CRO executive who commented that,

one of the things that troubles the CRO industry…is that people with no experience or very little training are sent out to operate independently. And of course they’re not equipped to do that and therefore they make mistakes and they don’t understand what they don’t know.” (CRO, 16/08/10).

Sponsors also noted this lack of experience as a challenge, with one participant observing that “monitors that work at [CROs] maybe have one-year experience versus a [sponsor] monitor with 20 years experience.” (Sponsor, 2/09/10) Another participant commented directly on training of CRO staff, and bluntly observed “[CROs] should have good employee relationships, and train the staff. I think that, you know, the training is just lacking.” (Consultant, 25/08/10). While training and experience levels of CRO staff were clearly recognized as areas that caused all parties some concern and where there was room for significant improvements, these tended to be further exacerbated by the tendency of CROs to also overextend their staff. As one participant explained,

[CROs] try to bill out their resources at 100% max all the time. So they’re going to try to bill them to your project, and your project, and your project. And if you added up all the hours it’d be more than, you know, 24 in a day sort of thing. And they, you know, a CRA almost has to be dead in the airport before they’ll do anything about it. (Consultant, 25/08/10)

In fact, some site staff were of the view that overextension, not lack of training or experience, was the main cause of the problems they experienced with CRO staff. For example, one coordinator observed that “it is a money problem more than anything…[CROs] get these guys to work to the bone so that they’re just…they don’t have time to spend to do a good job…They just get spread [too thin]” (Research Coordinator, 16/11/10). Other experienced monitors who had experience both as CRO and sponsor employees reiterated that burnout and being overextended
were serious issues for CRO staff, and that these often resulted in frustrations for site staff working with them because,

…they can hardly, you know, return messages in a good amount of time, or they're overwhelmed, and they're travelling all over the place, and they're overextended, and they're working, you know, 50, 60 hours a week. (CROs)'ll work you hard. They'll work you real hard until, well—until you burn out. And you get that a lot. (CRO, 3/08/10)

Many of the above noted challenges with CRO staff—from lack of knowledge and decision making authority, to inadequate training, to focusing on form rather than substance, and even issues associated with burnout—may be partially addressed by changes in staffing practices reported by some CRO participants. Participants across both CRO and sponsor categories described situations in which CROs would create designated staff to work with a particular sponsor. This might happen as a result of a sponsor choosing to outsource all monitoring activity and laying off their in house monitoring staff, as is described by this sponsor participant in relation to her own experience:

It was – most CROs – and we can talk about this after – but most CROs the way they hire their monitors is they will hire a monitor, let’s say, in London, or in Vancouver, whatever, and they give them protocols, and then they go all over the place. But [pharmaceutical company A] and [CRO B] came to an agreement where they had this – it was like a – it was called FSP, and it was functional service provider. Where they hired a group of us at [CRO B] to just handle [pharmaceutical company A’s] protocols. So we weren’t assigned any other sponsors, which is kind of a unique situation…That was the only way I could continue working at [pharmaceutical company A] because it was downsizing at that point in Canada. And so they had gone to this FSP model where they’re doing, like, sort of outsourcing their monitors. And they let all their monitors go and [CRO B] hired many of us….and then they realized that wasn’t such a good idea and then hired everybody back again. (Sponsor, 2/09/10)

The above suggests that where a sponsor has a close working relationship with a given CRO, that CRO may agree to absorb those staff and assign them to work for their previous employer. In such cases, the staff in question are by definition already trained and steeped in the sponsor’s operating procedures and have an intimate understanding of the preferences and requirements of that client. This obviously benefits the client, but also benefits the sites as this arrangement tends to go some distance towards bridging the distance between sponsor and site that the CRO in traditional arrangements only exacerbates.
Such a result can also occur even in the absence of sponsors laying off their own staff. As this CRO participant explained she did not have any previous affiliation with sponsor A, but was hired by the CRO and assigned to work only for that particular sponsor.

The reason why I went with a CRO is because they were assigned by the pharmaceutical company to hire people for them. I had applied to the pharmaceutical company, and they no longer hired CRAs, that’s why I had to go through a CRO. And a lot of pharmaceutical companies are doing that right now. They're hiring CROs to hire people exclusively for them...And sometimes they're doing that now, and that is what I think is going to be the future, because when—well, not all companies. But I think it works really well because then you're immersed in the [pharmaceutical] company's SOPs, and you—[the pharmaceutical company] treat you like you are one of their staff....So they've got you, they've got you for whatever study starts and finishes, and they've got you, you know, for sometimes as long as—if it's a full-time position for one study, then they've got you for the length of that study. (CRO, 3/08/10)

Such measures are obviously part of the broader trends in the industry around shifting from spot transactions to preferred partnerships. As with that overall trend, there seems to be a great deal of flux and variation in how frequently and effectively such arrangements are implemented. However, the data emerging from this study certainly points to this as one mechanism by which many of the problems associated with the “middleman” position of the CRO may be at least partially addressed.

All that being said however, it seems that even such sponsor specific staffing will not be a panacea. This is because sites reported problems with both CRO and sponsor staff, and some showed a great deal of ambivalence about which they preferred to work with. In discussing preferences of working with sites or sponsors, coordinators tended to initially express a preference for sponsor, but then many also tended to share the view that “from a site perspective, it really doesn’t matter who it is, or who does what, as long as you know what you’re doing and you appear to be competent” (Research Coordinator (2), 12/11/10). Another site participant echoed this view, noting that who she worked with didn’t matter as long as they were competent and “the CRO is well informed about the study, then everything can run smoothly…and as long as everyone knows what their roles are, that’s great” (Research Coordinator, 21/10/10). Another very experienced site coordinator observed that while she had concerns relating to CRO staff training, “you [also] see monitors that are strong and others that are weaker in both scenarios.
[i.e., both where a CRO is involved and not]. I can’t say that I generally see a trend one way or another…” (Site Manager, 22/10/10)

### 6.3.4.2 Staff Turnover

As noted above, sites are most concerned that the people they work with are competent, well trained and have solid knowledge of the protocol and processes in question so that they can help guide the site and answer questions where there are ambiguities. While sites tended to be of the view that this was more common with sponsor based staff, at the end of the day sites didn’t mind working with CROs if these criteria were met. However, what sites did find very problematic about working with CROs was a lack of consistent staff and the resulting inefficiencies and associated costs. Not surprisingly, the tendency of CROs to hire inexperienced staff and “work them to the bone”, frequently combined with a lack of investment in employee training and development, results in high staff turnover. CROs will also tend to shuffle their staff depending on workload and specific areas of expertise in order to maximize billings. Together, these two factors mean that sites will often deal with multiple monitors and even a number of different project managers over the life of a study. This issue of high turnover was a major bone of contention for site staff, especially when, as was often the case, the transition between monitors was poorly handled. As one site commented,

> The other bad thing with CROs is we do tend to see more turnover in monitoring with the CROs [than with sponsors]. And when that happens…we find that we have to take on the burden of doing the training of the new monitor, because they just kind of put them in there. And that takes up, that’s double the time…They should be doing that before they come to the site…So they should have a better system for cross training in transition between monitors, that would be much appreciated from the site perspective because it’s very onerous and it’s very stressful to have to put all that extra time in with the monitor when you’ve already done it in the beginning….Who’s going to bear the cost of that? It’s us—very much us. So it’s a problem because they don’t want to—they just say—that’s just the cost of doing business…you just have to do it. (Site Manager, 22/10/10)

Another coordinator also highlighted the cost factor of working with CROs as she discussed the challenge of working with shrinking budgets more generally,

> the budgets have just been decimated over the past eight years…well six years, and it’s been really difficult to get money that we need…[It is] hard to make sure we have enough money to pay for the amount of time it actually takes to do the study. Because when the sponsor says this should only take you two hours, I’m telling you it’s going to take four hours. And if you add a CRO in, add another hour at least. (Research Coordinator, 16/11/10)
Sponsors too were aware of this added cost that sites were expected to absorb and the frustration this created. As one sponsor participant acknowledged,

One of the biggest issues that sites seem to have is with personnel turnover…you as the site, have to train that person, and it takes a huge amount of time, and they’re not paid for it. It’s a big bone of contention with sites. Now, that happens with both sponsor and CRO staff. I’d say it happens more with CRO staff, but it’s a big pain. (Sponsor, 13/08/10)

It was less clear, however, whether sponsors and CROs were aware of other costs sites experienced as a result of monitor turnover. Monitoring staff were recognized as an important resource by site staff and a critical factor in sites being confident they were conducting studies correctly. As one site manager reflected, “you need that interface, especially when you enrol your first few patients, you want them to come...We give it our best efforts but there’s nothing like that first visit to dot your I’s here and cross your T’s there...” (Site Manager, 22/10/10) As such, it is perhaps not surprising that sites also reported an important emotional cost associated with frequent monitoring changes. For example, in addition to recognizing the economic impact sites were expected to absorb as “a cost of doing business”, this participant reflected that “the change is difficult for the site...you lose a lot of, I think, that personal connection or the trust or that relationship that you’ve built up [with the monitor] over time and have to start all over again.”(Research Coordinator, 18/11/10). The emotional toll high monitor turn over can have for site staff was reiterated by others too,

It’s not even just the cost. It’s just the emotions. It’s a lot of work. It’s a lot of stress. If you’ve finally gotten into the rhythm and you think everything is going smoothly, all of a sudden, big bam in your research study. It’s a lot of work and you feel dizzy sometimes. (Research Worker, 26/10/10)

6.3.5 Organizational Elements

Finally, sites reported lack of organization and consistency in approach as important obstacles to efficiency in their dealings with both sponsors and CROs. As described above, sites typically reported working on ever increasingly tight budgets, at times even incurring losses when participating in clinical trials. This is perhaps one of the reasons that any organizational element that tended to create more work or reduce efficiency was met with intense frustration. For example, many sites described being bombarded by requests for information, much of which
they had already provided to the same company at least once. As this participant explained, it gets

…very frustrating [when you] just get emails from God knows who and wanting some information and sometimes you would have provided that information to somebody and you don’t know where and how that information has gone...[and then] another person is asking for it again.” (Research Worker, 26/10/10)

Others echoed this concern, describing situations like the following wherein,

on average I have maybe three or four people ask me the exact same question, so it’s like the left hand doesn’t know what the right hand is doing...They know that they need a CV (curriculum vita) from us [but] what they don’t understand is that we’ve already sent it out to three of their peers. (Research Coordinator, 21/10/10)

Still others described being interrupted in their work multiple times with repeated requests, by people sending emails and calling you and sending you faxes, so a lot of chaotic communication at times. One will say one thing and then the other one will say something else...and sometimes you don't know who's who and then you might get duplication... (Research Coordinator, 18/11/10)

Sites also identified lack of quality control and consistency between different offices of a single CRO as being a big challenge. As described by one coordinator,

we were working with a [CRO] office out of California, they were great. They were just fine. But [their office] in Pittsburgh or something that we had worked with before were terrible. So there seems to be NOT a lot of quality control from one to another...you never know what you get. (Research Coordinator, 21/10/10)

In addition to concerns about variable quality, sites also described inconsistencies in terms of procedure and approach as sources of frustration. One participant suggested that the message to CROs generally should be

…standardize your procedures! Something so straightforward as the roll out of a study, shouldn’t vary based on the project team that you have working on it. They should have one standard way of doing things because then as a site…we will know how they do things... And why not choose the best way too and stick to it? But they don’t do that.” (Site Manager, 22/10/10)

While these kinds of organizational concerns are predictable when dealing with large complex organizations with multiple teams and departments spread across numerous jurisdictions, and while they were discussed in relation to both CROs and sponsors, there seemed
to be a heightened level of frustration in this regard in relation to CROs. In addition to the simple ratio of sponsors to CROs involved in a given study (i.e., one sponsor vs many possible CROs), another possible explanation for this is simply that—as illustrated throughout this chapter—sites tend to have a higher base level of frustration with CROs than with sponsors, so CROs may be more vulnerable to criticisms even where the issues are not unique to them.

6.3.6 CROs vs. AROs

Whereas many site participants raised concerns and frustrations when working with CROs, a few sites drew a distinction between commercial CROs and Academic Research Organizations. As described in Chapter 2, AROs can take a number of forms but are essentially organizations developed within the academic context to facilitate the conduct of clinical trials across multiple sites. More specifically, AROs typically both design and run their own research programs, as well as provide contract services to industry sponsors. As such, they can be involved in both investigator-initiated and industry-initiated clinical trials. When describing concerns and challenges that arose in relation to CROs, a couple of participants emphasized that they vastly preferred working with AROs over commercial CROs. As this coordinator explained,

Like Duke and the TIMI Group and the Vigour Centre in Edmonton; we would…and Cleveland Clinic. We would much prefer working with those, I guess, they are CROs—but academic ones basically…. [They] have clinical people so you can actually ask a question and get a reasonable answer. They…the right hand seems to know what the left hand is doing so they’re not divvying things up. There tends to be a staff that work on a study and you can usually find one of them and they know what’s going on. Their staff is pretty stable and they may switch projects around sometimes, but then you get somebody who also has experience and they’ve talked to each other. So it’s not…it doesn’t….they don’t have this fly by night feeling that certainly some of the larger CROs feel like…. So the academic CROs are not like that at all….And they usually have 24-hour hotlines. They are much more clinically organized….The other issue is the data. I feel much more…I mean, maybe it’s a false sense of security, but I’m much happier with our data going to Duke because I know….there’s more trust in the relationship...(Research Coordinator, 21/10/10).

189 See for example the description provided by the Canadian VIGOUR Centre (http://www.vigour.ualberta.ca/About/History.aspx), which is the Canadian Arm of a larger international organization the VIGOUR group.
In addition to expressing her preference, the above also highlights a number of the concerns and issues expressed already in this section, and suggests that in the absence of those problems a different level of trust and satisfaction in the overall relationship may develop.

6.3.7 Advantages For Sites Working With CROs

This paper has focused on the challenges reported by sites (and to a more limited extent by sponsors) when working with CROs, and it would be fair to say that most of my participants (across both site and sponsor categories) viewed CROs as “unfortunately necessary” in order to compete in the current clinical trials market. However, participants were also asked about the advantages and benefits of working with CROs. Sponsors not surprisingly tended to focus on benefits that closely mirrored the reasons for outsourcing (reduced costs, increased efficiency, expanding capacity, supplementing expertise and knowledge etc). The focus of this brief section is instead on the advantages identified by sites. While a few of these are alluded to earlier in this paper, there are others that should be mentioned even if they were for many participants overshadowed by the frustrations and challenges. For example, some site participants indicated that while the overall communication process took longer when CROs were involved (for the variety of reasons described earlier) CROs themselves were in fact often far more responsive to queries initially than were larger sponsors. Hence, while perhaps ultimately unable to provide an answer, there was a faster initial response to queries and concerns by CROs than by sponsors. Sites also suggested that in some cases, CROs were more responsive and aware of the challenges faced by sites and could serve almost as an advocate for the site in some limited circumstances. As described by one site participant,

[Working with a CRO] can be an advantage, yeah, it can be an advantage because they really understand what you are looking for, they know that you have to pay all sorts of things and they also know that, for example…if the sponsor is changing this EDC company, they know that you are going to work few more weeks on that. And once it actually happened to me that a monitor told me, “Well, ask for compensation for that. Definitely it’s out of your pay, so ask them. I’ll ask them…” (Research Coordinator, 19/10/10)

190 See for example suggestions by participants that CROs can in some instances serve as buffers to the numerous demands by sponsors, or that they can be important resources for sites when dealing with recruitment and other challenges (above, p. 139).
191 It is worth reiterating something here that has been discussed directly and indirectly throughout this paper, namely that both CROs and sponsors are hierarchical institutions and that
Other benefits sites identified in working with CROs included that they occasionally had more expertise in the running and management of clinical trials than did industry sponsors, and also tended to provide more in the way of creative practical tools that could help sites with some of the more menial but time consuming day to day trial tasks. As one participant explained, this kind of benefit is associated almost exclusively in trials sponsored by small biotech companies,

When you have a small biotech or a start-up company or a young company, it is highly preferable to have your study in the hands of a CRO. [Such] a sponsor does not know what they need, generally, and what kind of detail they need and what procedures they need to be able to follow, in order to make sure that they’re *ICH-GCP* compliant, they’re Health Canada compliant, and in cases with the U.S. sites, they’re FDA compliant, it’s much more preferable. (Research Coordinator, 12/11/10)

While site participants certainly focused more, and more passionately, on the challenges and frustrations associated with CROs, it is important not to overlook that a variety of benefits were also identified in the data. It is reasonable to expect that reflecting on how to expand and capitalize on this list of recognized advantages could increase not only site satisfaction in dealing with CROs but also stands to benefit the overall effectiveness and efficiencies of clinical trials.

### 6.4 Discussion

CRO proponents and industry insiders have suggested that far from raising or increasing ethical challenges in clinical trials, CROs in fact mitigate concerns present when the sponsor interacts directly with sites. For example, Beach (2001) who was in-house counsel for Quintiles, argued that

CROs, unlike sponsors, are not interested in the outcome of the study but like sponsors are subject to heavy regulation by the federal (U.S.) government and must follow applicable state laws, must respect international guidelines and are obliged to follow their many requests, questions and concerns raised by the site with the monitor must first go back to the CRO superior (often project manager) and then from there to the appropriate contact(s) at the sponsor. In this instance, the site participant indicated the request went from the monitor to the CRO project manager to the sponsor, but that ultimately the sponsor agreed to provide compensation. However, it is also very foreseeable that CROs will often act as a filter limiting the number of requests and questions that the sponsor needs to address—something that could be frustrating for sites.

Interestingly, this last point in relation to improved tools was also something that two CRO participants highlighted as a real strength that they bring to sites.
own operating procedures. Moreover, they are judged by the industry on the basis of the scope and quality of the services provided, including the degree of adherence to the research protocol, regulatory requirements, and timelines, the quality of the professional working relationships with investigators and institutions—both academic and community based and the validity of the data. Further, CROs are subject to comprehensive audits by sponsors, FDA and other regulatory authorities. For all these reasons CROs are being tasked with strict vigilance of all stages of the clinical trial process to ensure that laws, regs and industry standards designed for the protection of human subjects and data integrity are maintained. (Beach, 2001).

However, as the data and literature discussed above highlight, there are a number of practical elements and realities that turn each one of these points on its head and instead suggest that CROs, far from enhancing confidence in the quality and ethical soundness of clinical trials, in fact exacerbate and even introduce additional causes for concern over and above sponsor run trials.

The first point, that CROs aren’t interested in the outcome of the study suggests that they aren’t subject to the strong economic interests that might drive sponsors to act inappropriately and erode the quality and safety of the clinical trial. There are a number of responses to this point. First, while CROs may not be motivated by the ultimate goal of getting a drug successfully admitted to market, they are motivated to conduct trials quickly (to impress their sponsor clients), and below budget (in order to maximize their profits) and may well “see what they can get away with” to realize this objective. There is also data both from the literature (Azoulay, 2003; Azoulay, et al., 2010), and from this study suggesting that while some sponsors form close relationships with CROs—in which case CROs would be motivated to meet high standards to ensure future contracts, many sponsors do not use the same CRO again—which reduces the CROs motive to perform and instead look at the contract as a one-off opportunity with little opportunity for future projects.193 The data also suggests that sites and sponsors alike view the fact that CROs don’t have the same level of investment to the project not as a benefit but as a source of frustration and concern. Sponsors and sites alike complained that this leads to CROs...

tending to have a narrow, result “ticky box” oriented focus and that they often lack the inclination (and ability) to identify and solve substantive potential problems early and effectively—which could foreseeably have serious implications for the safety and quality of the trial being conducted. On a related note, the fact that important knowledge and information that the site learns and observes over the course of the clinical trial may not get transmitted from the site to the sponsor through the CRO has recently been discussed in industry literature as an area of concern for sponsors (Smed & Getz, 2013).

Beach’s statement that CROs (like sponsors) “are subject to heavy regulation by the federal (U.S.) government must follow applicable state laws, must respect international guidelines and are obliged to follow their own operating procedures” is accurate up to a certain point; however, as is explained in detail in Chapter 7, there is a recognized lack of oversight by the regulatory authorities—with authorities in both Canada and the U.S. having the very modest goal of auditing 2% of clinical trials—and both failing to meet this by about half (OAG, 2011). Moreover, and as stated earlier, there is a lack of explicit reference to CROs in the Food and Drugs Act and associated regulations, which arguably raises further accountability and responsibility questions. The fact that CROs may tend to exert more pressures on sites than sponsors directly is again relevant here in that given the lack of regulatory oversight CROs may be more inclined to “see what they can get away with” (Consultant, 17/11/10). On the flip side is the fact—also as stated by Beach, that CROs are subject to audits by the sponsor. This is true, and in fact as one of my participants indicated it is in fact industry, not the regulator, that keeps CROs (and sites) in line. That being said however, self-regulation by industry in such a high pressure high stakes industry hardly seems an effective or meaningful way of meeting what Weijer and Miller identified as the trust based obligations of the state to protect research participants.194

On a related note, it has been observed elsewhere that “fragmentation of tasks among several actors in the R&D chain blurs the oversight of the full trial process, and as such, the perception

194 An additional factor that is briefly described in Chapter 7 but that is relevant here in relation to transparency and accountability of CROs, is that CROs are shifting away from being publicly traded companies and are instead relying with greater frequency on private equity. As such, there are fewer reporting requirements and less opportunity for external scrutiny (Getz, 2011).
of responsibility might also become scattered” (Adobor, 2012; Schipper et al., 2011; Shuchman, 2007). This challenge of maintaining accountability and responsibility for each aspect of the clinical trial process would be problematic even where there was effective regulatory oversight of clinical trials. That there is both a blurring of responsibilities and accountabilities, and a lack of oversight, makes this CRO related challenge that much more concerning. This is discussed further in Chapter 7.

Finally, the recognized fact discussed in the industry literature as well as in the more limited academic literature of the tendency of CROs to hire inexperienced, poorly trained staff and to send these staff out to operate independently without sufficient oversight or training—combined with their tendency to dramatically overwork their staff to the point where CROs experience very high staff turnover—does not inspire confidence in the quality of the range of services provided by CROs, nor does it support their claim (often made in marketing materials for example) that they are committed to ensuring quality and safety of trials (Azoulay, 2003; Schipper et al., 2011; Schuchman, 2007). This is only exacerbated by other issues such as serious delays in payment, identified in the study and supported in the literature (Glass, 2009; Lamberti et al., 2011), that create added stress and uncertainty for sites.

While this study does not mean to suggest that CROs do not have an important role to play, nor that they can’t do so in a very effective and high quality manner, what is being argued is that there are a number of structural and practical concerns that need to be addressed in order to ensure subjects and the Canadian public as future consumers of the products of clinical trials are sufficiently protected and that the “trust based obligations of the state” are being met. Some practical suggestions for possible improvements as well as a detailed exploration of the Canadian oversight framework will be discussed in detail in Chapter 7.
Chapter 7: Legal And Policy Landscape For Clinical Trials In Canada

The purpose of the next two chapters is to examine and evaluate the law and policy landscape that shapes how clinical trials in Canada are conducted, and informs how those involved understand and define their roles and responsibilities. Chapter 7 focuses on the law and policy frameworks and provides a critique of their strengths and weaknesses. Chapter 8 then examines potential sources of liability that may further shape how the various parties involved in clinical trials identify, define and fulfill their obligations. Formal sources of law and policy are the starting points for the analysis and discussion; however, these two chapters are also informed by the issues and concerns raised by participants in the preceding three data chapters, with a number of cross references to the data chapters being made throughout Chapters 7 and 8. As such, the resulting analysis moves beyond a normative account of what should be happening under Canada’s laws and policies, and starts to provide a more descriptive, empirically informed evaluation of Canada’s clinical trial oversight framework.

This chapter starts by describing a number of important factors that influence the way in which research involving human subjects (including clinical trials) is governed in Canada. Against this backdrop, the law and policy components of the clinical trials oversight framework are examined and evaluated. I start this examination by providing a bird's eye view of the parties charged with regulating and overseeing clinical trials, and highlight some key areas of concern in relation to each. The next section describes prominent sources of obligation for those involved in clinical trials, including statutory and regulatory requirements, key international and national guidelines, and professional codes of conduct. The Canadian and American approaches to establishing and enforcing accountability in clinical trials are then compared, before looking more specifically at whether and how the CRO impacts this process. Finally, and building on the concerns and weaknesses discussed in this chapter, some suggestions for improvements are made.

7.1 Clinical Trials In Canada: Contextualizing Our Approach

The regulatory review and oversight of clinical trials in Canada is—to say the least-multifaceted and complex. McDonald et al. (2011) observe that our approach to the governance of health research (including clinical trials) defies the term “system”, given that it is made up of such a “complex set of standards, policies, procedures and practices.” The complex factors that
shape and inform regulation and policy in Canada in this area have been described in detail elsewhere (McDonald, 2000; McDonald & Meslin, 2003; McDonald et al., 2011; Vanderwel, 2012), but a brief summary is appropriate here. First, the relevant laws, policies and guidelines that inform governance in this area are developed, instituted and applied by a wide range of actors across multiple levels (McDonald et al., 2011). International organizations (e.g., ICH, World Medical Association (WMA)) and governments (e.g., U.S. FDA), domestic governments including both federal and provincial bodies and research sponsors are among the key actors (McDonald et al., 2011). Professional organizations (medical and nursing colleges; SoCRA; ACRP) and research institutions also actively shape how researchers and research staff ultimately carry out their research activities (McDonald et al., 2011).

In addition to the various actors, there are also a number of international and domestic contextual factors that wield profound influence. McDonald (2000) identifies “four pervasive international factors”: 1. Rapid scientific and technological innovation and advances; 2. Multiple disciplinary and interdisciplinary research modalities; 3. Commercialization and privatization with the growth of a huge private sector auxiliary service provider industry to support pharmaceutical sponsors, led by CROs; and 4. Globalization and harmonization. While on the one hand such factors facilitate research and innovation, they also work together to dramatically increase competition for what are becoming ever more scarce research dollars (McDonald, 2000; McDonald et al., 2011; Schipper et al., 2011; Vanderwel, 2012).

There are also (at least) 2 important domestic factors: (1) the now well established policy (in Canada and elsewhere) of relying on industry to help fund health research and the particularly heavy reliance on the pharmaceutical industry in this regard; and (2) the constitutional division of powers between federal and provincial governments. In relation to the first factor, it is

195 While many of the factors described in the remainder of this section are also raised in Chapter 2, I raise them again here for a couple of reasons. First, they are directly relevant to the points being made and in my view it is less disruptive to the flow of the dissertation to repeat certain elements than it is to force the reader back to earlier chapters. Second, in anticipation of future publication efforts, I have tried to make key chapters relatively complete instead of extensively referencing to other parts of this dissertation.

196 Reduced public funding for research, and the associated increased reliance on industry funding and push for public private partnerships are now well-established policies across major economies including, among others, the U.S. and the E.U. (Lemmens, 2004; Krimsky, 2003).
important to note that health research in Canada is funded by a variety of public sector organizations (e.g., CIHR, Genome Canada), the private sector and not-for-profit agencies (McDonald et al., 2011). One recent report suggests that as much as 80% of all clinical research is in fact publicly funded, but that phase I-III clinical trials of investigational drugs are funded exclusively by industry (Ogilvie, 2012). CIHR—the dominant public funder of health research—reportedly invested $966 million in research in 2010-2011, of which 13% (or $129 million) went to clinical research. In contrast, total R&D expenditures in Canada by pharmaceutical companies reporting to the Patented Medicines Price Review Board in 2010 was $1,178 million, which in fact represented a continuing decrease over previous years (Vanderwel, 2012; PMPRB, 2010). Phase I-III clinical trials together accounted for $465 million of this investment, with the majority ($317.8 million) being spent on phase III trials. However, and as noted by Vanderwel (2012), industry expenditures are actually much more than these figures would suggest, as this data does not include expenditures that do not qualify for tax credits.

Particularly relevant to the current study is the fact that charitable or other donations, grants or sponsorships directed toward R&D in Canada (which would include funding and other support provided for investigator-initiated research) are not reflected in this data. Hence, while public funding clearly represents an important source of support for health research, industry is the dominant player in this regard—particularly in the clinical research arena.

The heavy reliance on industry dollars to support scientific research, including (but not limited to) medical and clinical research, has resulted in a “paradigm shift” away from science as

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199 Vanderwel (2012) highlights that among the many items not reflected here are:

1) Phase IV clinical trials, observational studies, non-interventional studies or pharmacovigilance research studies;
2) Salaries of Canadian personnel directly engaged in eligible work outside Canada;
3) Administrative, supervisory and operational personnel;
4) Equipment utilized in R&D activities;
5) University Chair endowments; and
6) Charitable or other donations, grants or sponsorships directed toward R&D in Canada.
a social calling to it being recognized as a commodity in a knowledge based economy (Caulfield et al., 2012; Lemmens, 2004; McDonald & Preto, 2011). While a detailed exploration of this shift vastly exceeds the scope of this dissertation, it is important to acknowledge some of the tensions this creates—for example, in terms of policy development and priority setting. In relation to policy development, Caulfield et al. (2012) highlight that commercialization pressures have led governments and public funders to adopt policies that require scientists to forge close relationships with industry and maximize the commercial potential of their work. However, these same bodies also continue to direct scientists to meet international and national requirements to share and disseminate their data and findings so as to further science and promote humanitarian goals. While the authors maintain optimism that such policy objectives are not mutually exclusive and that with research and effort an optimal middle ground may be reached, they acknowledge there is a profound tension within which the scientific community must operate.

The tension between public and private sector interests also has profound and varied implications in relation to priority setting. At a global level, this has resulted in the general prioritization of the health needs of the developed world over those of the developing world (McDonald & Preto, 2011; Pratt & Loff, 2012). At a more local level, the tendency of public funders to prioritize areas that can attract industry interest has resulted in the chronic underfunding of areas like mental health and less common—and therefore less profitable—disease areas (McDonald et al., 2011; McDonald & Preto, 2011). This in turn affects decisions at the micro level, as scientists make decisions about their areas of expertise and research questions based at least in part on availability of funding (Anderson et al., 2011). Whereas it is expected and acceptable for priorities in the private sector to be established based on market considerations, public sector priorities must be established based on considerations of justice, fairness and social benefit (Anderson et al., 2011). With the growing reliance on private funds to support research, the line between public and private funding has become less defined, making it increasingly difficult to ensure public priorities are not being subsumed to private sector interests.

Canada’s heavy reliance on pharmaceutical dollars for clinical research combined with the fierce competition for increasingly scarce dollars has resulted in a number of initiatives at all
levels (federal, provincial, institutional) to attract more clinical trial business to Canada. A number of these initiatives are described in chapter 2 of this dissertation. Such pressures have also directly impacted the federal regulatory framework; for example, and as will be discussed in this chapter, they have resulted in shorter review times and (in some instances) increased exposure for Health Canada to penalties where they fail to meet those established targets.

The second domestic factor that influences the development of law and policy in relation to research involving human subjects is Canada’s constitutional division of powers (McDonald & Meslin, 2003). As will be described later in this chapter, clinical trials are subject to the Food and Drugs Act and Division 5 Regulations; however, this regulatory framework leaves much unsaid. For example, while the regulations address sponsor responsibilities none of the other actors (CROs, REBs, researchers, monitors etc) are mentioned. These and other gaps in the legislated framework are filled by guidelines and non-legislative policy instruments, including for example the ICH-GCP Guidelines and the TCPS2. As others have suggested, this largely non-legislated approach is in stark contrast to that adopted by the U.S., and is likely at least in part to avoid potential constitutional conflicts with the provinces (Lemmens, 2005; McDonald & Meslin, 2003). Briefly, the provinces have primary jurisdiction over health care and related issues, as well as education. This includes having the authority to enact regulations regarding many of the professions involved in health related research. Moreover, the province would also have jurisdiction to “impose a system of accreditation or licensing on researchers, and could mandate specific administrative bodies, such as REBs, to fulfill a role in this context” (Lemmens, 2005). As will be discussed further below, relative to its U.S. counterpart, Health Canada has been much more limited in its regulation of human subject protections and has provided much less in the way of guidance on a number of related issues, such as what constitutes sufficient training and qualification for investigators. Given how jealously provinces

200 The provinces could likely also claim jurisdiction over research governance issues under their authority over property and civil rights, as well as over matters of a local nature.
guard their jurisdictional borders (especially in relation to health care)\textsuperscript{201}, the lack of federal action in this arena is not surprising.\textsuperscript{202}

The interplay between law and policy, however, is not without its challenges and so in a system that relies heavily on policy instruments to fill in the gaps certain issues arise. In some instances, a policy document may rely on local legislation to provide important details as to how its requirements are to be met. Legislative silence in such instances can create confusion and inconsistency. Uncertainty and confusion can also arise where there is overlap or disagreement between legislative and policy instruments, or where two policy instruments disagree and the relevant legislation is silent on the question. The appropriate use of placebo provides a good illustration of this point. Health Canada has formally adopted the \textit{ICH} Guidance on placebo use \textit{(E10: Choice of Control Group and Related Issues in Clinical Trials)}, though as with the other \textit{ICH} documents adopted by Health Canada it has not been formally incorporated into the legislation and so its legal status is somewhat unclear (Lemmens, 2005). The \textit{ICH} \textit{E10} Guidance is significantly more permissive in its approach to placebo use than is the \textit{TCPS2}, which as is explained elsewhere outlines the applicable ethical requirements for research funded by one or more of the federal funding agencies\textsuperscript{203} (or taking place at an institution that receives such funding). This difference makes a good deal of sense when one accepts that the \textit{ICH Guidelines} (including \textit{Good Clinical Practice (E6) and Control Group (E10)}) are “first and foremost regulatory instruments and only indirectly moral policies”, whereas the \textit{TCPS2} is explicitly a moral policy the primary purpose of which is to establish requirements for the ethical conduct of research (Kimmelman et al., 2011). While the differences might be understandable, it does not

\textsuperscript{201} While hospitals are listed under s. 92 of the Constitution, health care itself is not specifically addressed under the division of powers; however, provincial jurisdiction over health care has been read in through case law.
\textsuperscript{202} What headway the federal government has made has been in areas that fall squarely within their jurisdiction. In commenting on the 1983 Supreme Court of Canada decision \textit{R. v. Wetmore}, Jackman (2000) notes that the court “held that the provisions of the federal \textit{Food and Drugs Act} relating to the safety of food, drugs and medical devices were supported under the criminal law power in as much as they were directed at protecting the physical health and safety of the public.” Moreover, the court in that decision also strongly suggested that comprehensive regulation of the pharmaceutical industry could also be upheld under the federal trade and commerce power.
\textsuperscript{203} As is explained elsewhere in this dissertation, these are CIHR, SSHRC and NSERC.
change the fact that they “present major navigational problems to those charged with planning, designing, reviewing, and conducting clinical research” (Kimmelman et al., 2011, p. 57).

Additional issues associated with the interplay between law and policy are discussed later in this chapter as well as in Chapter 9.

The analysis in this chapter focuses primarily on the three main actors responsible for oversight of clinical trials in Canada (namely Health Canada (the regulator), Research Ethics Boards and research sponsors) and also on four key sources of authority (Food and Drugs Act and Division 5 Regulations, the ICH-GCP Guidelines and to a lesser extent, the TCPS2 and professional codes of conduct). I recognize this is not an exhaustive discussion; however, I believe this somewhat selective focus provides sufficient detail for an accurate analysis that serves the purpose of this dissertation—that is, to evaluate the key aspects of Canada’s clinical trials governance frameworks and to do so in light of the issues and concerns raised by participants in the qualitative interview study.

7.2 Clinical Trial Oversight: Role Of The Regulator, The REB, And The Sponsor

Despite the complexities described above, for the purposes of this discussion it is still appropriate and useful to describe Canada’s approach to the governance and oversight of clinical trials as a system, but one with three main components. In the first, Health Canada as the regulator is responsible for (a) determining whether the drug may be imported for use in the proposed clinical trial; (b) overseeing the conduct of clinical trials; and ultimately for (c) reviewing the data generated by the clinical trials (among other things) to determine whether or not to approve the drug for sale in Canada. A second critical component of clinical trial regulatory review and oversight system takes place at the site level through the research ethics board (REB). The primary mandate of the REB is to ensure the rights and interests of the subjects are protected through initial and ongoing review of clinical trials. Hence, before a clinical trial may proceed at a given site, it must have passed both Health Canada and REB review and as the clinical trial progresses it is subject to oversight from both of these bodies. Finally, there is also a clear role for clinical trial sponsors. Pursuant to both Canadian regulations and international guidelines, sponsors are expected to be actively engaged in the oversight of their clinical trials—including ensuring those managing and conducting the trials on
their behalf are meeting regulatory and other requirements. The respective roles of these three parties, as well as some key areas of concern in relation to each, will be described briefly below.

7.2.1 Initial Assessment & Review

A sponsor initiates a clinical trial by submitting a Clinical Trial Application to Health Canada’s Therapeutic Products Directorate (TPD), under the Health Products and Food Branch. The TPD makes an initial assessment of the protection and safety of trial participants. This assessment is based largely on the investigator’s brochure, study protocol, consent form, list of any related trials approved by Health Canada and any rejections by Canadian or international REBs, as well as information on the quality of the drug. If there are no deficiencies with the application, the TPD has 30 days from the time of receipt to issue a No Objection Letter (NOL). Where the sponsor is not notified of deficiencies, and they have not received a NOL within 30 days, they may proceed with the trial.

Prior to commencing the trial at a given site, the sponsor must also provide a ‘clinical trial site information form’ to the TPD, and ensure that the trial has been approved by a research ethics board. Whereas Health Canada conducts a preliminary review and makes a finding as to whether or not the clinical trial may proceed, it relies heavily on research ethics boards to scrutinize the proposed clinical trial and ensure that the rights and welfare of human subjects are protected. In this role, the REB not only conducts a critical assessment and evaluation of the risks and benefits to trial participants, but also ensures that the research respects the established ethical norms based on such principles as justice and respect for persons (Miller, 2006; Glass, 2006). As described later in this chapter, Canadian REBs look to both important international documents such as the Declaration of Helsinki as well as to the Canadian Tri-Council Policy Statement 2 (TCPS2) for guidance in relation to the applicable ethical norms.

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204 While the TPD is responsible for the review and approval of new therapeutic products, this does not include biologics—which fall under the Health Product and Food Branch’s Biologics and Genetic Therapies Directorate (BGTD). This dissertation does not address the BGTD.
206 Critical documents outlining these norms are the Declaration of Helsinki and the Tri Council Policy Statement 2 (TCPS 2).
207 As will be described later in this chapter, the TCPS2 has a limited jurisdiction and does not apply to privately funded research that takes place in a private/community site. Likewise, private
7.2.2 Ongoing Review: Regulator (Health Canada)

Health Canada conducts oversight of ongoing clinical trials in two different ways. First, it monitors serious unexpected adverse drug reactions by requiring sponsors to report such events—regardless of whether they occur within or outside of Canada—on an expedited basis. Second, it conducts inspections of clinical trial sites including sponsors, CROs and investigators. Inspections are conducted by the Health Product and Foods Branch Inspectorate (the Inspectorate). The stated purpose of these inspections is to “strengthen the protection of the rights and safety of clinical trial participants and validate the integrity of the data generated through the conduct of clinical trials.” More specifically, they are intended to:

- minimize the risks associated with the use of a drug used in a clinical trial;
- verify compliance with Division 5 of the Food and Drug Regulations, including good clinical practices; and
- validate the integrity of the data generated.

Sites are selected for inspection pursuant to a risk-based inspection strategy, the key criteria of which are:

1) number of clinical trials conducted at the site,
2) number of subjects enrolled in the specified clinical trial,
3) number of serious unexpected adverse drug reactions at the clinical trial site, and
4) observations made during past inspections.

Although inspections are described as a means of ongoing oversight of clinical trials, Halloran (2012) observes that sponsors regard regulatory inspections as more likely to occur once the clinical trials are completed and the sponsor has submitted an application to have the drug approved for sale in a given country (this is called a New Drug Submission (NDS) in Canada). In this context, the backward looking objective of “validating the integrity of the data generated”

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209 Ibid.
makes more sense. As such, while these inspections do have a role in subject protection, at least in some instances this will be more in relation to future subjects (by informing the level of scrutiny a given site might receive in the future) as opposed to protecting the welfare of current trial subjects. This approach to inspections is also in line with the approach adopted by the U.S. FDA.\textsuperscript{211}

Finally, the Inspectorate also conducts compliance verifications (CVs) and investigations in response to specific complaints. While summary reports of the Inspectorate’s inspections are periodically released, these do not include any information or accounting for the CV and complaint initiated investigations.\textsuperscript{212}

\subsection*{7.2.3 Ongoing Review: REB}

Research ethics boards likewise have a role in the ongoing oversight of clinical trials. REBs are boards not affiliated with the sponsor, whose “principal mandate…is to approve the initiation of, and conduct periodic reviews of, biomedical research involving human subjects in order to ensure the protection of their rights, safety and well-being.”\textsuperscript{213} As will be described in further detail later in this chapter, the frequency of ongoing reviews should reflect the degree of risk to human subjects, and must be conducted at least annually. Such review activity does not involve site inspections, but instead is limited to documents and information provided by the investigator—including information relating to the progress of the trial and a summary of the safety information. Moreover, investigators are responsible for promptly reporting to the REB (among others) any changes significantly affecting the conduct of the trial, and/or increasing the risk to subjects.

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\begin{itemize}
\item \textsuperscript{211} Halloran (2012) explains the process as it tends to unfold in the U.S., noting that proactive preparation would only be undertaken for those sites most likely to be selected (based on similar criteria to that applied by Health Canada). As she describes the process, “several sites would be targeted for each application, with the expectation that if significant violations were identified at some sites, FDA could perform sensitivity analysis excluding those sites before moving forward with the application review. The data at other sites was assumed to be reliable, and if data at those key sites held up under sensitivity analysis, the application could be approved.”
\item \textsuperscript{213} Division 5 of the \textit{Food and Drugs Regulations}, s. C.05.001.
\end{itemize}
7.2.4 Shortcomings With Regulatory And REB Oversight

A. Regulator

The above suggests a fairly active role for each of the regulator and the REB in terms of both initial reviews and subsequent oversight; however, there are a number of factors that seriously limit their respective effectiveness in these regards. In the case of the regulator, for example, the first problem is that the 30-day timeline at least arguably does not provide sufficient time to conduct any kind of detailed scrutiny of the materials or meaningful risk assessment. By way of brief context, the 30-day timeline was instituted in 2001 as part of a major overhaul of the clinical trial regulatory framework undertaken in response to pressures from industry for Canada to become a more competitive location for clinical trials.\(^{214}\) Prior to this change, the default review process had been 60 days.\(^{215}\) While more time does not of course necessarily equal superior review, reducing this time period by half does suggest that this initial process may be more of a way to register what trials are occurring in Canada, than a detailed risk benefit analysis. Moreover, given the fact that REBs are charged with conducting risk- benefit analyses prior to the commencement of the trial at any given site, it is reasonable to expect that Health Canada would perhaps not feel as compelled to conduct its own thorough review.

Second, there are also a number of problems with the regulator’s inspection process. Health Canada’s goal is to inspect 2\% of clinical trial sites (in addition to inspections done in response to specific complaints). While underwhelming, this is in line with other major regulators including the U.S. FDA.\(^{216}\) The Inspectorate Program has been in place since 2002\(^{217}\); however, Health Canada has yet to meet this goal, and in 2011 inspected only 1.3\% of clinical

\(^{214}\) See for example the comment by Health Canada that the Regulations were revised in order “to recognize…internationally competitive submission review timelines.” \url{http://www.hc-sc.gc.ca/dhp-mps/prodpharma/appliq-demande/guide-lid/clini/cta_background-eng.php}. See also Lexchin, J. (2011) and Caulfield (2002).


\(^{216}\) Levinson, DR (2010). Challenges to FDA’s Ability to Monitor and Inspect Foreign Clinical Trials. Available at \url{http://oig.hhs.gov/oei/reports/oei-01-08-00510.pdf} Accessed April 14th, 2013.

trial sites-thereby leaving 98.7% of sites uninspected (OAG, 2011). Given the recent budget cuts that will ultimately result in the elimination of at least 840 positions at Health Canada218, it is reasonable to expect that this shortfall will persist into the foreseeable future. Third, while Health Canada does have a risk-based strategy in place to select sites for inspection, the Auditor General in its 2011 report found that “Health Canada does not regularly collect all of the information necessary to assess these factors and to make comparative risk-based decisions.”219 This lack of information is based in large part on the fact that trial sponsors are not required to provide up to date information on clinical trial sites, hence Health Canada inspectors must proactively contact the sites to obtain the data.220 As noted by the Auditor General’s report, officials with the Inspectorate program reported that “acquiring this information through direct contact with each clinical trial site is inefficient and that a significant amount of time is devoted to identifying potential inspection sites. Thus, inspectors have up-to-date information only for sites that they call and are unable to compare the risks posed by all sites.”221 Fourth, even those few inspections that are conducted are quite limited in scope. While inspectors do attend the site in person typically over a 5 day period222 and review “documents, facilities, records, and any other resources that are deemed by the authority to be related to the clinical trial”223 they do not tend to inspect how trial related tasks-including, for example, the consent process, are actually being conducted. Finally, even in cases where audits are conducted in active trials, such audits are not repeated during the life of the trial, but are instead limited to a very narrow point in time. Clinical trials are becoming longer and more complex, increasingly evolving and unfolding over multiple years (Roy, 2012). Subjects are frequently recruited over extensive time periods (in fact, failure of a site to recruit sufficient or any subjects is a major concern for sponsors), and

practices and key documents will often evolve and change many times in response to new information that emerges as the trial unfolds. Hence, what such regulatory audits capture is at best only a snapshot of how the trial is unfolding at the site at a given time, and do not address anything beyond that brief window. Recognition of such deficiencies in regulatory oversight prompted Flood & Dyke (2012) to describe Health Canada’s approach as “hands off”, and to comment that instead of direct regulation and oversight, there is a strong reliance by the regulator on others to ensure that clinical trials meet applicable regulatory requirements and standards.

B. REB

There are also a number of factors undermining the REB’s ability to effectively fulfill its mandate. In addition to the limited scope of the review described above, there are also a number of systemic challenges. While these are well discussed and described in the literature\(^\text{224}\), it is helpful to briefly review the key issues here. Research ethics boards, as creations of hospitals, universities or even private companies, are dependent on their home institutions to structure and support them in a way that will enable them to fulfill their mandate of human subject protection even and especially where this conflicts with other institutional interests. However, and despite the importance of such support many REBs function without sufficient independence, infrastructure and resources (Glass, 2006; McDonald, 2000). For example, while TCPS2 article 6.2 calls for the appointment of REBs by the highest level of the institution so as to promote the board’s independence, in fact in practice REBs are generally appointed by the Vice President for Research (VP Research) and report there (McDonald, 2000). This is problematic, given that the role of the office of the VP Research is to bring in and promote research in the university. It is foreseeable that the REB, which is charged with protecting subjects’ interests by ensuring protocols comply with ethical standards, could find itself in conflict with the VP Research’s mandate. The Ontario Cancer Research Ethics Board (OCREB) has addressed this concern by establishing an independent Governance Committee of outsiders who provide advice to the

\(^{224}\) See for example, Glass, 2006; Glass & Lemmens, 2002; Hirtle, Lemmens & Sprumont, 2000; Marshall, 2000; McDonald, 2001; Waring & Lemmens, 2004; McDonald 2000 among others.
Ontario Institute for Cancer Research (OICR) (OCREB's home) and advise the board of the OICR on the appointment of the chair and vice chair of the REB.\textsuperscript{225}

This lack of resources and independence is exacerbated by other factors such as the current lack in the Canadian context of accreditation or certification processes, no standard mechanisms by which to enforce guidelines or policies, and a lack of education and training opportunities for REB members (among others) (Anderson et al., 2011; Flood & Dyke, 2012; Glass, 2006; McDonald 2000; McDonald et al., 2011). Given the very high stakes involved, both individuals and institutions can be extremely keen to have research move forward with as few delays as possible. It is certainly foreseeable that REBs may well find themselves under extreme pressure not to hold up research that represents significant funding, for example. Such a scenario highlights why it is crucially important that REBs have the independence and security to be able to stand up to such pressures and withhold approval or send protocols back for amendments—regardless of the consequences such actions may have for the institution. It is troubling that the primary (and often only) mechanism by which human subjects’ interests are protected often function without such support or sufficient resources in place.

### 7.2.5 Role Of The Sponsor

Hence, while Health Canada and REBs each have a role to play in the initial and ongoing oversight of clinical trials there are a number of factors that tend to erode their effectiveness. Sponsors are relied upon to do most of the work in relation to ongoing oversight. For example, pursuant to the \textit{Division 5 Regulations} under the \textit{Food and Drugs Act}, sponsors are responsible for ensuring that the clinical trials are conducted according to \textit{Good Clinical Practices}, for tracking and reporting adverse drug reactions and for ensuring that those who are conducting trials on their behalf are appropriately qualified through training, education and experience. Sponsors are often, but not always, pharmaceutical companies. In the context of investigator-initiated studies, for example, the sponsor will be the investigator or his/her institution. However, for clinical trials involving new drugs the sponsor is invariably the pharmaceutical company developing the product. Pharmaceutical sponsors have a strong interest in ensuring that their data is acceptable to the regulators who will ultimately use such data as the basis for

\textsuperscript{225} Additionally, the Governance Committee has the right to open public reporting of its views, including potential disagreements with OICR. (Comment provided by Dr. Michael McDonald).
approving or rejecting the sponsors’ products for sale in a given jurisdiction. Moreover, clinical trials conducted in one country may be used to support a sponsor’s application to market the drug in multiple jurisdictions. This means that data found to be compromised can have profound financial implications if it negatively impacts the drug approval process in one or more countries. As such, industry sponsors conduct significant oversight activities of clinical trials—both in terms of regular site monitoring, but also through audits. Such activities may be conducted directly with their own staff, indirectly through the contracted services of CROs, or both. For example, a 2010 Tufts centre report indicated that “aggregated globally, the typical investigative site (in industry-initiated trials) had 5.5 study monitor visits each month, with half handled by CROs, and received three site audits from sponsors or CROs in 2008. Sites also report having been inspected by a regulatory agency once on average during the past five years” (Getz & Zuckermann, 2010). This illustrates the point made earlier that most of the oversight activity in clinical trials is conducted by sponsors and, more particularly, by industry sponsors.

7.2.6 Sponsor Oversight: Areas Of Concern

While such heavy reliance on sponsors for trial oversight may well be better than nothing (essentially the alternative where one relies on the regulator), it raises at least a couple of challenges. First, relying on commercial sponsors to monitor themselves lacks transparency and objectivity and, particularly in such a high stakes industry, is fraught with conflicts of interest and potential for abuse unless seriously augmented by independent arm’s length expert oversight. The concern is that industry sponsors will adopt inappropriate practices in the

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226 However, and as will be discussed further in the next section, sponsors also have a very strong interest in presenting their data in the best possible light and in fact research suggests that sponsors do engage in inappropriate twisting of data in order to achieve this (Lundh et al., 2012).

227 157 respondents (6% response rate), one-third (32%) of survey respondents were operating in ascending regions (e.g., Central and Eastern Europe, Latin America, India, and China), 16% in Western Europe, and 52% in North America (Getz & Zuckerman, 2010).

228 As a 2002 report by the IOM observed, “Sponsors are also responsible for selecting monitors to oversee the progress of an investigation and report to the sponsor their findings regarding investigator compliance with the protocol, reporting of adverse events, and the proper consent of subjects….monitoring reports that are currently performed for the sponsor are not routinely shared with the IRB. Yet, monitoring visits performed on behalf of the sponsor are usually the only real-time oversight activities that are conducted at the site, and they would be extremely useful for ethics review purposes.” (IOM, 2002)
design, conduct and/or reporting of their studies in order to further their own economic interests. Such concerns are far from theoretical. As noted by the authors of a recent Cochrane review, their findings were just the latest in an extensive empirical literature suggesting that, pharmaceutical industry sponsored studies tend to favor the sponsors’ drugs much more than studies with any other sources of sponsorship. This suggests that industry sponsored studies are biased in favor of the sponsor’s products. (Lundh et al., 2012).

Hence, while it may be possible to imagine an effective and trustworthy system where sponsors play a critical oversight role, such a system would have to involve strong checks and balances (entirely absent in the current system) to ensure the quality and integrity of the research was appropriately protected.

Second, recent developments in the United States indicate a general shift away from on site monitoring and data checking to a largely centralized (remote) risk based approach. While such an approach has been sought by CROs and sponsors alike for a number of years (Rosenfelder, 2013) the FDA only recently released its finalized guidance on this area in August 2013.229 The guidance document states that the “FDA believes that risk-based monitoring (including increased use of centralized or remote monitoring) could improve sponsor oversight of clinical investigations.” It goes on to explain that there is a “growing consensus that risk-based approaches to monitoring, focused on risks to the most critical data elements and processes necessary to achieve study objectives, are more likely than routine visits to all clinical sites and 100% data verification to ensure subject protection and overall study quality.”230 Overall, this shift has been described as welcome news for industry, although some observe that the transition may take some time as risk adverse CROs and sponsors try to get a sense of how potential problems and findings will be addressed and resolved (Henderson, 2012; 2013; Rosenfelder, 2013). While the guidance includes suggestions on factors to consider in assessing risk and selecting data for audit and inspection, it remains to be seen how these guidelines will be interpreted by industry and what the implications will be for safety and integrity of clinical trials. Given the dominant influence of the U.S. FDA in establishing standards, it seems reasonable

230 Ibid.
other countries including Canada will follow suit and that centralized, risk based monitoring will become the international standard.

A third important aspect of the heavy reliance on sponsors is that industry oversight only covers industry sponsored trials; that is, investigator-initiated trials do not have the (albeit uncertain) benefit of such oversight. In contrast to their industry counterparts, it has been noted that sponsor-investigators commonly are unfamiliar with their sponsor responsibilities (Arbit & Paller, 2006; Sedgeworth & Derewlany, 2006), and as reported in Chapter 4, this also emerged as a major concern reported by my participants. This gap in knowledge is troubling in and of itself, but is arguably exacerbated by the proportional approach to oversight adopted by both Health Canada and REBs. For both the regulator and REBs, resources for the oversight of clinical trials are extremely limited and vastly insufficient (Glass, 2006; McDonald, 2000; OAG, 2011), and as such oversight is an endeavor based on the relative risk of the studies being reviewed. For example, and as described above, Health Canada adopts a risk-based approach to its selection of clinical trial sites for inspection. Likewise, REBs adopt a proportionate approach to research review with closer inspection being done where there is a greater degree of perceived risk to participants. While it can be difficult to ascertain the criteria and/or processes by which such risk assessments are made, some generalizations are possible. For instance, Health Canada has indicated that they tend to focus on trials involving innovative new breakthrough drugs which are invariably industry-initiated (Ogilvie, 2012). This intuitively makes sense. Such drugs present great unknowns and so require a high degree of scrutiny because the risks associated with them are potentially significant. It is reasonable to expect that REBs would also tend to prioritize these as high risk studies requiring a relatively greater degree of scrutiny than other kinds of clinical trial protocols. Prioritizing such studies is of course not in itself problematic, as long as other studies are getting an appropriate review. However, if in addition to having little or no sponsor oversight, investigator-initiated studies are also routinely subjected to less rigorous regulatory and REB review than their industry sponsored counterparts, then there

\[231\] Some criteria are listed (e.g., HC site selection process), but such lists tend to not be exhaustive and how the individual items are to be weighed is also somewhat unclear. In other words, implementing the risk based approach may be described as somewhat more of an art than a science, and the exact process and criteria may vary in any given instance.
is a very worrying gap. That this may in fact be the case was suggested both by site based
participants in the current study (see Chapter 4), and by a reminder issued by the U.S. FDA in
November 2012 to ethics committees to ensure that they carefully scrutinize investigator-
initiated research—exactly because it does not have the benefit of industry oversight.232

It is also relevant here to say something about the weaknesses of the proportional
approach to oversight and protocol review generally. As seen above, the regulator determines the
level of scrutiny it will bring to a given site based on what they perceive to be the relative degree
of risk. With the advent of risk based monitoring, it seems sponsors will be formally engaged in
similar activities—albeit with a different mandate and motivation233. Similarly, REBs weigh the
foreseeable risks, potential benefits and ethical implications in deciding whether a protocol is
acceptable. This sounds deceptively straightforward and simple. However, a key problem with
this approach is that it assumes that these parties actually have a good handle on proportional
risk. That is, it assumes they can adequately differentiate areas of higher from lower risk. But
without a sufficient level of base line monitoring of a representative range of studies that
knowledge will be deficient. Simply put, without gathering relevant data they will not know
whether what are essentially their respective best guesses, are correct (McDonald et al., 2008).

There is then a real risk of a strong confirmation bias in assessing what is high and low
risk. In other words, the regulator and REB come to habitually classify certain kinds of sites or
studies or protocols as higher or lower risk without any feedback from key sources (in particular
research subjects) as to whether they have got it right or whether they are in fact weighing some
risks too heavily, and overlooking others (for example). In fact, in relation to protocol review, a
recent study exploring the experience of human subjects in health research suggests that it is not
at all clear that REBs actually have the information to know what is experienced by subjects as
higher or lower risk (McDonald et al., 2008). Since there is no real attempt to find out what
subjects experience it is hard to see how much confidence can be placed in REBs proportionate
risk assessment. This dilemma is one part of a broader concern that our current approach to

233 Whereas regulators and REBs are charged with protecting Canadians and human subjects
respectively, sponsors will be conducting their risk assessments from a very different, profit
oriented vantage point.
research ethics lacks an empirical foundation, a concern that has prompted many to conduct “research on research ethics” to build such baselines and support the development of a more informed “evidence based” approach to research ethics (Anderson et al., 2011; Cox et al., 2009; McDonald et al., 2008; McDonald & Cox, 2009; McDonald, Cox & Townsend, 2013; Owen et al., 2009).

While the challenges with proportionate review described above are important, the key point here is that oversight of clinical trials falls largely to sponsors. In most cases, these are industry sponsors who conduct their oversight activities without any kind of meaningful checks to ensure their profound economic interests are not influencing their activities and decisions. In the case of non-industry-initiated trials where the investigator wears both investigator and sponsor hats, there is reason to believe that the oversight provided is minimal given that investigators are not necessarily familiar with their sponsor responsibilities and also often lack sufficient resources and infrastructure to be effective in this regard. In either case, and as will be discussed later in this chapter, there are clear and profound problems with the heavy reliance on sponsors in clinical trial oversight.

7.2.7 The Final Assessment: New Drug Submissions

Finally, and as noted at the outset—Health Canada is also responsible for ultimately reviewing and approving the data generated by the clinical trials and submitted by the sponsor as a New Drug Submission (NDS) to determine whether or not the drug meets a basic level of safety and efficacy\(^ {234}\). While the focus of this chapter is more specifically on the processes and events leading up to this ultimate approval process, a few brief comments in relation to the NDS submission and review process are contextually appropriate.

Canada, like many other jurisdictions, has implemented a cost recovery system whereby the regulator relies on industry to fund a portion of its drug review activity. Currently, Canada recovers just under half of its costs from industry ($33 million of a total of $80 million spent in

\(^ {234}\) There is a critical, yet perhaps underappreciated, difference between efficacy and effectiveness. The former refers to the benefit of the drug under ideal, highly controlled circumstances of the clinical trial (often reflected as against placebo). In contrast, effectiveness reflects the drug’s net benefit in actual practice—that is as compared to standard practice in the context of everyday clinical practice. (Flood & Dyke, 2012).
In exchange for these fees, Canada has established service goals for its review times. The goal for review of a standard NDS is 300 days. In both 2009 and 2010, Health Canada only managed to achieve this goal 70% of the time. Inherent inefficiencies in the process itself may well be at least partially to blame. For example, in his testimony to the Senate Standing Committee on Social Affairs, Science and Technology, the Assistant Deputy Minister of Health Products and Food Branch (Paul Glover) explained in part why the process takes so much time,

> There literally are 18-wheelers that back up and off-load boxes and boxes of data. It is remarkable. We build hallways a little wider than normal so that carts can move those palettes of boxes to some poor reviewer who off-loads them and starts plowing through them, page after page. That is a typical new drug submission...We open up all those boxes and log them into the system. You get a sense of the amount of time...

Mr. Glover also commented that it typically takes up to 45 days just to do the initial scan of the documents to ensure that “the data is accurate and the studies are reputable” before sending the application to reviewers. In response to a committee query as to whether the process would become digital, Mr. Glover responded

> We are moving very aggressively into digital electronic submission. We have, through the Regulatory Cooperation Council, just reached a deal with the USFDA that had us submit a process for electronic submissions, and we will be using that system. We will be shared between the two jurisdictions. However, we still have a number of companies who prefer to submit in paper to us. We will eventually be turning that off over time, but we are not there yet, believe it or not.

This response suggests that while some progress is being made, Canada has not yet fully embraced a digital system—which could result in significant time-savings and improved use of resources. What is particularly interesting is that it seems this is at least in part because of a push

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236 Canada’s fee structure was most recently revised in March 2011, with the hope that the increased revenue would help improve review times. 2011 Fall Report Of the Auditor General of Canada. Chapter 4—Regulating Pharmaceutical Drugs—Health Canada. Exhibit 4.2 Available at: [http://www.oag-bvg.gc.ca/internet/english/parl_oag_201111_04_e_35936.html](http://www.oag-bvg.gc.ca/internet/english/parl_oag_201111_04_e_35936.html)

back from industry. While this seems counterintuitive given the interest industry has in having its drug approved as quickly as possible, there are certain advantages (of sorts) for industry when Health Canada fails to meet its target. Pursuant to the User Fees Act, which came into effect in 2004, where Health Canada does not meet the established standards by a percentage greater than ten per cent in a given fiscal year, the corresponding fee will be reduced proportionately by up to 50% of the fee level for the next fiscal year. This means that if approvals are 30% overtime, the fee for review will drop by 30% in the next fiscal year. An additional factor is that as the deadline for meeting the service standard looms, there is some evidence suggesting that (at least in the U.S.) the regulator will tend to do “a less thorough job of reviewing drugs in order to avoid crossing the deadline and potentially jeopardizing its revenue from drug companies” (Lexchin, 2011), thereby resulting in faster reviews. As demonstrated by Carpenter et al. (2008), the consequence of such diminished scrutiny in the review process is that there is “a substantially higher rate” of drug withdrawals and/or safety labeling changes compared to drugs approved after the deadline. The above suggests a troubling conflict of interest on the part of the regulator, whose primary obligation to protect the health and safety of its population seems at least in some cases, to be vulnerable to the economic interests of industry.

To this point, this chapter has examined the parties involved in the regulation of clinical trials, and reviewed key challenges associated with such oversight. The next sections will review the legal and policy documents that establish the regulatory framework in Canada.

239 The U.S. FDA also has a system whereby the regulator is penalized if they fail to complete 90% of new drug applications within their service targets. Failure by the FDA to meet this statutory requirement could result in an inability to renew the legislation that allows it to collect user fees from industry (Carpenter et al., 2008; Lexchin, 2011). It is certainly reasonable to expect that the Canadian regulator would respond to such economic pressures in a similar fashion.
240 It is also interesting to note that in the stakeholder consultation process leading up to the 2007 revisions of the cost recovery framework, Health Canada had initially intended to have the penalty take effect when they exceeded 121% of their service target. However, in response to pressures from stakeholders they reduced this to 110%. http://www.hc-sc.gc.ca/dhp- mps/finance/costs-couts/off_notice-eng.php
### 7.3 What Are The Applicable Rules And To Whom Do They Apply?

The *Food and Drugs Act* (“the Act”), and its *Division 5 Regulations* (“the Regulations”) together provide the basic statutory framework for the testing and approval of new drugs\(^{241}\) in Canada. In addition, Health Canada has adopted many of the international guidelines developed by the *International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use* (“ICH guidelines”) as guidance documents, which provide additional detail and assistance on how to comply with the *Regulations*.\(^{242}\) As the focus of this dissertation is on the conduct of clinical trials, the most relevant ICH guidelines are the efficacy guidelines that provide additional information on a variety of topics related to the design, conduct, safety and reporting of clinical trials.\(^{243}\) Key among these are the *Good Clinical Practice (GCP)*\(^{244}\) guidelines, which constitute an international standard for the ethical and scientific conduct of clinical trials, providing principles and practices related to the protection of clinical trial subjects rooted in the Declaration of Helsinki, as well as standards to ensure the integrity and reliability of clinical trial data. A third governing document is the *Tri-Council Policy Statement 2 (TCPS2)*, which establishes principles and standards for the protection of human subjects involved in research funded by, or taking place at an institution that receives funding from, one of the three federal research funding bodies or that voluntarily agrees to abide by *TCPS2* (e.g., Department of National Defense, Canadian Blood Services, Health Canada, the National Research Council).\(^{245}\) Professional codes of conduct are another important source of responsibility and obligation that inform the context within which clinical trials take place.

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\(^{241}\) A discussion of the generic drug testing and approval process would involve the *Patent Act* and the *Patented Medicines (Notice of Compliance) Regulations*, which together “control entry of generic drugs into the market…” (Lemmens & Bouchard, 2007, p.319). Given the focus of this dissertation, I will not be discussing the process as it relates to generics.

\(^{242}\) While not formally involved, Canada does have observer status in the ICH process.


\(^{244}\) These are the *Guidelines for Good Clinical Practice established by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use* (ICH-GCP), E6(R1), June 10, 1996.

\(^{245}\) These are CIHR, NSERC and SSHRC (define and describe in brief). In addition to the general principles and standards established by the *TCPS2* document, there is also a specific chapter on clinical trials (Chapter 11).
While not an exhaustive list, taken together these legislative documents and guidelines constitute the mainframe of the legal framework governing clinical trials in Canada. Each of these will now be considered in turn.

### 7.3.1 Food And Drugs Act And Division 5 Regulations

The Act and the Regulations together control the introduction of new drugs onto the market, setting out the “precise conditions under which a manufacturer may distribute a new medication to ‘qualified investigators’ for clinical testing” (Law Reform Commission of Canada (LRCC), 1989, p.12). While the Act itself does not address the issue of importation or distribution of drugs for use in clinical trials, it does authorize the Governor in Council to make regulations in this regard. While the Regulations mention the REB and briefly allude to its role (initial and ongoing review), their sole focus is otherwise on the role and responsibilities of the sponsor. As mentioned above, pursuant to the Regulations, a sponsor commences a clinical trial by submitting a Clinical Trial Application (CTA) to Health Canada. Applications are required for all phase I-III clinical trials, including comparative bioavailability trials.

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246 For example, federal and provincial privacy legislation also is relevant for the governance of clinical trials (and other research involving human subjects).

247 Sponsor is defined in the Regulations as “an individual, corporate body, institution or organization that conducts a clinical trial.”

248 Where the drug in question is a regular pharmaceutical, the application goes to Health Canada's Therapeutic Products Directorate (TPD), which is the Canadian federal authority that regulates pharmaceutical drugs and medical devices for human use. Where the product or drug in question is a radiopharmaceutical intended for human use or a biological drug (derived from living sources), then the application goes to Health Canada's Biologics and Genetic Therapies Directorate (BGTD). The processes involved in each of these two categories of product are described in Division 3 and 4 of the Regulations respectively and are relatively similar but not identical to drugs. Given that the purpose here is to provide a general overview of the regulatory framework, instead of an analysis of the requirements of any particular subgroup of products, I will be focusing solely on the process involving new drugs, and will not be addressing the particulars of biologics/radiopharmaceuticals.

249 Comparative bioavailability or bioequivalence trials are those studies that involve testing a product that is expected to have the same therapeutic effects and safety profile as the reference product when administered to patients under the conditions specified in the labelling. See Health Canada Guidance on Conduct and Analysis of Comparative Bioavailability Studies (2012) http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/prodpharma/appli-demande/guide-lb/bio/gd CBS_EBC_LD-ENG.pdf See http://www.gov.ns.ca/health/Pharmacare/info_pro/physicians_bulletins/BA_Bioavailability_Bio...
Moreover, applications are required for trials of marketed products if the proposed application of the product falls outside the parameters for which the drug has been approved.\textsuperscript{250} Phase IV trials (namely, trials of previously approved products for applications within the approved parameters) do not require filing of an application with Health Canada, but must still be conducted pursuant to Good Clinical Practice principles (which include, for example, getting REB approval).\textsuperscript{251} While beyond the scope of this dissertation, it is important to highlight that many phase IV trials constitute so-called “seeding trials”, that is, trials that are primarily designed to familiarize physicians with the product and increase their prescription thereof. While such trials may meet the requirements under \textit{GCP Guidelines}, they raise a number of important ethical concerns. London et al (2012), explain that because the only prospective review these trials typically receive is done by research ethics boards, critics have tended to describe their concerns in the language of risk-benefit ratio and informed consent. In these terms, the key issues are that (1) exposing participants to any kind of risk for what amounts to marketing purposes is unethical, and (2) that by not clearly stating the objective of the study, participants are being deceived and are not providing informed consent (London et al, 2012)\textsuperscript{252}. It could also be argued that such trials gain added, and undeserved legitimacy, through the imprimatur gained by REB approval.

The information required in the CTA is detailed in the \textit{Regulations} at section C.05.005. As noted by Klein and Tomalin (2005), “unlike Investigational New Drug Applications (INDs) in the United States, CTAs in Canada include only summary information; except for CTAs involving biologics, where complete chemistry and manufacturing data are required” (p. e246).

\textsuperscript{250} That is, if the use or application falls outside those approved by the issued Notice of Compliance (NOC) or Drug Identification Number (DIN). It should be noted that a CTA is also required where the product being tested has been approved under a Notice of Compliance with Conditions (NOC/c)—even where the trial being conducted is within the approved parameters of the NOC/c. (Health Canada Guidance for Clinical Trial Sponsors: Clinical Trial Applications (2009) \texttt{http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/ctdcta-ctdde:geng.pdf})

\textsuperscript{251} Ibid.

\textsuperscript{252} These authors problematize this characterization of the concerns, highlighting that they are neither convincing (in terms of the risk consideration) nor reflective of the full spectrum of issues associated the practice of using clinical trials as marketing tools.
Upon receipt of the application, Health Canada has 30 days within which to issue either a ‘No Objection Letter’ (NOL) allowing the sponsor to proceed with the trial, or a ‘Not Satisfactory Letter’, by which the sponsor is advised of the problems with its application.\textsuperscript{253} Under the Regulations, if the sponsor has not had any reply from Health Canada by the end of the 30 day review period, and it has provided all necessary information, then it may proceed with the trial.\textsuperscript{254} Prior to the commencement of the trial, the sponsor must also submit to Health Canada the name and contact information for the qualified investigator who will be responsible for the research at each clinical trial site, as well as the name and contact information of the research ethics board that approved the protocol at each site.

In addition to outlining the requirements for CTA content, authorization and amendment notification processes, the Regulations also specifically enumerate a number of sponsor obligations in the clinical trial process, including a clear statement that “every sponsor shall ensure that a clinical trial is conducted in accordance with good clinical practices”, and then proceeds to identify a non-exhaustive list of responsibilities in this regard. The Regulations stipulate that in order to meet good clinical practice, the sponsor must ensure that the clinical trial is conducted in accordance with the regulations and pursuant to a clearly described, scientifically sound protocol and that there are systems and procedures in place to ensure the quality of every aspect of the clinical trial. The sponsor must also ensure that REB approval is obtained at every site prior to commencement of the trial at that site, that there is only one qualified investigator (QI) at every site, and that all medical care and medical decisions at that site are under the supervision of that QI. The requirement to obtain written informed consent from participants prior to their involvement in the trial is also explicitly stated. Under the regulations, it is also the sponsor’s responsibility to ensure that any person involved in the conduct of the trial is qualified by education, training and experience to perform his or her respective tasks. There are also, \textit{inter alia}, provisions outlining labeling requirements, record

\textsuperscript{253} Food and Drugs Act, Division 5 Regulations, s.C.05.006(1)(b).

\textsuperscript{254} Klein & Tomalin (2005) suggest that while this is technically permitted, it is recommended that sponsors wait for the NOL before moving ahead with the trial. It should also be noted that for most phase I studies in healthy adult volunteers and in comparative bioequivalence studies, the 30 day target review period is reduced to 7 days from the date of receipt of the CTA (HC Canada Guidance, 2009 CTA)
retention requirements, sponsor’s reporting requirements for serious adverse drug reactions and requirements upon discontinuance of a trial. In addition, s. C.05.016 of the Regulations outlines the grounds upon which Health Canada “shall suspend [or cancel] the authorization to sell or import a drug for the purposes of a clinical trial.” Finally, the Act also stipulates terms of punishment for contraventions of the Act or Regulations, which include both fines and prison terms.  

7.3.2 ICH-GCP Guidelines

While they provide a starting point, the Act and relevant Regulations leave much unsaid. For example, although they detail some of the sponsor’s obligations, they do not address the common practice of outsourcing these responsibilities to others (specifically, contract research organizations (CROs)), nor do they discuss what is expected of any of the other parties involved in the clinical trial process. For these elements, one must turn to the GCP Guidelines. These Guidelines are not part of the regulations; instead, they have been adopted by Health Canada as a guidance document. As explained by the regulator, “guidance documents are administrative instruments not having force of law and, as such, allow for flexibility in approach.” Their lack of clear legal status at least arguably gives rise to questions pertaining to their enforceability and effectiveness at establishing responsibility. There are no clear consequences for breaching the requirements, nor are there clear means of implementation or enforcement. Despite these shortcomings, the GCP Guidelines do provide a relatively clear and detailed description of the responsibilities of the range of parties involved in clinical trials including the REB, the investigator and the research institution, the sponsor and (under the sponsor heading), the CRO and the monitor. Each of these is described briefly below.

255 The maximum penalties for indictable offences are $5000 and prison terms to a maximum of 3 years. The penalties for summary offences are fines up to $1000 and a prison term not exceeding 6 months.
256 Lemmens (2005) has also commented on the uncertain legal status of GCP Guidelines in the Canadian context.
257 The description provided is not at all intended to be exhaustive; instead, it is simply to outline the kinds of responsibilities that fall to each party. More detailed discussion of specific issues and elements of these responsibilities is provided as relevant throughout this dissertation.
7.3.2.1 Research Ethics Board

Section 3.1 of the GCP Guidelines lists the responsibilities of the research ethics board (REB). Pursuant to the guidelines, the REB is responsible for safeguarding the rights, safety and well-being of all trial subjects, with special attention being paid to vulnerable subjects. The guidelines then identify further responsibilities in this regard, including a list of the documents that the REB should consider in their examination of the research study, the fact that the REB should consider the qualifications of the investigator for the proposed trial, and the requirement for at minimum annual reviews of the clinical trial. A number of specific considerations relating to the consent process (including payment, for example) are also listed. Sections 3.2-3.4 of the GCP Guidelines then describe REB composition, functions, operations, as well as procedures and record keeping requirements. For example, the guidelines indicate that the REB should establish procedures requiring the investigator to promptly report to the REB, inter alia, all adverse drug reactions that are both serious and unexpected as well as any new information that may adversely affect the safety of subjects of conduct of the trial.

7.3.2.2 Investigator

Section 4 of the GCP Guidelines outlines the role and responsibilities of the investigator. The investigator is responsible for the conduct of the trial at the site, and should be qualified by education, training and experience to assume responsibility for the conduct of the trial. In addition to this general requirement, the investigator should be thoroughly familiar with the specifics of the trial in question and should also be aware of and comply with the GCP Guidelines and “other applicable regulatory requirements”. It is also the responsibility of the investigator to ensure that all persons assisting with the trial are adequately aware of and informed about the protocol, and their duties. The investigator is also made explicitly responsible for all the trial related medical decisions in relation to trial subjects pursuant to section 4.3 (1-4). While the guidelines state that the investigator should have sufficient resources—it is not entirely clear whether this is the responsibility of the investigator or if it is an obligation of the sponsor—or both (it is listed under both headings). Other responsibilities of the investigator include timely and effective communication with the REB, compliance with the protocol (deviations only.

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258 What we refer to in Canada as the Research Ethics Board (REB) is referred to in the ICH-GCP Guidelines as the institutional review board/independent ethics committee (IRB/IEC).
permitted with prior approval of the sponsor and REB approval, except where immediate action is required to protect the safety of subjects), and management of and accountability for the investigational product. The guidelines also go into significant detail as to the responsibilities of the investigator in relation to informed consent, and describe what information must be covered (among other elements). Section 4.9 makes the investigator responsible for the accuracy, completeness, legibility and timeliness of the data reported to the sponsor and for maintaining those records in accordance with the guidelines and other regulatory requirements. Section 4.11 makes the investigator responsible for immediate reporting of serious adverse events (SAEs)\(^{259}\) to the sponsor, and where specified under other applicable regulations- to the regulatory authorities and REB. In the Canadian context, the Regulations make the sponsor responsible for reporting a subset of SAEs, notably Serious Unexpected Adverse Drug Reaction (SUADRs) to the regulator (but not to the REB). The Regulations do not identify roles or responsibilities of the investigator (or REB or anyone other than the sponsor). It should be noted, however, that the TCPS2 which applies to all researchers and research institutions that receiving funding from one of the three federal funding agencies, makes it the responsibility of the researcher to ensure all new information that may affect the welfare and consent of human subjects (including specifically unanticipated adverse drug reactions) is shared with the REB and appropriate regulatory authorities (TCPS2, s.11.8). Finally the guidelines also list the responsibilities of the investigator in relation to early termination or suspension of trials—whether that termination is initiated by the sponsor, by the investigator or by the REB. While there are slightly different reporting obligations in each instance, all require prompt notification to the subjects and appropriate follow up.

As highlighted by my participants and discussed in Chapters 4 and 5, it seems that while these responsibilities may be being met by many investigators, this cannot be taken for granted

\(^{259}\) Defined in GCP as: “any untoward medical occurrence that at any dose:
- results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
or
- is a congenital anomaly/birth defect.”
or assumed. Gaps in training and oversight, failure to follow protocol and insufficiently trained staff are among some of the many problems that are described both in this study and the broader literature.

## 7.3.2.3 Sponsor

Given that the sponsor retains ultimate responsibility for the quality and integrity of the trial data, it is not surprising that the *GCP Guidelines* go into most detail in relation to sponsor obligations. Section 5 of the *Guidelines* first establish that it is the sponsor’s obligation to implement and maintain quality assurance and control systems and written standard operating procedures (SOPs) to ensure that all aspects of clinical trials are conducted according to the protocol, *GCP* and applicable regulatory requirements. As alluded to earlier, the *Guidelines* then recognize that the sponsor may transfer all or some of its trial related duties and functions to a CRO, though always retaining ultimate responsibility for the quality and integrity of the data. The *Guidelines* detail sponsor responsibilities as including, *inter alia*, ensuring appropriate medical and other expertise is available in the design and implementation of the trial, that trial management, data handling and record keeping meet articulated criteria, and that the sponsor selects appropriately qualified investigators and ensures they have adequate resources to properly conduct the trial. The sponsor must also obtain from the investigator an agreement that the protocol will be followed, that all *GCP Guidelines* and other applicable regulatory requirements will be met, and that monitoring and auditing of the site will be permitted. The guidelines describe the sponsor’s adverse event reporting obligations, specifying for example that the sponsor is responsible for expedited reporting of all serious, unexpected adverse drug reactions to all investigators, REBs where required and to the regulatory agencies. In terms of quality assurance and control, relatively extensive detail is provided as to the purpose and responsibilities of monitors and relevant considerations for when sponsors conduct audits, as well as how to handle non-compliance-be it with the protocol, SOPs, GCP, or other regulatory requirements. Finally, sponsor’s obligations in relation to premature termination or suspension of trials are outlined, as are some specific requirements in relation to the organization and oversight of multicenter trials.

As was discussed in detail in Chapter 4, the above sponsor obligations are also assumed by investigators in investigator-initiated studies; however, and unlike their industry counterparts,
the evidence from this study supports concerns in the literature that investigators are not sufficiently familiar with their obligations in this regard.

7.3.2.4 CRO

Where the sponsor transfers any or all of their trial responsibilities to a CRO, the GCP Guidelines specify that this should be documented in writing, and clarify that any duties not specifically transferred to a CRO are retained by the sponsor (s.5.2.2 & 3). Unsurprisingly, they also state that “all references to a sponsor in this guideline also apply to a CRO to the extent that a CRO has assumed the trial related duties and functions of a sponsor” (s.5.2.4). Apart from stating that the CRO should implement quality assurance and control systems (even though the sponsor retains responsibility for the quality and integrity of the data), the GCP does not establish any duties or responsibilities on the CRO separate and apart from whatever responsibilities are transferred to it by the sponsor in a given instance.

Interestingly, while the process of transferring responsibilities from the sponsor to the CRO seems clear, it has been observed (and recognized by the FDA) that some question exists as to the reporting obligations of the CRO to the regulator, and whether these are direct or through the sponsor (Korieth, 2010; Shuchman, 2007). Given that there are no additional provisions in this regard in Canada, it seems reasonable to conclude that the similar quandary exists here. Such questions, combined with a lack of sufficient oversight of CROs by sponsors (a problem echoed by my participants, as described in Chapter 6), have led to an increased focus by the U.S. FDA on the sponsor-CRO relationship by regulators, something that is creating concern in the industry (Getz, 2012; Halloran, 2012; Korieth, 2010).

7.3.2.5 Monitor

Within the description of the sponsor’s obligations, the GCP Guidelines also describe the role and responsibilities of the Monitor. Pursuant to section 5.18 of the guidelines, the purpose of the Monitor is to verify that:

- The rights and well-being of human subjects are protected.
- The reported trial data are accurate, complete and verifiable from source documents.
- The conduct of the trial is in compliance with the currently approved protocol/amendments, with GCP, and with the applicable regulatory requirements.
Moreover, the guidelines state that monitors should be appointed by the sponsor, be the main line of communication between the sponsor and the investigator, be appropriately trained and have the scientific and/or clinical knowledge needed to monitor the trial adequately. While there may be significant diversity in any additional roles a monitor is assigned, the basic process of monitoring a clinical trial involves selecting an appropriate site, monitoring the conduct of the trial at that site, and closing the site. Each of these stages generally requires the monitor to attend in person, although the guidelines do suggest that in exceptional circumstances centralized remote monitoring in conjunction with meetings, training sessions and extensive written guidance can satisfy GCP requirements. In practical terms, monitors may be employees of either the sponsor or the CRO, or independent contractors hired by either the sponsor or CRO depending on how responsibilities for monitoring are assigned.

7.3.3 TCPS2

The Tri-Council Policy Statement 2 establishes clearly that the welfare of participants takes precedence over the interests of sponsors and researchers. The document provides guidance for the interpretation of three core principles of research ethics (described in the policy as respect for persons, concern for welfare and justice), and also establishes a number of mandatory requirements for researchers, institutions and members of REBs. For example, the TCPS2 establishes that REBs are to adopt a proportional approach in their reviews of research protocols, focusing on an assessment of the foreseeable risks, the potential benefits and the ethical implications of the research—both initially and for the duration of the study. By way of another example, the TCPS2 makes the principal investigator of a study responsible for ensuring that the informed consent process meets all requirements as set out in the document, and any other applicable regulatory requirements in this regard. It also clarifies that the PI is responsible for the actions of any team member involved in the consent process. In addition to these and other generally applicable provisions (for example, relating to privacy considerations, fairness and equity in research participation and conflicts of interest) there is also a chapter addressing issues specific to clinical trials. This focus of that chapter is on ethical issues relating to the design,
review, and conduct of clinical trials and it establishes a number of responsibilities in this regard—primarily for researchers and REB members.260

The TCPS 2 serves as a “benchmark for the ethical conduct of research involving humans.”261 However, it is not part of the legislated framework. Researchers and research institutions must adhere to the principles and standards it outlines, as well as to policies established in a Memorandum of Understanding262, in order to be eligible for funding from the three federal funding agencies (CIHR, SSHRC, NSERC, collectively the “Agencies”). While an important document, there are a number of challenges that raise questions about its effectiveness. These have been described in detail elsewhere (McDonald, 2001; McDonald 2009), but very briefly, key concerns relate to their limited jurisdiction and to their enforceability (among others). The TCPS 2 does not address, for example, privately funded research taking place in the community. Specifically for present purposes, this means that industry funded clinical trials that take place in the community setting are not covered. The second major problem is enforceability and demonstrated effectiveness. As McDonald (2009) observes, we simply do not know the extent to which the TCPS2 is being followed and whether, “if followed, it achieves its stated ends of ensuring the rights of subjects and advancing socially beneficial research.”

7.3.4 Codes Of Conduct

In addition to the documents described above, professional Codes of Conduct, such as those issued by the Canadian Medical Association and the Canadian Nurses Association, constitute another source of responsibility for those involved in the conduct of clinical trials. Very briefly, the Canadian Medical Association (CMA)’s Code of Ethics has as its explicit focus “the core activities of medicine—such as health promotion, advocacy…and research”. Research is explicitly acknowledged (in s. 8) as one means of contributing to the development of the medical profession (which development all physicians are called upon to further).

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262 The MOU includes policies on research integrity, peer review and conflicts of interest.
While perhaps very familiar, a few of the fundamental principles are worth repeating here. The *Code* requires the physician to “consider first the well-being of the patient”, and to ensure that they practice with integrity. This includes disclosing conflicts of interest to the patient and resolving them in the patient’s best interest, and entering into “associations, contracts and agreements only if you can maintain your professional integrity and safeguard the interests of your patients.” Research is also specifically mentioned. Physicians must ensure any research in which they participate has been evaluated ethically and scientifically and approved by an REB. They must also obtain free and informed consent and advise the potential subject of the nature, purpose of the study, its funding, potential harms and benefits, and the nature of the physician’s participation and any compensation the physician may receive. In addition, the CMA has also issued a policy document entitled *Guidelines for Physicians in Interactions with Industry*. The guidelines explicitly note that relationships between physicians and industry are guided by the CMA’s *Code of Ethics* and by the guidelines, and that the practicing physician’s primary obligation is to the patient. Relationships with industry are inappropriate if they negatively affect the fiduciary nature of the patient-physician relationship. Finally, it is noteworthy that the guidelines require physicians involved in clinical trials to ensure that such trials are registered in a publicly accessible registry prior to commencement, something that is not yet required by Health Canada. In addition to the guidance provided by the CMA, provincial professional colleges such as the College of Physicians and Surgeons of Ontario (CPSO) have issued relevant guidelines, including for example, guidance on appropriate relationships with industry including issues associated with financial conflicts of interest.²⁶³

Also relevant would be codes of conduct established specifically for research professionals such as those established by the Association of Clinical Research Professionals (ACRP). Not unlike the medical and nursing codes of ethics, this code draws attention to the distinction between medical practice and research, requiring members to be mindful and respectful of this tension. It also underlines the importance of adhering to all relevant ethical standards and practices of responsible conduct of research and medical practice, and reminds its

members to abide not only by the code but also by the laws and ethical codes of their own disciplines.

Professional codes of conduct are relevant to physicians and nurses involved in research in several ways. First, professionals who fail to meet the standards established by their governing bodies (e.g., College of Physicians and Surgeons in a particular province) may face licensing consequences. Less directly, and as will be discussed further in Chapter 8, professional codes of conduct may help inform (but do not constitute) the standard of care in negligence law suits arising out of research related activities. As others have noted, “courts remain the final arbiters of the legal standard of care and are thus free to base their judgments on considerations that reach beyond the professional norms and guidelines” (Campbell & Glass, 2001)\textsuperscript{264}. However, and particularly where there is a dearth of clear evidence or case law as to the relevant standard of care, codes of conduct and other well established guidelines help inform what a reasonable person in the defendant professional’s position would have done, and as such are relevant to the standard of care (Campbell & Glass, 2001).

Taken together, the above sources of law and policy constitute the main components of the oversight framework for clinical trials in Canada. The next section examines further how Canada’s approach measures up in terms of the protection it provides Canadians.

### 7.4 Clinical Trial Governance: How Does Canada Compare?

Clinical trials are big business, and Canada’s share of the pie has been shrinking in recent years (Vanderwel, 2012; Leclerc, Laberge & Marion, 2012). As such, it is hardly surprising that there are numerous and diverse initiatives in both the private and public sectors to try to make Canada a more attractive place for industry to conduct their trials. While on the one hand, this is desirable given both the economic and (potential)\textsuperscript{265} health benefits, it is also critically important

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\textsuperscript{265} As discussed in Chapter 9, the extent to which the vast majority of clinical trials even have the potential to yield health benefits is extremely low. Even where a new drug successfully makes it through the clinical trial process (wherein there is an extremely high attrition rate), it has been reported that nearly 4/5 of newly patented drugs provide no therapeutic advantage over existing drugs on the Canadian market. (Gagnon, MA (2010) Rev Prescrire; 32 (342): 311-314, citing the 2010 annual report of the Patented Medicines Prices Review Board. The 2011 annual PMPRB report classified 72 of the 104 new patented drugs in 2011 as being of slight or no
to understand the weaknesses of the regulatory and oversight mechanisms in order to appreciate where risks may arise and be able to take steps to mitigate them. This chapter has already outlined a number of problems with Canada’s regulatory and oversight framework for clinical trials. Minimal and arguably ineffective regulatory oversight, a heavy reliance on REBs to ensure the protection of human subjects despite well recognized problems, and looking to sponsors to oversee trials without any efforts to address or manage the conflict of interest and lack of transparency in such an approach—are among the weaknesses that erode the effectiveness of clinical trial oversight in Canada. Drawing support from the findings of the qualitative interview study (reported in Chapters 4-6), the remainder of this chapter will argue that in addition to these challenges, the Canadian system is both less transparent than it’s U.S. counterpart, and less effective at clearly ascribing accountability to, and fostering a strong sense of responsibility in, those working across the clinical trials industry. I will argue further that, to the extent that CROs fracture relationships between the frontlines of clinical research and those funding, designing and ultimately reaping the rewards of successful trials, they also contribute to this diffusion of responsibility and complicate the ascription of accountability at the very least on a moral, if not clearly on a legal, level. Finally, I will outline a number of measures that might help improve accountability and facilitate enforcement of standards for clinical trials conducted in Canada.

7.4.1 Concerns With Opacity

There has been much criticism of Health Canada for failing to be adequately transparent in relation to clinical trials that are conducted in Canada (Belluz, 2013; Ogilvie, 2012; Shuchman, 2013). A key concern in this regard is that whereas other jurisdictions, including the United States and the European Union, require sponsors to register their clinical trials in public registries, including the results of such trials, Canada does not. Such a step is widely considered an essential (though not sufficient) step in ensuring that health care providers, patients and the improvement over existing therapies. These numbers exclude those drugs that were reported to PMPRB in 2011, but sold prior to introduction of new guidelines in 2010 (number would then be 77/109).  

http://www.pmprb-cepmb.gc.ca/english/view.asp?x=1625&all=true

266 As described elsewhere, these include a lack of established standards, training, support, monitoring and feedback from subjects-as well as other well documented challenges.
public have access to objective data regarding medicines that are ultimately available on the
Canadian market. Herder (2012) comments,

Health Canada should publicly disclose information about the safety and efficacy of
pharmaceuticals, biologics and medical devices, and should especially disclose the
designs and results of clinical trials. This disclosure is necessary to preserve public trust,
address weaknesses in the evidence base and protect Canadians from harm. (p. 194)

Failing to do so, as the author indicates, feeds the concern that the regulator is industry friendly.
Moreover, transparency is particularly important given the resource constraints and other
challenges undermining Canada’s oversight of this high stakes industry (Herder, 2012).
Transparency at the regulatory level is arguably even more important as transparency in the
industry decreases. There seems to be a trend in the industry whereby CROs are shifting away
from being publically traded companies and are instead relying with greater frequency on private
equity (Getz, 2011; Redfern, 2013).267 As one analyst explains,

behind the veil afforded by the private markets, CROs have far greater latitude to not
only complete transactions that complement their capacity and expertise and permit a
founder to exit, but also to pursue novel leading strategies that may ultimately redefine
integrated drug development services in the future. (Getz, 2011)

While a detailed discussion of this concern exceeds the scope of this dissertation, the relevant
point here is simply that this shift to private equity represents an additional layer of opacity since
there are fewer reporting requirements and less opportunity for external scrutiny.

Health Canada has itself recognized that it has failed to keep up with international
standards in terms of their levels of transparency in this area and are apparently working to
address this over time.268,269 In order to maintain public trust, the regulator must avoid—and be

267 See for example this discussion on CROs as an interesting investment option (August 1,
2013): http://www.mwe.com/Private-Equity-Activity-in-Contract-Research-Organizations-
Recent-Deals-and-Key-Issues-for-Consideration-08-01-2013/

268 See comments of Paul Glover, Assistant Deputy Minister, Health Products and Food Branch
(HPFB) (Health Canada), to The Senate Standing Committee on Social Affairs, Science and
Technology for a study on prescription pharmaceuticals in Canada (topic: Clinical trials). March
28th, 2012

269 Canada is also lagging in other transparency related initiatives in this area. For example,
while the U.S. has recently (August 2013) enhanced its reporting requirements in terms of (inter
seen to avoid the conflict of interest that would place attracting clinical trials and industry business to Canada over the protection of the health and wellbeing of Canadians. Improving their transparency and openness are important steps in any such efforts. In May 2013, after 8 years of considering the issue of transparency and trial registration, Health Canada at long last launched its clinical trial database. Unfortunately, the initiative falls far short of registration requirements established in other jurisdictions (U.S., EU) and is largely ineffective at addressing key issues generally associated with the need for registration (Shuchman, 2013). In fact, by Health Canada’s own definition what it has created is not in fact a registry but an administrative list of clinical trials authorized by Health Canada.\textsuperscript{270} Instead of promoting transparency, this move is intended to help physicians and their patients as well as the public know about clinical trials that have been approved, in an effort to improve recruitment. Poor recruitment has been identified as a major obstacle to attracting more clinical trials to this country (Saryeddine al, 2011; Vanderwel, 2012).

Although bringing more clinical trials to Canada and trying to boost Canada’s attractiveness to industry definitely has some economic and health benefits, and should be a priority for private sector and some public sector organizations, it is not at all clear that given the powerful interests at stake and the weaknesses described in regulatory oversight, that it is a reasonable priority for Health Canada, whose mandate is to “help Canadians maintain and improve their health.”\textsuperscript{271} This is particularly true in light of the high number of trials that bring little or no prospect of therapeutic gains or benefits. For example, and as will be discussed in more detail in Chapter 9, the Patented Medicines Prices Review Board has reported that 4 out of 5 newly patented drugs provide no therapeutic advantage over drugs already on the Canadian market (Gagnon, 2012; PMPRB, 2010).


\textsuperscript{271} http://www.hc-sc.gc.ca/hcs-sss/index-eng.php
7.4.2 A Flexible Approach But At What Cost?

As previously described, Canada has chosen to adopt a hybrid approach to regulating clinical trials, wherein the formal regulatory framework consists of a relatively sparse set of regulations supplemented by a much more expansive set of non-binding guidelines. Under this framework, the only party expressly identified and considered by the regulator in any detail is the sponsor.\footnote{While the regulations do also mention the Research Ethics Board, this is simply to briefly describe its mandate and composition in the definition section.} Health Canada has also explicitly stated\footnote{As reported in the Regulatory Impact Analysis Statement accompanying the Food and Drug Regulations-Amendment (Schedule No.1024) Clinical Trial Framework SOR/2001-203.} that their express jurisdiction is limited to the sponsor, and that in keeping with \textit{ICH-GCP}, it is the sponsor who bears responsibility for ensuring those with whom they contract comply with the regulations. The roles and responsibilities of other important parties-including in particular the CRO to whom the sponsor contracts some or all of their clinical trial obligations, as well as the REB, the investigator, and the monitor, are all described in some detail within the \textit{GCP Guidelines}. While this approach provides for increased flexibility in interpretation and application, it raises questions about the extent to which the standards established by the guidelines are enforceable, by whom, and what the consequences of breaching them would be (Hirtle et al., 2000; Lemmens, 2005).

In the United States, ultimate responsibility for quality and integrity of the trial data also rests with the sponsor; however, the U.S. FDA has adopted a different approach that arguably provides more clarity in terms of accountability for specific trial activities by making it clear to the various named parties that they each have obligations not simply to the sponsor but also directly to the regulator.\footnote{For a superb discussion of the benefits of such an approach and an argument that research under the U.S. Common Rule should also be subject to similar provisions, see Shah, 2013.} The U.S. Food and Drug Administration has specifically incorporated the \textit{GCP Guidelines} into its \textit{Code of Federal Regulations (CFR)}, which means that the responsibilities of sponsors, CROs, monitors, investigators and ethics boards are given the force of law and that the FDA has direct jurisdiction over each of those parties to enforce the requirements set out in the \textit{CFR}. This is evidenced, for example, by the direct contract investigators (both within and outside of the U.S.) must sign and file with the U.S. FDA for trials

\footnote{While the regulations do also mention the Research Ethics Board, this is simply to briefly describe its mandate and composition in the definition section.}
within its jurisdiction, commonly known as form 1572. By explicitly claiming jurisdiction over the various parties involved in clinical trials (i.e., through their inclusion in the CFR), there is a clearer indication that the regulator will seek to enforce obligations and responsibilities in relation to conduct of specific trial related activities as against the party responsible for those activities, as opposed to simply limiting such oversight to the sponsor.

Hence, under the FDA concerns such as those raised by participants in the present study, including for example, lack of investigator training and oversight (Chapters 4 and 5), as well as a lack of sufficient monitoring by CROs (Chapter 6) are squarely within the jurisdiction of regulatory authorities. Where such issues come to light-for example through regulatory inspections- they can result in a variety of penalties including for example suspension or cancellation of FDA approval for the clinical trial and the issuance of public warning letters by the FDA (Halloran, 2012; Shah, 2011). In contrast, while audit results in Canada can lead to suspensions or cancellations of approvals for the conduct of trials, individual results are not made public and instead are (eventually) aggregated, stripped of identifiers and published. The lack of public consequences in this regard is yet another factor contributing to what is at least arguably a less effective system of oversight for clinical trials in Canada (Shah, 2013).

7.4.3 Another Comparison: Investigator Training

On a separate but closely related point, the U.S. has also been much clearer in stipulating exactly what they expect in terms of investigator qualifications and training. As highlighted in

275 In Canada the qualified investigator also signs a qualified investigator undertaking promising, among other things, to conduct the trial in accordance with Good Clinical Practices; however, this form is not filed with Health Canada but instead is retained by the sponsor for 25 years. The U.S. form 1572 is also much more detailed than its Canadian counterpart. For example, as opposed to simply asserting conformance with good clinical practices, the U.S. form highlights key provisions particularly relevant to the investigator’s responsibilities for safeguarding the wellbeing of trial subjects including reiterating the importance of informed consent, ethics review and adverse event reporting. The form is submitted by the sponsor to the FDA as part of the Investigational New Drug (IND) Application.


277 While the arguments certainly can be transferred, it should be noted that Shah (2013) argues these points not in relation to Canada, but in comparing the Common Rule to the the FDA Code of Federal Regulations.
Chapter 4, participants in this study identified lack of investigator awareness of GCP and other regulatory requirements—in relation both to investigator and sponsor-investigator obligations—as an important area of concern. Increased attention to training in this regard was suggested by my participants and is also called for in the literature (Dodsworth, 2012; Fisher, 2009). While the Division 5 Regulations and key guidelines stipulate that those involved with clinical trials (including investigators and monitors, among others) must be appropriately qualified by education, training, experience to fulfill their responsibilities, there are no standardized requirements in this regard. This has resulted in a huge array of courses being offered by a range of institutions with varying credentials (see Chapter 4).

In the absence of established accredited training standards and requirements, the FDA has taken steps to provide some clarity on this issue—for example, by establishing an annual three day training course and providing other training opportunities in collaboration with other government departments and organizations. In contrast, Health Canada has declined to provide any guidance in this area. This is not for lack of interest from the community. In November 2010, Health Canada conducted a series of GCP information sessions across the country “to improve understanding of regulatory requirements pertaining to clinical trials…and facilitate compliance”. During this process, Health Canada was asked repeatedly whether it could provide recommendations or guidance in relation to appropriate investigator training. That investigators have turned to the regulator attempting to find some measure about what constitutes “appropriately trained” suggests that those at the front lines are unclear as to what the regulator requires of them and are unsure how to obtain and demonstrate their qualifications. While perhaps related to constitutional concerns and treading on provincial jurisdiction (discussed at the outset of this Chapter), Health Canada’s response that it “cannot support or

278 See for example the FDA’s description of their training initiatives found at: http://www.fda.gov/scienceresearch/specialtopics/runningclinicaltrials/educationalmaterials/ucm112925.htm
280 Following this process, Health Canada created a list of Frequently Asked Questions that had arisen out of the sessions. This list included three questions pertaining directly to training—specifically whether Health Canada provides or recommends any GCP training, what is considered adequate training and how often should this be received, and finally how should such training be demonstrated.
endorse any specific GCP courses or resources” seems shortsighted and its inconclusive comments about what constitutes training\textsuperscript{281} are simply not helpful. By failing to provide the investigators and research staff with any real guidance on appropriate training, and yet also requiring that investigators and their staff be adequately trained, it is certainly arguable that Health Canada is contributing to very real enforceability and accountability problems that not only could reasonably be expected to undermine the confidence of those working in the field, but also of subjects involved in clinical trials and Canadians consuming the products that have been tested in this process.

While the heavier regulatory approach adopted in the U.S. may well be more bureaucratic and rigid, it is reasonable to expect that the increased clarity around the obligations and expectations of those involved in clinical trials under the U.S. administration contributes to greater accountability and facilitates enforcement. That being said, it is hard to ascertain the actual impact of such differences (e.g., how these have affected the oversight activities of regulators, and the actions of regulated parties). Interestingly, industry literature (Getz, 2010; Halloran, 2012; Shah, 2011) suggests that in practice the FDA has actually also (at least until very recently) tended to focus most of its authority on sponsors. However, in light of growing concerns related to inadequate sponsor oversight, there are suggestions that it is now considering still more explicit regulation and, in particular, closer scrutiny of the relationship between CRO and sponsor (Halloran, 2012; Shah, 2011). This suggests on the one hand that there may actually be less of a difference in practice as between the U.S. and Canada, but also supports the claim that there is currently a recognized lack of accountability in the context of clinical trials and that more explicit regulation of parties may help address this concern. The relative lack of clarity and accountability in Canada in relation to clinical trial responsibilities, and the hands-off, diffused approach adopted by the regulator in relation to oversight and enforcement described above could all reasonably be expected to not only make those involved in clinical trials less certain of their responsibilities, but perhaps also less concerned about fulfilling them in the absence of

\textsuperscript{281} In response to this question Health Canada indicates that training should include the legislated regulatory requirements (\textit{Food and Drugs Act} and \textit{Regulations} (Part C, Division 5)) and “relevant supporting guidance, including but not limited to, ICH E6: Good Clinical Practices.”
effective, meaningful oversight (Shah, 2013). It is also worth briefly noting that an additional exacerbating factor in this regard could be the relative lack of litigation and case law in relation to clinical trials in Canada as compared, for example, to the U.S..\textsuperscript{282} As Mello et al. (2003) point out, in addition to regulation “our society also relies on private litigation to deter poor practices and compensate persons injured by substandard conduct.” Even in the absence of a strong regulatory presence the real threat of litigation could encourage parties to meet established standards and fulfill their responsibilities with due care and attention. On each of these fronts, it seems the U.S. is well ahead of Canada in terms of establishing and enforcing accountability in clinical trials.

7.5 CRO: Diffused Accountability

Despite the above discussion, at least on paper there is a fairly clear delineation of legal responsibility for parties involved in clinical trials—even in Canada. For example, from a review of the applicable legislation and other authoritative sources, it seems quite clear that while a sponsor may transfer any or all of its obligations to the CRO—and the CRO in turn will be responsible as if it were the sponsor for those specific activities—the ultimate responsibility for the quality and integrity of the data (including for ensuring that the trial is conducted according to GCP) remains with the sponsor. What this means is that the sponsor must be actively engaged in effective oversight of all parties with whom it contracts to ensure that they are meeting regulatory and other (e.g., GCP) requirements. Failure to do so could result not only in fines and other penalties pursuant to the Food and Drugs Act, but also in delays and even rejections by the regulator in the New Drug Submission process depending on whether and how the integrity of the data is deemed compromised. It would then presumably be up to the sponsor to pursue the CRO (most likely in contract and/or negligence) for damages. In contrast, what is arguably of greater concern is the diffusion of moral accountability for the conduct and outcomes of clinical trials, and their impact on human subjects. The role of the CRO, as the primary means through which sponsor responsibilities are diffused, is particularly interesting in this regard. (Adobor, 2012; Schipper et al. 2011).

As was clearly described by my participants (see in particular Chapter 6) and as is

\textsuperscript{282} Legal liability and exposure of parties involved in clinical trials in Canada are discussed in Chapter 8.
mentioned elsewhere (Fisher, 2009; Lamberti et al., 2011; Schipper et al., 2011), the introduction of a CRO has real implications for investigative sites. While there can certainly be advantages to CRO involvement from a site perspective, there are also a number of significant challenges. It is well known that a key measurement of a CRO’s success from a sponsor-client’s perspective is the extent to which a trial is completed on time and under budget (Halloran, 2012; Mirowski & Van Horne, 2005; Schipper et al., 2011). As such, some have observed that most of the concerns associated with outsourcing to CROs are “over tradeoffs between costs, speed and quality of clinical trials” (Schipper et al., 2011). CROs can bring additional pressures to investigative sites to, among other things, recruit subjects more quickly. These aims may be realized by a variety of means, some of which will be more problematic than others. For example, and as reported by my participants, such pressures have resulted in inappropriate accessing of patient databases with potentially serious privacy implications. Other problems might include implementing weak consent processes or stretching inclusion/exclusion criteria. Moreover, CROs can create challenging situations in terms of cash flow as a result of slow payments (Glass, 2009; Lamberti et al., 2011), which can result in staff shortages or other problems at sites. CROs also do not have the same sense of investment in the study (as many of my participants observed, “it’s not their baby”) and, especially in the context of transactional (as opposed to longer term integrated) relationships have profit driven incentives to cut corners. All of these factors are exacerbated by the current economic climate wherein sponsors, feeling financially pinched, are reducing budgets and demanding more for less from their service providers (Getz, 2012).

In addition, the introduction of a middleman can also create confusion on the part of the site as to where the pressures or demands are coming from (whether from sponsor or from CRO) and, by definition, create added distance between the sponsor and the site, meaning that the sponsor is often less aware and in less control of what is going on at the site (with management and oversight responsibilities commonly contracted to the CRO). Halloran (2012), for example highlights two FDA warning letters to major pharmaceutical sponsors in 2009 that identified “significant issues with lapses in decision-making, oversight, and the corrective and preventive

\[^{283}\text{For example, and as described in Chapter 6, my participants described improved responsiveness, heightened appreciation for site based challenges and even in some cases greater understanding of clinical realities than some sponsors.}\]
actions required of all sponsors…which could result in harm to subjects.” Problems relating to
the lack of adequate CRO oversight and “lack of clarity in responsibility and accountability of
third parties” (Halloran, 2012) were prominent. Such challenges are compounded in cases where
CROs themselves outsource or subcontract services to additional service providers (Schipper et
al., 2011), thereby further fragmenting trial related tasks. While not a sure recipe for disaster in
and of themselves, and while it is not possible to claim that these factors will result in more harm
to subjects, it is reasonable to suggest that taken together and combined with the above noted
lack of regulatory clarity and oversight (real time or otherwise), these factors tend to blur lines of
responsibility and make ensuring the safety of human subjects more challenging.

7.6 Moving Forward: Suggestions For Greater Accountability

Canada, like many countries around the world, relies on volunteers to advance the public
interest through research in science and medicine. As such, it has been convincingly argued that
Health Canada has trust-based obligations to protect the interests of those involved in research
(Miller & Weijer, 2006). These obligations are heightened by the fact that Health Canada holds
itself out as protecting the health and wellbeing of its citizens. However, as has been discussed
in this chapter, there are a number of weaknesses in the current oversight system that need to be
addressed to ensure that such obligations are being met. Key issues include limited involvement
of the regulator, an overreliance on REBs, and challenges associated with sponsors being the
primary overseers of their own ongoing trials. Such challenges are arguably compounded by the
lack of express regulatory authority over the various parties involved in clinical trials (other than
the sponsor), as well as a failure by the regulator to provide guidance on key established, but
largely undefined, requirements (for example, what constitutes sufficient training for key parties
including investigators and their staff). This suggests some key areas for improvement, and
some recommendations to this effect are outlined below.

7.6.1 Establishing Clear Jurisdiction Of Health Canada Over Key Parties

Despite the strong motivations industry sponsors have to maintain tight reins on their
CROs to ensure the quality and integrity of their data, there seems to be growing evidence of
insufficient sponsor oversight. In fact, and as seen above, such evidence is prompting the FDA,
which already exercises more explicit oversight than Health Canada, to consider further
regulation in this area with a particular focus on the sponsor-CRO relationship (Getz, 2010;
While it is entirely possible that industry sponsors have an important role to play in trial oversight, it seems clear that relying almost exclusively on industry (as is the current case in Canada) is neither appropriate (given the conflict of interest issues and lack of transparency concerns described earlier in this chapter) nor sufficient. As such, Health Canada should consider extending its direct jurisdiction from the sponsor to all of the other key parties involved in clinical trials, including: the CRO, the monitor, the REB and investigators. One way of accomplishing this would be to incorporate the GCP Guidelines more fully into the relevant regulatory framework (Division 5 Regulations under the Food and Drugs Act) as was done by the U.S. FDA. By unambiguously claiming authority in this regard, Health Canada would be better situated and motivated to ensure standards are met and to heighten oversight as needed—instead of relying on sponsors in this regard. Such a move would also be a clear indication to Canadians that the regulator considers safe, ethical clinical trials a priority and one for which it is directly responsible. This in turn may help motivate all involved to strive to meet not only the letter of the established requirements and standards for clinical trials, but also to internalize the spirit of the ethical principles behind them (Shah, 2013).

**7.6.2 Increase Training And Independence Of REBs & Clarify Scope**

A second important area for improvement is in relation to REBs. As already discussed, REBs play a critical role in the oversight of clinical trials; however, they face a number of well-documented challenges. Lack of training, support, institutional independence and accreditation are common challenges described in the literature (Glass, 2006; Lemmens, 2005; McDonald, 2000; 2001) with important implications for human subject protection. There is also a concern that research ethics considerations have become synonymous with REB review, with two important implications. First, REBs get saddled with responsibilities that go beyond their mandate—taxing an already stretched system; and second, that there are many issues that should be addressed that simply are not because they do not fall within the scope of REB review (Anderson et al., 2011; McDonald, 2001). A number of efforts and initiatives have been undertaken over the past 10+ years to try to address many of these challenges (including—among others—efforts to establish standards and support accreditation, enhance oversight and improve ethics education for REB members and researchers), though success has been modest (Anderson et al., 2011). Some advances have certainly been made, and there are exciting examples of how
things may be improved. As alluded to earlier, for example, the Ontario Cancer Research Ethics Board (OCREB) has addressed the independence concern by establishing an independent governance committee of outsiders who play the major role in the appointment of the chair and vice chair(s) of the REB. However, there is still a great deal of work to be done to ensure that REBs are an effective means of protecting human subjects.

7.6.3 Clearly Articulate Roles And Limitations Of Regulator, REB And Sponsor

Canadians are entitled to have as clear an understanding as possible of the extent to which their interests are protected under the current clinical trial oversight structure. Clearly articulating the respective roles of the regulator, REB and sponsor, and just as importantly, explicitly acknowledging their respective limitations, is an important first step both in improving Canada’s oversight system and in ensuring Canadians have an accurate picture of the protections that are in place and how well they are working. Through increased transparency and openness, the strengths and weaknesses of the current system may be analyzed and meaningful solutions considered. The following are some examples to illustrate this point.

7.6.3.1 Clarify Role Of Health Canada In Initial Review

The respective roles of Health Canada and REBs in the initial review of clinical trials could benefit from being more clearly articulated. Currently, before a trial can begin in Canada Health Canada conducts an initial review of the Clinical Trial Application and then the REB conducts its own review. As previously discussed, Health Canada has only thirty days to review the extensive materials submitted by sponsors in their Clinical Trial Applications. A reasonable question would be whether thirty days is sufficient time for Health Canada to conduct a meaningful review, and what exactly is assessed in that time. It certainly may be the case that effective reviews are conducted; however, it may also be the case that the short time limits and the default that allows sponsors to proceed after 30 days even in the absence of a No Objection Letter (NOL), may be more indicative of a simple registration system instead of a thorough review. Clarifying what is actually achieved in this process, and what is not achieved, would help determine whether additional steps are required, and whether and to what extent the other source of initial review-namely the REB-is sufficient.
7.6.3.2 Clarify Role Of Health Canada In Ongoing Reviews

Another example is in relation to Health Canada Inspections. Health Canada indicates that it conducts inspections as a means of strengthening the protection of the rights and safety of subjects in clinical trials and validating the integrity of trial data. Very briefly, clinical trial sites are inspected to ensure that they are adhering to the principles of Good Clinical Practice (GCP), and that they comply with the Division 5 Regulations under the Food and Drugs Act. However, as described earlier in this chapter, less than 2% of sites get inspected and there is serious reason to doubt the process by which those get selected. It seems likely that increased funding for the inspection program, as well as requiring sponsors to provide the information that will better enable sites to be selected on the basis of risk, would be important factors in improving inspections.

Given the profound shortcomings with regulatory inspections, it is important to ask whether by quietly falling dramatically short of even its most modest commitments, Health Canada is contributing to a false sense of security among clinical trial participants and Canadians more generally. This question becomes even more compelling when one considers that it is in fact the sponsor that does most of the work in terms of clinical trial oversight. Acknowledging that there is in fact no meaningful regulatory oversight would likely promote discussion and hopefully result in more promising solutions being enacted. For example, one possible solution would be to directly acknowledge that sponsors are solely responsible for clinical trial oversight, but that the regulator’s role is to establish an arm’s length oversight body to verify such inspections in order to mitigate concerns related to conflicts of interest and lack of transparency associated with relying on industry in this way. In addition, and specifically in relation to issues identified by my participants around poor sponsor-investigator training, (see Chapter 4), the regulator could also establish (perhaps in conjunction with provincial authorities) a training

285 As noted in the Auditor General’s 2011 Report, Health Canada regularly does not collect the information from sponsors that would enable them to effectively implement their risk based site selection strategy.
program to ensure that sponsor-investigators are qualified and prepared to fulfill their responsibilities.

7.6.4 Additional Suggestions

A. Inspections

As described earlier in this chapter, other problems with the inspection system go to the very limited window of time captured by a regulatory audit, as well as weaknesses associated with proportionate review. In relation to the former, one idea would be to formalize what apparently already tends to happen in practice and have the regulatory audit triggered by the New Drug Submission. Inspections taking place would then be formally retrospective, but would have a much more complete picture of the entire trial, which might lead to more accurate and complete inspection findings. While clearly such an approach would do nothing to protect the interests of the subjects in the trial under inspection, the findings could be used to create a site file against which the site could be assessed in future trials. This could mean, for example, that a site would have to undergo specific (re)training prior to being authorized as a site in a subsequent trial or that a site could be spot checked in future trials to help ensure problems and deficiencies are not repeated.

B. Establish Evidence Based Proportional Review

As discussed earlier in this chapter, the whole idea of proportional review requires baseline monitoring and empirical data to support the criteria upon which high risk or low risk designations are made. In relation to regulatory oversight, for example, research is required to verify whether and to what extent the criteria used to select sites in fact translate into the selection of the right sites—i.e., those where subjects are exposed to greater risk. In addition to the listed criteria\(^{286}\), it has been suggested that Health Canada also tends to select sites involved in industry-initiated studies over investigator-initiated trials (Ogilvie, 2012). While this makes sense on the one hand especially in the context of new breakthrough drugs, it seems to discount the imbalance in sponsor oversight between investigator and industry-initiated trials described

\(^{286}\) As per both the Inspectorate’s report of findings between 2004-2011, and the Auditor General’s 2011 report, the listed criteria by which sites are selected include: (a) number of clinical trials conducted at the site, (b) number of subjects enrolled in the specified clinical trial, (c) number of serious unexpected adverse drug reactions at the clinical trial site, and (d) observations made during past inspections.
earlier. Without empirical verification, there is no way to know whether important criteria are being omitted from consideration or to what extent the identified criteria correlate with subject risk.

C. New Drug Submissions: Penalties

Another concern described earlier in this chapter related to the conflict of interest that arises wherein the regulator charges user fees to sponsors to support the review process for New Drug Submissions. This is done by a number of regulators, and makes good sense from a cost recovery perspective. However, it does create a danger that the regulator will be less critical or thorough in its review so as not to jeopardize a revenue stream. This concern is increased where there are penalties for late reviews by the regulator as there are in Canada (Lexchin, 2011). While user fees are likely not going anywhere given their importance to cost recovery and supporting the review process, it may be desirable to eliminate late penalties. Presumably, such measures were implemented to ensure accountability of the regulator in meeting its targets. However, and as discussed elsewhere in this dissertation, Canada is keen to attract more clinical trial business and as such would want to protect its reputation among sponsors for providing timely reviews. In this context, a reasonable alternative to penalties for late reviews would simply be to rely on market pressures to ensure Canada meets its competitive targets; that is, where Health Canada fails to meet targets, Canada’s ability to attract trials will be negatively affected. While such a measure will obviously not eliminate the pressures that could compromise the effectiveness and thoroughness of regulatory reviews of New Drug Submissions, it could serve to reduce the negative incentives and also remove a possible motivation for sponsors opposing system enhancements that would tend to improve review efficiency.

7.7 Summary

The pharmaceutical industry has undeniably revolutionized medicine and continues to make important contributions to human health and wellbeing. However, as has been described

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287 See discussion on this point earlier in this chapter
288 As described earlier, Health Canada suggested in the Senate committee hearings that a number of industry sponsors are opposed to the implementation of an electronic submission system that would save time and resources and that this resistance has been a key reason such a system has not been adopted.
elsewhere in this dissertation, the clinical trials industry is a high stakes arena at many levels for many different stakeholders. From the pharmaceutical companies sponsoring the development and testing of new drugs, to the CROs who conduct the trials, to the monitors who help maintain the quality and integrity of the data and the researchers who interact with subjects to generate that data, as well as the vast array of research institutions, auxiliary service providers and related businesses, there are at once significant profits to be gained and losses to be suffered. In the midst of such high stakes, it can be somewhat easy to forget that the health and wellbeing of Canadians is what hangs in the balance—both as trial subjects and future consumers of the drugs being tested. With so much attention across the public and private sectors currently focused on protecting and expanding Canada’s share of the global clinical trial industry, it is critical to be aware of the weaknesses in the oversight framework so that steps can be taken to ensure that the health and wellbeing of Canadians are not subverted to broader economic interests. In this context, the problems and challenges described in this chapter, including but not limited to Health Canada’s heavy reliance on sponsors who are either in a profound conflict of interest or largely unaware and/or under supported in their oversight efforts and the continuing challenges facing research ethics boards, become deeply troubling and take on a renewed sense of urgency. There remains a great deal of work to be done to clearly demonstrate to Canadians that while economic interests are of course extremely important and compelling, such priorities do not trump their health and wellbeing.
Chapter 8: Contractual Agreements & Other Sources Of Legal Obligation

As described in detail in the previous chapter, at the macro and meso levels clinical trials in Canada are governed by a complex “system” of laws and policies that are shaped by a wide range of influences and interests. However, in addition to the laws, policies and codes of conduct outlined in Chapter 7, there are two other highly influential mechanisms functioning at the micro level that inform how particular organizations and individuals behave. The first is the web of contractual agreements entered into by the various parties to define the scope and substance of their individual responsibilities. The second are the consequences—in terms of legal liability and exposure—that arise when an organization or individual fails to adequately fulfill its legal obligations. This chapter will first describe some of the key contractual relationships that shape clinical trials in Canada. It will then shift focus and, building on the sources of responsibility outlined in this chapter and the one before it, and also drawing on some of the concerns raised in the previous data chapters, examine the sources of legal exposure for those working in the clinical trials industry in Canada.

8.1 Contractual Obligations

Contracts by definition confer rights and delineate responsibilities as agreed to by the parties involved. While it is impossible to discuss specifics without a concrete example, a hypothetical case helps to illustrate the parties generally involved and their typical contractual connections. Figure 8.1 depicts parties that might commonly be involved in a phase III clinical drug trial and the contractual links that would generally be formed by and between them.
Figure 8.1: Key Contractual Relationships in Outsourced Clinical Trials

8.1.1 Sponsor-CRO

The first relationship to explore is that between the sponsor and the CRO.\textsuperscript{289} Although every contract will be different and while it is beyond the scope of this paper to explore the range

\textsuperscript{289}Mello & Joffe (2007) in their discussion of the \textit{Abney v. Amgen} case influenced this portion of the discussion. That case did not involve a CRO; however, the way in which they unpacked and explained the various contractual relationships and their implications is effective, and I draw on that in my discussion of the above case scenario.
of approaches or typical clauses contained within the contract between sponsor and CRO, a few general comments are warranted. First, as mentioned above, the *GCP Guidelines* provide for the transfer of responsibilities from sponsors to CROs, with the specification that this needs to be in writing. A second general logistical observation is that due in large part to the tight timelines associated with contract negotiation prior to the start of a trial, master service agreements between sponsors and CROs are commonly adopted as a way of streamlining the contract negotiating process. Where there is some ongoing relationship between a sponsor and a CRO, these agreements provide a mechanism by which many of the standard challenging issues such as liability and indemnification can be determined as a baseline, leaving only the more study specific issues to be finalized for any given trial (Ranson, 2006). On the topic of indemnification, contracts between sponsors and CROs typically contain indemnification clauses whereby the sponsor indemnifies the CRO against any claims made by third parties for injuries and damage arising from the clinical trial of the sponsor’s drug, with such obligation being negated by the usual exceptions of negligence, misconduct or breach of contract by the CRO (Ranson, 2006). In terms of consequential damages (i.e., losses incurred by sponsor when a CRO fails to perform over and above cost of service (for reasons other than negligence, misconduct or breach))

291, pharmaceutical sponsors and CROs will often agree on some multiple of the value of the contract that is not too burdensome on the CRO, but allows the sponsor to recover more than just the direct costs of services that were to be rendered (Miller, 2004). In addition, the contract may well provide that both the sponsor and the CRO must maintain insurance to appropriate amounts against all claims that may arise during the life of the contract.

In terms of proprietary protections, the contract between the sponsor and the CRO will generally confirm the sponsor’s ownership of all records relating to the trial, and will often outline confidentiality provisions. Moreover, while it is not usual for intellectual property rights

290 These points, as well as a general discussion of some common contractual terms between sponsor and CRO are discussed in detail by Paul Ranson (2006).

291 Consequential damages can be exorbitant—and might include, for example, the cost of needing to delay, forego or repeat a clinical trial due to some failure on the part of the CRO.

292 Miller (2004) also suggested that sponsors may be becoming less willing to absolve CROs of consequential damages, which could in turn have implications for insurance premiums and coverage for contractors.
to arise during the course of clinical research, a typical contract confirms that the sponsor shall own all intellectual property rights associated with the drug and the study more generally arising before or during the clinical trial (Ranson, 2006). As such the CRO is generally obligated to formally transfer all such interests to the sponsor.

8.1.2 Sponsor/CRO-Site

The contract governing the relationship between the sponsor or CRO and site is generally referred to as a Clinical Trial Agreement. Where a CRO has been delegated all responsibilities and functions related to the conduct of the clinical trial, it will often be responsible for negotiating contracts with investigative sites and principal investigators. By way of these agreements, the institutional site (or investigator if a physician in private practice) accepts payment in exchange for the services required in the conduct of the clinical trial, and use of the facilities. The research protocol for the clinical trial in question is often referenced in the Clinical Trial Agreement as a way of clarifying expectations and delineating responsibilities (Mello & Joffe, 2007). Sponsors may be, but are not always parties to these contracts; that is, these contracts can be between the CRO and the site. In such instances, however, the sponsor would tend to be bound to the terms of the contract by a separate letter of agreement and indemnification, which would also commonly include making the sponsor responsible for indemnifying the investigator, research staff and the investigator’s institution including the REB from claims arising in relation to the clinical trial, except for claims arising from the investigator’s malpractice and/or negligence.294

293 While in the institutional context, the contract is often between the institution (as opposed to the investigator) the investigator is, at the very least, a signatory to the contract indicating that he or she has read and understands their responsibilities under the contract. As an example, please see the standard UBC contract template for services to commercial sponsors, available at: http://www.uilo.ubc.ca/sites/research.ubc.ca/files/uploads/documents/UILO/Service_Contract7026.pdf, last accessed August 29, 2013.

294 Section 5.8.1 of the ICH-GCP Guidelines stipulates that “the sponsor should provide insurance or should indemnify (legal and financial coverage) the investigator/the institution against claims arising from the trial, except for claims that arise from malpractice and/or negligence.”
8.1.3 Sponsor/CRO-Other

Monitoring functions are also frequently delegated to the CRO, which typically will have its own in-house monitoring staff, but may also contract with independent monitors to complete this function. In addition, the sponsor or CRO may contract with other auxiliary service providers for services it is not able to provide in-house. Finally, the sponsor or CRO must also contract with an ethics review board where one is not otherwise charged with reviewing protocols at the site in question. To respond to this need, private for profit REBs have emerged. As others have observed, this solution brings with it a variety of problems related to conflicts of interest and the independence and objectivity of the review which, while not absent in the institutional context, are arguably more pronounced where boards are either directly affiliated with the CRO or free standing for profit organizations (Lemmens, 2005). While extremely important, such issues exceed the scope of this dissertation. The point here is simply to identify this as yet another contractual relationship that forms part of the web of responsibilities and relationships in clinical trials.

8.1.4 Sites

In addition to their Clinical Trial Agreements, some sites contract with site management organizations (SMOs) to access additional research infrastructure, training and/or to improve their ability to market themselves to CROs and sponsors. SMOs tend to be used mainly by primary care physicians or other physicians based in the community, as opposed to those affiliated with a university or teaching hospital, which tend to have at least some support and infrastructure in place.295 One example of such an organization is the Trial Management Group, which according to its website is the largest SMO in Canada.296 The many benefits they advertise to CROs and sponsors include streamlined budget and contract negotiations when using their member sites.

Among the many responsibilities that accrue to the investigative site through the clinical trial agreement is subject recruitment, and general conduct of clinical trial activities as they relate

295 For additional information on the kind of infrastructure that may be available to institutional research units such as universities and teaching hospitals, please see the Genome B.C. Clinical Trials and Preclinical Infrastructure Asset Map developed in 2010. Available at: http://www.genomebc.ca/profile/publications/asset-maps/
296 http://www.tmginvestigators.com/index.html
to subjects and data collection. Investigators are responsible for ensuring that participants are properly recruited into the trial through the informed consent process. The informed consent document has been described as a “unilateral contract.” Such documents do not create binding obligations on subjects (who must be free to withdraw their participation at any time), but are binding on the investigator (and where applicable, the research institution)-who must act according to the promises and tasks described in the document.

In practice, many of the investigator’s trial responsibilities are subsequently delegated to a research coordinator and other research staff. However, pursuant to good clinical practices, the investigator is responsible for providing sufficient oversight and guidance to research staff engaged in trial related activities and retains ultimate responsibility for the conduct of the clinical trial at the site. As described in detail in Chapter 7, professional codes of conduct for physicians, nurses and other research staff also give rise to obligations that inform how those at the frontline of clinical trials fulfill their trial related responsibilities.

Hence, whereas the laws, policies and guidelines developed by actors at the macro (international and national governments and organizations) and meso (research funders, research institutions, professional bodies and others) levels shape the broad parameters within which clinical trials unfold, the micro level individual relationships are also defined to a large extent by contractual obligations. Together, these multiple components make up much of the Canadian legal framework governing clinical trials and establish the obligations and responsibilities of those sponsoring, managing and conducting clinical trials in Canada.

8.2 Potential Sources Of Liability

Failure to meet responsibilities defined at one or more of these levels can result in legal liability. Key sources of legal liability in the clinical trial context are described below.298

297 See for example, Mello & Joffe (2007).
298 This section is not meant to be exhaustive. I have selected certain key areas that are most relevant to the frontline focus of this study. To this end, and while I address to some extent sponsor and CRO exposure, the main focus is on investigative sites. In addition, it is worth noting that I have not addressed the potential liability of the regulator. For a superb discussion on this point, please see Halwani (2006). Her Majesty’s Research Subjects: Liability of the Crown in Research Involving Humans.
8.2.1 Breach Of Statute

Health Canada has expressly stated that their jurisdiction is limited to sponsors, and that “it is up to the sponsor to ensure that any person or organization contracted by them complies with the regulations.” This suggests that Health Canada (and more specifically in our context, the Therapeutics Product Directorate (TPD)) would hold the sponsor responsible for any act or omission contrary to statutory requirements—even where the activity in question was clearly contracted by the sponsor to a third party (typically a contract research organization (CRO)). There is no tort of Breach of Statute, but parties can be liable for specific penalties set out in the Act and Regulations. Any consequences in terms of fees or costs incurred as a result of the breach could then be sought by the sponsor as against the offending third party. This would most likely be by way of an action for breach of contract or negligence, and probably both.

8.2.2 Breach Of Contract

As can be seen from Figure 8.1, clinical trials involve a series of contracts between various parties. An implied (and sometimes express) term of each of these contracts is that the parties will fulfill all of their obligations, and do so in a competent manner. Where one party fails in this regard, the other party can bring a legal action for breach of contract. The primary purpose of damages for breach of contract is to compensate the plaintiff for losses suffered as a result of the failure of the defendant to fulfill its contractual obligations—or in other words, to put the plaintiff in the position s/he would have been in had the contact been performed. In

299 Regulatory Analysis Impact Statement accompanying Regulations Amending the Food and Drug Regulations (1024 — Clinical Trials).
1. Expectation interest: Damages are awarded in order to put the plaintiff in the position they would have been in if the defendant had performed their contractual obligations;
2. Reliance interest: Where the plaintiff changes their position based on the defendant’s promise, damages are awarded to put the plaintiff in as good a position as they would have been in prior to the promise; and
3. Restitution interest and unjust enrichment: where a plaintiff—relying on the defendant’s promise—has provided some benefit to the defendant who in turn fails to perform their contractual obligations. In such situations, the court may require the defendant to relinquish the value they received in order to prevent unjust enrichment. (Fuller and Perdue, “The Reliance Interest in
very general terms, in order to be successful a plaintiff must prove that a contract existed\textsuperscript{301}, and that the defendant was in breach of its obligations under that contract. Unlike claims of negligence (described further below), plaintiffs do not need to prove that the defendant’s breach caused the harm (causation). While this makes breach of contract theoretically easier to prove than a negligence claim, the damages to which a plaintiff will be entitled may be more limited.\textsuperscript{302} In considering the wide range of relationships and cases in which breach of contract claims may arise in relation to clinical trials, it seems likely that such claims would typically be brought both in contract and in negligence.\textsuperscript{303}

8.2.3 Tort (Negligence)

A third source of potential liability for the parties involved in clinical trials is in negligence (tort law). Very briefly, a finding of negligence requires that the defendant owed a duty of care to the plaintiff, that the standard of care has been breached and that the breach of the standard of care is causally related to the harm suffered by the plaintiff (Linden & Feldthusen, 2011; Picard & Robertson, 2007). While it exceeds the scope of this paper to consider the wide range of negligence claims that may be brought against or by any of the various parties in the clinical trials industry, some examples help to further illustrate the range of possibilities and the nature of the responsibilities and obligations in question.

\textsuperscript{301}The four basic requirements of a legally enforceable contract are:
1) Intention to create legal relations;
2) Parties to the contract are known and mentally competent;
3) Terms of contract are certain or ascertainable;
4) There is consideration (a balance of benefits and detriments on both sides). As described by Fridman, G. (1994) The Law of Contracts in Canada (3\textsuperscript{rd} ed). (Toronto: Carswell)

\textsuperscript{302}For a superb discussion relating to the relationship between tort and contract, and what is described as the diminishing gap between them, see Fridman, G.(1974) The Basis of Contractual Obligation: An Essay in Speculative Jurisprudence. 7 Loy L.A.L. Rev. Available at http://digitalcommons.lmu.edu/litr/vol17/iss1/1.

\textsuperscript{303}These include, for example: sponsors claiming breach of contract against CROs for failure to manage the conduct of the clinical trial adequately or at all; investigators claiming against CROs for failure to adequately monitor trial activities at the site; and subjects suing physician-investigators for failure to provide them with new information relevant to their ongoing consent.
8.2.3.1 CRO/Sponsor

In their role, CROs (among other things) monitor the generation, recording, and reporting of data from the clinical trials which will then serve to support the sponsor’s application to the regulator (e.g. Health Canada) to have its new pharmaceutical approved for sale and marketing. In Canada, this application is called the New Drug Submission. As has been mentioned elsewhere in this dissertation, any delay in obtaining marketing approval results in significant economic loss to the sponsor. It is entirely foreseeable then that a sponsor could sue a CRO where, due to alleged CRO negligence, the clinical trial data supporting the NDS application is compromised and the application is rejected.304 Somewhat surprisingly, there do not appear to be many examples of decided cases involving CROs, including claims brought by sponsors. One Canadian example in this regard involved a Canadian non-clinical CRO (LAB Research) being sued by a Canadian pharmaceutical company (Akela Pharma). The litigation arose from inhalation toxicology studies conducted by the Hungarian subsidiary of LAB Research. The problems related to the dry powder inhaler mechanism, and not the toxicology of the drug. The FDA rejected Akela’s submission for approval of the drug in January 2008 due to Good Laboratory Practice deficiencies in the tests conducted at the Hungarian site. This case highlights the nature and extent of damages which may be sought by a sponsor against a CRO in similar circumstances. In this case Akela sought, reimbursement for the costs of the studies, which came to €2.74 million…payment for the costs of repeating the studies (estimated at U.S.$5 million) and damages amounting to U.S.$20 million for licensing fees that the company [Akela] said it would have received from a potential partner.305

While this case could have provided some interesting legal guidance and insight as to the legal liabilities of CROs vis a vis sponsors, the parties settled this claim out of court in March 2009. It is also worth remembering that the cost of repeating clinical trials would have been substantially higher than the non-clinical tests, and that any clinical contract research

304 As alluded to in the previous section, this claim would likely be brought in both negligence and breach of contract. The argument in the latter would likely include that there was a breach of the implied term of the contract to conduct the services provided in a competent and reasonable manner.
organization would therefore face dramatically increased exposure in terms of study costs. In light of the earlier discussion on the importance of contractual relationships in clinical trials, it is also worth noting the kinds of contractual provisions related to liability and indemnification that were included in the agreement between Akela and LAB Research. LAB Research claimed that under the terms of the contract it had signed with Akela, “it could not be held liable for any incidental, indirect or consequential damages sustained by Akela; that the CRO’s liability was limited to the amount received for the toxicology studies; and that, even in the case of gross negligence, the liability could not exceed two times the amount paid for the work.”

From the facts available, and the tendency of the court to uphold contracts—especially as between two sophisticated parties—there does not appear to be any prima facie reason that the terms of the agreement would not have been binding.

**8.2.3.2 Subject Injury**

While there are still very few Canadian cases addressing liability for subject injury in clinical trials, it seems clear that litigation in this area is on the rise in the U.S. (Mello et al., 2003; Singh, 2009; Thomson, 2006; Zlotnik Shaul et al., 2005). Research related claims have traditionally been brought against researchers (and their institutions) predominantly in relation to issues pertaining to informed consent—for example, the subject not being advised adequately or at all of the risks involved in the research (Mello et al., 2003). The two leading cases on subject injury in Canada (Halushka v. University of Saskatchewan and Weiss v. Solomon) are good

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307 That a court would work to uphold the agreement between two parties in such a situation is further suggested by judicial comments in another case, Astellas Pharma Canada Inc. v. WellSpring Pharmaceutical Canada Corp. [2008] O.J. No. 3568. Astellas claimed Wellspring was negligent in how it provided its services and that as a result the clinical trial being conducted had to be terminated. Astellas sought $10,000,000 in damages for negligence. Welspring sought to limit its damages to fees paid by relying on a term of the contract that stipulated this was to be the case. However, another term in the contract stipulated an exception to this limitation in the event of negligence. The court dismissed Welspring’s application for summary judgment, indicating that a trial was necessary to determine the intent of the two parties in creating the contract. Again, while not decisive—this is in line with the general tendency of courts to uphold contractual rights and obligations particularly as between two sophisticated parties.

examples. More recently, and particularly since high profile cases such as that of Jesse Gelsinger, conflicts of interest and their disclosure have become an important aspect of informed consent litigation and in fact have come to dominate much of the focus and discussion related to industry sponsored clinical trials and protecting human subjects.

However, and as others have observed, both the spectrum of claims and the list of defendants have vastly expanded in recent years as “enterprising plaintiffs attorneys have turned to a daunting array of legal doctrines in framing law suits against those who perform and oversee research” (Mello et al., 2003). Such claims may now include allegations of defective products, fraud, negligent conduct and monitoring of research, intentional infliction of emotional distress, breach of contract and breach of privacy — to name but a few (Mello et al., 2003; Singh, 2009). Goldfarb (2013) highlights the 2003 class action case for breach of dignitary harm, *Diaz vs. Hillsborough County Hospital Authority*. The plaintiffs in this case (5000 pregnant women seeking prenatal care at the defendant hospital), claimed that they were duped into participating in a trial involving painful and risky procedures by an extremely faulty consent process. They sought damages not for physical injury, but for injury to their dignity (a lack of respect for their right to self determination). The case ultimately settled for $3.8 million.  

The list of potential defendants in subject injury claims is also changing and growing to include those directly and indirectly involved with the clinical trial. The most likely suspects include the researchers (principal investigator & others); research institution (university and/or hospital); individual research staff members; the REB and its individual members; consulting bioethicists; sponsor company; and the CRO and monitors (Mello et al., 2003; Singh, 2009; Thomson, 2006; Zlotnik Shaul et al., 2005). The very high profile case of Jesse Gelsinger, for example, named the trustees of the university and two hospitals affiliated with the research, the investigators, the sponsoring company, the former dean of the medical school and the bioethicist who advised the researchers to conduct the study in healthy adults instead of terminally ill infants (Fretwell Wilson, 2009). Again, this case settled out of court for an undisclosed amount.

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Weiss v. Solomon (1989), 48 C.C.L.T. 280 (Que. Sup. Ct.). In Weiss v. Solomon, the researcher and the institution were held liable for the plaintiff’s injuries. The institution was held vicariously liable for the negligent ethics review conducted by its REB.

309 For a review of this, please see Hanlon & Shapiro (2003). Ethical Issues in Biomedical Research: Diaz v. Hillsborough County Hospital Authority. Human Rights, 30(2), 16.
though the bioethicist was dropped from the suit prior to its conclusion (Zlotnik-Shaul et al., 2005).

There are a number of benefits to casting such a wide net. In addition to the evidentiary advantages it brings—i.e., the ability to examine each party for discovery, and disclosure of documents (Picard & Robertson, 2007), it also increases the number of parties potentially liable to pay any settlement or judgment. However, the dearth of decided cases in this area (most particularly in Canada) makes it extremely difficult to assess the extent to which a court will ascribe fault to defendants with less than direct connections to the harms suffered by plaintiffs (Zimmerman, 2005; Zlotnik Shaul et al., 2005). Finally, Mello et al. (2003) suggest that other advantages might also include increased media exposure as more high profile individuals and institutions are named as parties.

8.2.3.3 Sponsor Liability: A Closer Look

Despite the dearth of directly applicable case law in Canada, there is little question that investigators, their staff and their institutions (hospitals or universities) can and will be held accountable in negligence for injuries to human subjects arising from clinical trials—that is—these parties owe a duty of care to the patient subject and will be held accountable either directly or indirectly through vicarious liability. While there is quite clearly a duty owed between the investigator (and investigator’s institution) and the subject, it is arguably less clear that a duty of care exists between the sponsor and/or CRO and subjects. In reviewing the limited precedents (American) that were available at the time Mello & Joffe (2007) concluded that “there appears to be no precedent supporting the notion that sponsors of research conducted at academic medical centres have direct legal duties-of any kind to subjects.” A main factor supporting this conclusion (and as was explicitly stated by at least one of the court decisions cited) was that the sponsor did not conduct the trial. In the case of a CRO that contracts with a sponsor to assume all responsibilities related to the oversight and management of a clinical trial, the dynamics would seem to be similar. The CRO does not conduct the trial, for in much the same way as the

310 The extent to which there may be a fiduciary duty owed is explored in the next section.
311 These included Abney v. Amgen (6th circuit appeals); Drake v estate of Isner; Hamlet v. Genentech (NC Sup Ct).
sponsor would if no CRO were involved, it contracts with investigative sites and investigators for this purpose.

While the above discussion based on a limited number of American cases seems to suggest that a plaintiff could have a tough uphill battle to successfully sue either a sponsor or a CRO for injuries sustained in a clinical trial, it is not at all clear that other courts in other jurisdictions would be persuaded by such decisions. Even if there is not an established duty of care as between sponsors and subjects, Canadian courts have traditionally adopted an expansionist approach to establishing whether or not a duty of care exists as between two parties, based on assessing the degree of foreseeability of harm to the plaintiff and the proximity or closeness of the relationship. 312

As seen above, the sponsor has a number of obligations (which may in turn be delegated in whole or in part to CROs) both under the Regulations and international guidelines that could arguably give rise to a duty of care to plaintiffs. For example, it is the sponsor’s responsibility to ensure:

- the scientific soundness of the protocol, and that the trial is conducted in accordance with the protocol;
- that there are quality assurance mechanisms in place;
- that the protocol is approved by an REB at each site;
- that medical care and medical decisions relating to the clinical trial are provided by a qualified investigator;
- that each individual involved in the trial is qualified by education, training and experience to fulfill their trial related responsibilities; and
- that free and informed consent is obtained from participants prior to their involvement in the trial (among others).

Despite the views expressed above by some U.S. courts, it seems entirely possible that a court could find a sponsor either directly liable for failing to ensure that such obligations were fulfilled, or for the negligence of an intermediary through the doctrine of vicarious liability. While certainly the relationship with the subject is not as close as that between the investigator and subject, the sponsor is the driving force behind the trial with the most to gain and with ultimate responsibility to ensure those conducting the trial on its behalf do so in accordance with

312 See Currie (2004), for a great discussion of the development/evolution of the duty of care tests in Canada.
established standards. Whatever the ultimate outcome, and as speculated by Thomson (2006), it is very likely that any litigation will name the clinical trial sponsor as a defendant since “their involvement and obligations are too great and their pockets are too deep to be ignored by plaintiffs, regardless of their level of active participation in the clinical trial.”

Likewise, where a CRO is involved it seems probable that it too would be named as a defendant. Although there do not appear to be any Canadian cases directly on point, there is at least one American decision addressing the specific question of whether a CRO can owe a duty of care to human subjects. In Wawrzynek v. Statprobe et al., the defendant CRO (Statprobe) was seeking summary judgment dismissing the plaintiff’s claims against it, including a claim in negligence. The plaintiff in this case claimed she suffered injury caused by a medical device (ADCON-L) that was applied during spinal surgery. Statprobe had provided extensive clinical trial services to ADCON-L’s manufacturer, including but not limited to clinical trial monitoring, data management, and final report writing. Based on data from the clinical trials monitored and reported by Statprobe, the FDA gave conditional approval to the sponsor (Gliatech) to manufacture and distribute ADCON-L. Subsequently, it came to light that the sponsor had included revised and inaccurate data in the report to FDA, and that this had been done with the knowledge of Statprobe. Ultimately Gliatech entered a guilty plea for, inter alia, submitting a false report to the FDA. No formal action was taken against Statprobe. The plaintiff alleged that Statprobe’s involvement in the study and its awareness of the inclusion of the revised data supported a claim of negligence. Statprobe claimed that it did not owe the plaintiff a duty of care. In his decision, the judge found that Statprobe had failed to demonstrate that as a matter of law it owed no duty to the plaintiff and determined that this would be decided at trial. While this was only a decision denying Statprobe’s summary judgment application and therefore not decisive on the question of whether Statprobe did in fact owe a duty of care to the plaintiff, it is interesting to note that the judge pointed specifically to the extensive involvement of the CRO in the management (not conduct) of the clinical trial as one ground which arguably gave rise to a

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313 Of course, where the investigator is both sponsor and investigator (in investigator-initiated trials), the question of sponsor remoteness becomes entirely moot.
duty of care to the plaintiff in this case. Although certainly not decisive, it does at the very least suggest that the law on whether or not a CRO can owe a duty of care to a subject is not decided.

8.2.4 Fiduciary Duties

Finally it is interesting to consider how a finding of fiduciary duty or relationship might impact litigation arising from clinical trials. The application of the fiduciary concept is the subject of much confusion and ongoing debate. In fact, it has been observed that “there are few legal concepts more frequently invoked, but less conceptually certain than that of the fiduciary relationship.”

In the context of clinical trial litigation what can be said with some certainty is that some relationships are more likely to be deemed fiduciary-or at least to give rise to fiduciary obligations-than others. The next section will look very briefly at how the fiduciary concept has been applied, identify the most likely candidates for fiduciary relationships in the clinical trial context and very briefly detail the consequences that such a finding would have on the conduct of litigation in this area.

8.2.4.1 Tying Down An Elusive Concept

As noted, determining whether or not a given relationship or obligation is fiduciary is not easy. As an initial definition, the fiduciary relationship is broadly described as one in which, “one person is under a duty to act for the benefit of the other on matters within the scope of the relationship. [Such] relationships…require the highest duty of care.”

An early, but frequently cited, judicial consideration on this topic suggests that,

Relationships in which fiduciary obligations have been imposed seem to possess three general characteristics:
1. The fiduciary has scope for the exercise of some discretion or power;
2. The fiduciary can unilaterally exercise that power or discretion so as to affect the beneficiary’s legal or practical interests;
3. The beneficiary is peculiarly vulnerable to or at the mercy of the fiduciary holding the discretion or power.

In subsequent decisions, the Supreme Court of Canada has elaborated further on this, adding other indicators (though not hallmarks) of fiduciary relationships as involving “disclosure of

confidential information, trust, confidence and vulnerability.”

It should be noted however that while most fiduciary relationships will bear these characteristics, it seems that they are neither necessary nor sufficient. Instead, “the prevailing judicial view appears to be that even if all the indicia are present, a relationship may not be fiduciary, and conversely, if none are present, a relationship may nevertheless be fiduciary.” (Litman, 2002, p.88) To supplement the indicia, then, other measures are necessary and in this regard, further tests suggested by the Supreme Court of Canada are helpful. As summarized by Litman,

pursuant to these tests, a relationship is fiduciary if there is either (i) an undertaking by a party (whether unilateral or as part of an agreement, or even legislatively imposed) to selflessly and exclusively dedicate oneself to the interests of another; (ii) a reasonable expectation of such dedication; or (iii) a reasonable basis for reliance on such dedication. (2002, p.89)

Two additional points also bear mentioning. First, while there is a list of recognized fiduciary relationships (including for example, physicians towards their patients and agents towards their principals) fiduciary obligations can arise outside of such relationships. Second, not all obligations within a recognized fiduciary relationship will be deemed to be fiduciary (Miller & Weijer, 2006a).

8.2.4.2 Researcher As Fiduciary

Bearing this admittedly preliminary description in mind, it is interesting to briefly consider the extent to which there may be fiduciary obligations within the complex web of relationships that are such an integral part of clinical trials. Undoubtedly the most obvious potential fiduciary relationship in this context is that between the physician-investigator and patient-subject; however, even this has been the subject of much debate.319 While it exceeds the scope of this paper to delve into the specifics of this debate in any detail, a couple of brief comments are appropriate. First, the argument against the finding of a fiduciary relationship is

319 This is still the subject of debate in the literature. For arguments against the clinician/researcher and patient/subject being fiduciary in nature, see for example Brody, H. and Miller, F.G. (2003); Miller, F.G. and Rosenstein, D. (2003); or Morreim, E.H. (2005). For what are, in my view, the more compelling arguments that such a relationship is fiduciary, see Miller, P.B. and Weijer, C. (2006a).
typically grounded in the claim that unlike clinical care, where the goal is the therapeutic benefit of the patient, the goal of research is to advance knowledge. Given this ‘non-patient’ oriented goal, and the constraints it places on the physician-investigator to attend to the individual preferences and therapeutic goals of the patient, this side of the debate claims that “physician investigators are not, and can not possibly be, fiduciaries” to human subjects. (Morreim, 2005, p.586). In contrast, the other side of the debate tends to focus on inter alia the vulnerability of the patient-subject and the fact that they also rely on the physician-researcher for care, much as in the therapeutic relationship. As Lemmens and Freedman note, “the fiduciary nature of the doctor-patient relationship remains a cornerstone of medicine and should not be abandoned when physicians and patients are involved in research.”(2000, p.557) Moreover, even though there may, prima facie, be a conflict between the goals of research and the goals of care, such conflict does not necessarily preclude the existence of a fiduciary relationship. As Litman explains, while it is true that Canadian courts have, in the context of insurance cases, indicated that it is ‘conceptually difficult to apply fiduciary law to parties who are inherently in a conflict of interest,’ it would be a mistake to regard inherent conflict between parties as an insuperable hurdle to a fiduciary relationship. In the case of a permitted or inescapable conflict of interest, the common law rule is that the fiduciary must resolve the conflict in favor of the beneficiary. Implicit in this rule is the notion that a relationship may be fiduciary notwithstanding the existence of inherent conflict of interest. (2002, p.90)

8.2.4.3 REB As Fiduciary

While a more distant relationship than the investigator-subject, reasonable arguments could also be made in support of fiduciary obligations as between REBs (and their home institutions) and human subjects. For example, it is clear that REBs are in a position to exercise their discretion in such a way as to affect the rights of human subjects (Pullman, 2001; 1999). As discussed in Chapter 7, these boards have primary responsibility for reviewing protocols and determining whether to allow such protocols to proceed depending on whether they meet the applicable standards for the conduct of ethical research (for example, such as those established by the Tri-Council Policy Statement2 (TCPS2) as minimum requirements). Where the REB determines that the research does not meet such standards, the research is not permitted to go ahead until the concerns are adequately addressed. Hence, the REB’s review and resulting decision impact the interests of human subjects in determining what research is and is not available for them to participate in. Moreover, potential subjects are in a position to have to trust
that the REB has reviewed the protocol, weighed the risks and benefits as well as other aspects of the proposed research and deemed it to meet the requisite ethical standards as they are not in a position to check and verify this themselves (Pullman, 1999). Hence, it is at least arguable that the relationship between REBs and human subjects meets all three of the indicia of fiduciary relationships outlined above. In relation to the second test outlined above, it is widely held that the primary obligation and responsibility of the REB is to protect the interests of human subjects by ensuring that the principles governing ethical conduct of research involving human subjects are adhered to. Such responsibilities are outlined in Division 5 of the regulations under the federal Food and Drugs Act320, as well as the TCPS 2 and GCP Guidelines. As such, it seems quite reasonable to characterize the REB as having a legislatively imposed mandate to protect the interests of human subjects in research, and that consequently the public (as potential research subjects) would have a reasonable expectation that this would happen. Hence, application of both the indicia and other tests developed by the Supreme Court of Canada (summarized above by Litman) could arguably support the claim that the REB at the very least has some fiduciary obligations in relation to human subjects.

8.2.4.4 Sponsor As Fiduciary

In contrast, it seems highly unlikely that any fiduciary obligation or relationship would be found as between the CRO and/or sponsor and human subjects, and in fact such a claim was rejected by an American court on the grounds that “the company’s reasons for sponsoring the trial were not primarily to benefit the subjects” (Mello & Joffe, 2007).

8.2.4.5 Implications Of Fiduciary Obligations And Relationships

Finally, and very briefly, a finding that a fiduciary duty is owed stands to have a variety of very real consequences. Not least among these are the implications such a designation will have on the way in which a legal action for breach of such a duty proceeds. Some of the key differences from a negligence claim include an extended period of time in which the plaintiff may bring the action, compensation or damages awards unfettered by the doctrine of foreseeability, and perhaps most significantly, a reversal in who has to prove that the breach caused the harm at issue (Litman, 2002). In a negligence action, the so called “burden of proof”

320 R.S., 1985, c. F-27 (Division 5 of the Food and Drug Regulations (C.R.C., c. 870))

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is on the plaintiff; however, in fiduciary claims, the onus is reversed so that the alleged fiduciary must prove that regardless of his or her breach, the beneficiary would have suffered the alleged damages (Litman, 2002). Hence, while it can be a difficult case to make and while there is lots of legal uncertainty around the application of this concept, incorporating a claim for breach of fiduciary obligation can significantly alter the way in which litigation unfolds.

8.2.5 Criminal Law

The criminal investigations into the “blood scandal” of the late 1990s and the resulting charges strongly indicate that criminal charges arising out of negligence in the field of human experimentation are entirely within the realm of possibility; however, to date, criminal law has not yet been applied to medical research (Marshall, 2000). The applicability of the Criminal Code to medical research is further indicated by the Law Reform Commission of Canada’s comment that “the traditional offences against the person…[under the Criminal Code] make it possible to penalize those causing harm to a subject who has not given valid consent to an experiment” (LRCC, 1989). While containing no direct or implied discussion of research, the Criminal Code has a number of provisions that could conceivably apply to research. Of particular interest are the sections that relate to assault (s. 265), consent to death (s.14), duty of persons undertaking acts dangerous to life (s.216), duty of persons directing the work of others (s.217.1), injury or death resulting from criminal negligence (s.219 and 220), acceleration of death (s.226), and the duty to provide the necessaries of life (s.215) (Marshall, 2000).

8.2.6 Charter

Last, but not least, are the applicable sections of the Canadian Charter of Rights and Freedoms. Again, this document does not consider research, research subjects or those conducting, sponsoring or overseeing research directly or at all. However, it is certainly possible that sections 7, 8, 15 and 24 could all be applied to protect research subjects. Section 7 protects the “life, liberty and security of the person”, which in the research context could be translated into respecting, inter alia, the autonomy of the individual, and could provide the basis of a cause of action where valid consent was not obtained from the participant. Section 8 states “everyone has the right to be secure against unreasonable search or seizure”. This section has been interpreted as prohibiting the gathering of human material (e.g., blood) without consent or appropriate court or statutory warrant. This could also have an impact on the use or misuse of
personal health information collected by the researcher. Although from a somewhat different angle, section 15 (the equality provision) may also be applicable in helping to ensure equal access to the benefits of, and protection from the burdens of, research. Finally, section 24 discusses possible remedies where one’s rights under the Charter have been violated. As the Charter forms part of our Constitution, all other pieces of legislation must conform to its principles. Further, even though the Charter only applies to actions by government, this has been interpreted more broadly to include government funded research, research in hospitals, and government funded institutions. It is unlikely, however, that research without any government funding or with no connection to a publicly funded institution, would come within the parameters of the Charter (Marshall, 2000).

### 8.3 Clinical Trial Litigation: An Evolving Field

While there is a suggestion in the literature that litigation arising from injury to subjects participating in clinical trials is on the rise (Mello et al., 2003; Mello & Joffe, 2007; Singh, 2009 Zarzeczný & Caulfield, 2012; Zlotnik Shaul, Birenbaum, & Evans, 2005), it remains very much an evolving area with only a relatively small number of decided cases in the U.S. and almost none in Canada. There are a number of possible reasons for this. First, it may be the case that there simply are very few injuries or other harms (breach of privacy, for example) suffered by subjects. In considering this possibility, it is worth reflecting on the findings reported in Chapters 4-6 of this study. For example, site staff raised concerns about level of training in relation to both investigators (Chapter 4) and staff (Chapter 5) pertaining to their respective obligations under GCP Guidelines and other regulatory mechanisms ostensibly in place to promote safe and ethical conduct of clinical trials. Physicians failing to follow protocol, lack of clear study documentation and weak consent processes were among the specifically enumerated areas of concern that suggested training gaps. As described in Chapter 6, site participants also reported at least in some instances feeling pressured particularly by CROs to at times cut corners or otherwise act inappropriately in the interest of saving time and/or expense. Inappropriately accessing patient databases to facilitate recruitment efforts was just one example provided. The

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321 As such, the Charter would apply to intra-mural research by a government. This would include, for example, research conducted directly by the Department of National Defense as well as Health Canada.
combination of inadequate training at the site level and the intense pressures from CROs and sponsors to conduct ever more complicated trials on tighter budgets in shorter time simply does not support the conclusion that subject injury of one form (e.g., breach of privacy) or another (e.g., physical injury) is an exceedingly rare occurrence.

Another possible explanation is that, particularly in cases involving subjects with significant acute or chronic health concerns, the extent of damages that are likely to be awarded may simply not be sufficient to justify the costs associated with bringing a law suit. This is because the damages will be based on the degree of change in the subject’s condition that resulted from the alleged negligence, and in such instances the plaintiff’s condition would not go from good to bad, but from bad to some degree of worse. There are also challenges associated with proving causation, including the extent to which the harm suffered resulted from the negligence of the defendants instead of the underlying condition.

Despite the above obstacles, and as described above and elsewhere, it seems that litigation in this area is on the rise and that plaintiffs in individual, and increasingly in class action, suits are diversifying their approach in terms of both the basis of their claims and those against whom they are seeking damages (Mello et al., 2003; Singh, 2009). If indeed the threat of litigation can to some extent motivate positive behavioral change and promote accountability (Mello et al., 2003; Shah, 2013), then the apparently rising tide in this regard may help reinforce calls for positive change at all levels, including heightened clarity, transparency and oversight from the regulator, increased monitoring and support (including providing realistic timelines and budgets) from sponsors and CROs, and improved training, oversight and practices at the frontlines. It seems likely that such initiatives would go a long way towards promoting safe, ethical conduct of clinical trials in Canada and help ensure the protection of the health and wellbeing of Canadians in this extremely high stakes industry. These and other initiatives are described further in Chapter 9.
Chapter 9: Conclusion

This dissertation examines investigative sites and their relationship with CROs to offer insight into (a) the challenges that arise at this interface and (b) the extent to which Canadians are protected by Canada’s clinical trials oversight framework. This is done in two parts, the first being a qualitative interview study and the second is a critical ethical and legal analysis of the law and policy frameworks governing clinical trials in Canada. This critical assessment is informed by and sensitive to the issues identified in the findings of the interview study, and as such moves beyond a normative account to provide some insight on the extent to which the legal and policy frameworks are attune to current research realities at the Canadian frontlines.

As my work on this research study progressed, findings emerged that challenged a number of what I perceived to be common ideas or narratives about clinical trials, and the way such trials are regulated in Canada. Key among these are the ideas that:

- If clinical trials could be extricated from profound commercialized interests of pharmaceutical sponsors, there would be a return to a golden age of high quality, objective and unbiased research;
- Health Canada is the body that keeps sites, CROs and sponsors in line and makes sure their obligations are met so that the interests of Canadians and human subjects are protected;
- Clinical trials bring potential medical benefits both in their own right and in terms of the drugs they ultimately support to market. It is on the basis of this potential therapeutic benefit and hope for health improvements that the risks associated with clinical trials—and with drug development and marketing more generally—are justified by regulators, investigators and even by industry sponsors themselves.

I have structured the discussion in this conclusion around the issues that arose under each of these narratives, and describe each of them in turn below.

9.1 Narrative A: If clinical trials could be extricated from profound commercialized interests of pharmaceutical sponsors, there would be a return to a golden age of high quality, objective and unbiased research.

The problems associated with commercialized clinical trials are many and varied, with some having received more attention than others. Issues associated with the identification,
management and mitigation of conflicts of interest in relation to both the academic and non-academic sectors for example have garnered significant attention (AAMC, 2008; Angell, 2008; Ferris & Naylor, 2006; Krimsy, 2003; Krimsy, 2006; Lemmens & Freedman, 2000; Lemmens, 2004; Lenzer, 2008; Lipton et al., 2004; Shnier et al., 2013; Weinfurt et al., 2009). Biased or otherwise scientifically or ethically flawed trial designs, suppressed negative results, ghostwriting and other questionable reporting practices have also been well documented and discussed (Mirowski & Van Horne, 2005; Ross et al., 2008). More directly relevant to the focus of this dissertation, the trend towards outsourcing in order to increase flexibility of workforce and ultimately conduct faster, cheaper clinical trials has resulted in a booming CRO industry, bringing with it some additional challenges (Adobor, 2012; Fisher, 2009; Mirowski & Van Horne, 2005; Schipper et al., 2011; Shuchman, 2007). As explored in Chapter 6, while there are benefits associated with the rise of the CRO for both sponsors and sites alike, there are also some important areas of concern, many of which have received little attention from academics or regulators. The findings of this study suggest that increased pressures on sites, delayed and ineffective communication, and a narrow results-oriented focus by CROs that contributes to poor problem identification and solving abilities are only some of the challenges that can emerge between CROs and the sites they work with and manage. Such challenges, and a number of others that were reported by my participants (see Chapter 6), are exacerbated by an increased fracturing of accountability with the introduction of the CRO and a number of deficiencies in Canada’s oversight system for clinical trials as described in my discussion of issue 2 (below), and more generally in Chapter 7.

Although the specific problems and issues relating to commercialized clinical trials have received varying degrees of attention (with some being more or less ignored), as a group they have been the subject of a great deal of academic and policy analysis. The prevalence and scope of these writings, it could be argued, have in fact eclipsed to a great extent discussion of other challenges that exist in relation to another category of clinical trials taking place primarily in academic institutions-namely investigator-initiated (or grant funded) trials. However, the data that emerged from this study supports the more limited suggestions in the literature that other challenges do in fact exist and are sources of real concern. Many of the internal site challenges raised by my participants reflect concerns that have been raised by others. For example, the fact
that investigators often fail to provide sufficient oversight has been discussed in the academic literature (Fisher, 2006; Mueller & Mamo, 2002; Roberts et al., 2006; Speicher et al., 2012). However, what has not been done previously is to look at these problems in the context of the oversight and regulatory framework for clinical trials in Canada and assess the extent to which they are sufficiently addressed (or not) and if not-what changes may be required to ensure that they are. As seen and discussed in great detail in Chapters 4 and 5 of this dissertation, gaps in investigator training and familiarity with their research roles and responsibilities, lack of investigator involvement with the research team and research processes, as well as insufficient staff training and problems with institutional support are among some of the many hurdles raised by my participants working at academic health centres and corroborated by participants in other categories.

What emerges from the data, then, is twofold: (1) that there are many investigators who fulfill all of their responsibilities and who are well trained, provide sufficient oversight, and seek appropriate input from their qualified staff; but also (2) that this can not be assumed or taken for granted. Where such elements are absent, the data identifies concerns with excessive workload, insufficient oversight, poor fit between studies and sites, and reluctance to bring the concerns or issues forward for discussion. As one participant notes, in such circumstances things start to “fall through the cracks”. It seems reasonable to expect that such concerns could have profoundly negative consequences not only for the quality and integrity of the clinical trial and the data it generates—but also for the safety and wellbeing of the human subjects who participate in them.

While such problems are not unique to investigator-initiated trials and can certainly arise in the commercialized context too, the concern is exacerbated in the former context. This is in large part because of the next erroneous narrative; that is, that Health Canada as the federal body responsible for regulating clinical trials and drug development oversees these trials. This will be discussed in greater detail in the next section; however, it is relevant here to highlight that while on paper there are three sources of oversight for clinical trials—Health Canada, REBs and sponsors—in actual fact the oversight and monitoring of clinical trials falls to sponsors. Whereas this might be relatively effective for industry sponsors who are highly motivated by fiscal considerations to ensure the quality and integrity of their trials (setting aside for the
moment concerns associated with such self-regulation in such a highly competitive, high-stakes industry, it leaves a rather large gap when the sponsor (the investigator in investigator-initiated trials) is unfamiliar with its responsibilities and does not have the resources, time or support to ensure those responsibilities are met. Such concerns were raised by many of my site participants, and have also been addressed to varying degrees by others (Arbit & Paller, 2006; Lad & Dahl, 2013; Pierce, 2004; Sedgeworth & Delwani, 2006; Shah, 2013; Tyndall, 2008).

Interestingly, the two realms (investigator and industry-initiated research) are not as distinct or separate as they might seem. Many investigators and their staff will work across both—that is, investigators and their research teams will conduct both investigator-initiated trials and industry-initiated trials. Although one might reasonably expect investigator (and staff) exposure to the highly structured and quite stringently monitored industry trials to help foster an awareness and familiarity with the requirements under the GCP Guidelines and applicable legislation (Food and Drugs Act and Division 5 Regulations), it seems that this is not necessarily the case. One possible explanation for this lack of knowledge transfer—and one that was raised in the data—is the extent to which sponsors “babysit” sites. That is, in the case of industry-initiated clinical trials investigators and staff do not have to rely on their own knowledge—but can rely instead on their industry overseers to ensure they are doing things appropriately. Given the problems associated with training for investigators and site staff described in Chapters 4 and 5 in particular, this is hardly surprising. Examples of problem areas discussed by site participants range from documentation issues to protocol design and consent issues. Such gaps are troubling for a number of reasons. First, sites are responsible for the conduct of the trial at the site—and for the wellbeing of the subjects. If they are relying on sponsors/CROs to ensure they are fulfilling their responsibilities—then it is reasonable to conclude they are not being sufficiently independent of the sponsors’ powerful interests to do this effectively. Second, even with high levels of oversight, the sponsor/CRO is not there all the time. Ensuring that investigators and

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322 Such problems include lack of clear standardized training requirements, and problems with accessibility and availability, among others.
323 While some areas covered by GCP are also covered by the TCPS2 (which should be more familiar to academically affiliated investigators given mandatory tutorial) this does not seem to completely eradicate the problem. For example, issues associated with how consent was obtained were still raised by some of the participating research coordinators.
their staff are well trained and competent would seem a critical element of ensuring safe, quality clinical trials. Finally, and particularly relevant to the point being made here—where there is no industry oversight, poorly trained investigators and staff are left to their own devices essentially without any backup or checks.

The above suggests that increased oversight is particularly important for investigator-initiated clinical trials. This could include a combination of strengthening the mechanisms that are already in place, but also creating new ones. Klitzman (2013) identifies the question of whether the relative degree of scrutiny brought to bear by research ethics boards should vary depending on whether a protocol is industry or investigator-initiated as one that is in critical need of additional debate and research. Until such debate is resolved, both regulatory inspectors and research ethics boards should be advised not to reduce their scrutiny of investigator-initiated studies based on (mistaken) assumptions that academic investigators are familiar with, and meet, all of their research related obligations. In addition, however, some kind of additional public sector oversight is likely warranted to provide an additional systemic check. One possibility in this regard could be heightened involvement from the relevant university’s research office (not the REB), or on a broader scale, an increased role for the health authority or region—perhaps through something like the Clinical Trial Support Units\(^\text{324}\) that already exist in some areas.

**Recommendation: Increase oversight for investigator-initiated trials by strengthening current mechanisms and implementing additional public sector oversight.**

### 9.1.1 Should GCP Apply To Investigator-Initiated Trials?

As alluded to above, many of the gaps in investigator knowledge that become particularly problematic in investigator-initiated studies are in relation to sponsor requirements set out in the *GCP Guidelines* (and which have subsequently been incorporated to varying degrees into the regulatory framework).\(^\text{325}\) An interesting question is to what extent gaps in this regard are important to subject protection and/or the integrity of investigator-initiated trials. This question

\(^\text{324}\) See description of clinical trial support units, their role and the services they provide in Chapter 2.

\(^\text{325}\) For example—while *ICH-GCP* goes into detail in relation to roles and responsibilities of sponsors, investigators, REBs, monitors etc—and describes the relationship between CRO and sponsor—the only part of the *GCP Guidelines* that are explicitly incorporated into the regulations are a subset of the sponsor regulations.
goes beyond looking simply at whether there is compliance with the rules and looks at the substance of the rules themselves—and whether they are in fact useful and effective in meeting their stated goals of subject protection and data quality and integrity.326

While a detailed exploration of this question vastly exceeds the scope of this dissertation, a brief discussion is appropriate. It is important to acknowledge that the process and content of the ICH Guidelines are not without their critics. Developed in 1996, the preamble to the ICH-GCP Guidelines states that the purpose of the guideline was “to provide a unified standard…to facilitate the mutual acceptance of clinical data by regulatory authorities…” The countries directly involved in this process were the European Union, Japan and the U.S.. Canada and a number of other countries held observer status. As Lang et al. (2010) note, criticisms of the GCP Guidelines consistently include that it is outdated, that there should have been more countries involved in its development, and that it is far too focused on the needs of industry and drug registration with minimal representation from academia and noncommercial organizations.

Of particular relevance to the issue in question (i.e., the applicability of GCP to investigator-initiated studies) there is also some suggestion in the literature that requiring academic physicians to comply with GCP standards is wrong headed and is having and will continue to have negative implications for investigator-initiated trials. Some critics argue, for example, that while the potential for conflicts of interest in commercialized clinical trials make the GCP requirements reasonable, such measures are not required in the context of academic or investigator-initiated trials “where commercial conflicts of interest are mostly not an issue” (Tyndall, 2008). In such cases, these critics argue, the costs associated with GCP compliance

326 For example, as described by Health Canada in its Guidance Document for Industry on the ICH Good Clinical Practice (GCP) guideline: “GCP is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.”

327 Whether and to what extent this perception that investigator-initiated trials are relatively immune from commercialized conflicts of interest is correct would need to be assessed in relation to the complex funding arrangements of academic clinical trials (many of which are funded in whole or in part by industry (Johnston & Vohra, 2006). Moreover, even where there may be less risk of commercialized conflicts of interest in the context of academic clinical trials,
present a major obstacle that seriously threatens academic trials (Tyndall, 2008). Others argue for a more proportional approach to the application of certain GCP requirements (such as monitoring and SAE reporting for example) that would reduce costs of such activities in the “lower risk” academic context (Bergmann et al., 2010; Swank et al., 2011; Morice, 2003).328

Many of the concerns with the development process and perhaps even some of the substance of the GCP Guidelines are likely well founded; however, the suggestion that these standards ought not apply to investigator-initiated research is highly problematic. As has been widely acknowledged by Health Canada and others, “compliance with [the GCP] standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.”329 Many of the requirements set out in the GCP Guidelines relate to clear documentation and being able to demonstrate accuracy and precision in the execution of research and recording of data. Other critical provisions address protocol adherence and consent requirements. Interestingly, these are the provisions that, according to my participants330, seem to be particularly problematic for investigator-initiated studies. As their name in fact suggests, such standards simply constitute good practice, and it hardly seems reasonable to lower the standards in any context, regardless of who is funding or sponsoring the research.

This position is further supported by the fact that far from being immune to conflicts of interest as some critics suggest, there is ample evidence indicating that a variety of interests, commercial and otherwise, can compromise the conduct of investigator or grant funded studies.

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328 It is worth noting that much of the literature suggesting that GCP requirements should not be applied-or be restricted in their application to academic clinical trials emerged from Europe following the 2004 implementation of the GCP Guidelines into the national legislation, and following a 2009 report of a pan European survey that suggested a 25% drop in the number of academic clinical trials (Swank et al., 2011). Interestingly, Kimmelman et al.,(2011) also tentatively suggest that perhaps strict application of GCP to investigator-initiated trials is a case of choosing the wrong tool for the job.


330 Both U.S. FDA Warning Letters and results from Health Canada inspections also suggest that most investigator citations relate to these provisions.
(Levinsky, 2002; Shnier et al., 2013). For example, institutional and personal pressures to commercialize one’s research, generate publications and achieve tenure can all negatively erode objectivity and proper scientific and professional judgment. Given the imprimatur of quality that tends to be enjoyed by academic affiliated research, and the possibility that such research may be subjected to less scrutiny than industry sponsored trials (see Chapters 4 and 7 in particular), it would in fact be reasonable to demand higher, not lower, standards from the investigators and staff working in this domain.

While the *GCP Guidelines* are not perfect, and while they are accurately described as “first and foremost [a] regulatory [instrument] and only indirectly moral [policy]” (Kimmelman et al., 2011), they are the currently accepted standard and if applied, go a considerable distance towards ensuring quality, safety, accountability and transparency in research. As such, the *GCP Guidelines* should apply to all clinical trials regardless of sponsor, and all investigators and their staff should be appropriately trained in, and know how to meet, their *GCP* responsibilities. As suggested by one of my participants, one way to implement *GCP* training would be to follow the approach taken in relation to the *TCPS 2* and require all investigators to pass a *GCP* tutorial in order to be able to conduct research. Given the research indicating that *GCP* adherence is better following training and best in sites where both investigators and coordinators are trained (Haeusler, 2009; Vulcano, 2012), it would be reasonable to implement this requirement for all investigators and their staff. Addressing the concern of cost related to *GCP* compliance, it would also be reasonable to require those funding investigator-initiated trials (be they public or private granting agencies, industry etc) to factor in an amount designated for *GCP* compliance.

It must also be noted that in Canada, of course, most investigator-initiated (as well as some industry-initiated) research will be subject to the *TCPS2* as well as to the *GCP Guidelines*. While the *TCPS2* does address some of the same ground as the *GCP Guidelines* (consent, trial design—particularly placebo, with a more restrictive stance on when they may be

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331 While *TCPS2* most often applies to investigator-initiated research, it can also apply to industry-initiated research, where for example the research takes place in academic health centers that receive funding from one or more of the three federal funding agencies (CIHR, NSERC, SSHRC).
used—safety monitoring and adverse event reporting among others) these topics are generally\textsuperscript{332} not described in the same level of detail in TCPS2. Instead, they are mostly discussed in general terms with the stipulation that REBs are responsible for developing SOPs to detail how such things will be handled. Interestingly, even though TCPS2 training is mandatory for investigators, research staff still reported problems with elements covered in detail by the TCPS2 (including, for example, the substance and process of consent and collection and use of samples—see Chapter 4). This suggests that while clearly important, training alone is not sufficient and that enforcement of applicable standards across both industry and investigator-initiated trials requires a combination of training and oversight.

**Recommendation:** *ICH-GCP Guidelines* should continue to apply to both industry and investigator-initiated trials. *GCP* training should be made mandatory for both investigators and their staff. A mechanism similar to the TCPS 2 Tutorial should be considered.

**Recommendation:** Health Canada should ensure REBs and Inspectors provide effective oversight of investigator-initiated trials and do not reduce their scrutiny of such trials based on assumptions of high quality (e.g., appropriate standards are being met) and reduced risk (e.g., minimal conflicts of interest).

**Recommendation:** Health Canada should require those funding investigator-initiated trials to provide budgets sufficient to support GCP compliance.

In addition to the recommendations at the systemic level in terms of oversight and training requirements for investigator-initiated trials highlighted in this section, it is also important to address the frontline realities of the research coordinators. For example, and as was described in detail in Chapter 5, research coordinators and staff can find themselves in situations where they strongly disagree with decisions being made by the investigator in terms of study design, consent processes, or other aspects of the clinical trial. Such disagreements may or may not be rooted in the investigator being unfamiliar with GCP or other regulatory requirements; however, they invariably create a difficult situation for the staff involved. As was described by participants, there is no clear mechanism by which such disagreements or concerns may be

\textsuperscript{332} A few notable exceptions to this statement include consent, which is described in detail and the requirements in relation to placebo use.
raised or addressed and as such staff may resort to surreptitious approaches—for example, anonymously raising concerns to the REB or undermining recruitment efforts. While there seem to be improvements being made in this regard in some institutions—including creating a research liaison manager to facilitate communication and collaboration between academic investigators and the clinic (see Chapter 5), it seems likely that additional efforts are required to ensure research coordinators and staff have the support and infrastructure to enable them to raise their research related concerns. Some suggestions might include establishing required research team meetings, or creating a neutral research ethics resource that could be contacted (other than the REB) to discuss concerns staff may have. Moreover, fostering a greater sense of community and networking opportunities between sites could also help build support for research staff, as would the formal development of mentoring programs. Finally, increased efforts by research institutions to promote support for research among clinical staff generally would also address some concerns raised by site participants. Additional research may help to develop effective, practical solutions.

**Recommendation:** Improve on-site mechanisms to support research staff in bringing research related concerns forward to investigators. The development of networking opportunities for research site staff and mentoring programs is also encouraged. Additional research may be required to identify barriers and develop practical solutions.

Effective oversight plays a critical role in ensuring standards are met and that those involved in clinical trials are sufficiently supported and are fulfilling their obligations. Challenges in this regard are summarized again under the discussion of (B) below.

**9.2 Narrative B: Health Canada is the body that keeps sites, CROs and sponsors in line and makes sure their obligations are met so that the interests of Canadians and Human Subjects are protected.**

The second narrative that is undermined in various ways by the findings in this study is that clinical trials are under the close oversight of Health Canada, as the regulatory body responsible for the health and wellbeing of Canadians. While Health Canada does oversee the
clinical trial and drug development process, they have delegated much of their oversight role to others—in particular research ethics boards and sponsors. While delegation is not inherently problematic, it becomes problematic where there are no mechanisms in place to ensure that the delegated tasks are being done effectively. Things become critical where problems are identified and described and yet nothing is done to correct, improve or mitigate the issues. As has been described in more detail elsewhere in this dissertation (Chapter 7), and in a well developed literature on this point (Anderson et al., 2011; Glass & Lemmens, 2002; Glass, 2006; Hirtle, Lemmens & Sprumont, 2000; Lemmens, 2005; McDonald, 2000; McDonald, 2001; McDonald et al., 2011; Vanderwel, 2012), there are well known and described problems with research ethics boards who are really the primary bodies responsible for ensuring the wellbeing and interest of human subjects are protected. These include, for example, no accreditation system for REBs, poorly trained or insufficiently qualified REB members, limited resources and independence, and poor mechanisms by which to obtain feedback from subjects (Davies, 2008; Glass, 2006; Lemmens, 2005; McDonald, 2000; McDonald, 2001; McDonald et al., 2008).

Despite this, Health Canada continues to rely very heavily on such boards—with very little in the way of backup. Apart from the exceedingly rare regulatory inspection, REBs are left to ensure clinical trials are conducted according to established legal and ethical standards.

Likewise—Health Canada relies heavily on sponsors to ensure that clinical trials are conducted according to regulatory and ethical standards. This creates somewhat different problems across industry and investigator-initiated trials. In the former, Health Canada relies on industry to essentially self regulate. While self-regulation by industry can be appropriate in certain circumstances with proper checks and balances in place, there are a number of factors

333 As noted on the Health Canada “Clinical Trials and Drug Safety” website, Health Canada “protects the health of Canadians who take part in clinical trials. For example, we:
1. review clinical trial applications
2. make sure drug companies do all of the safety tests needed to reduce the risk of side effects
3. visit sites where clinical trials take place to make sure patients are being monitored properly by their doctors and that the trials are conducted properly
4. keep track of negative side effects that occur in clinical trials and take action when needed” (http://www.hc-sc.gc.ca/hl-vs/iyh-vsv/med/clinical_trials-essais_cliniques-eng.php)
that make the current situation in relation to clinical trials in Canada somewhat troubling. The extremely high stakes and widely reported economic pressures that are leading to shrinking budgets and increased financial pressures on the industry are important contextual factors (Vanderwel, 2012). In addition, the fact that the pharmaceutical industry is an extremely powerful lobby and that stakeholders at all levels in Canada—from Health Canada with visible support from Industry Canada, to public and private funding agencies, to industry groups such as Rx&D, to provincial health authorities, research institutions and individual investigators—are working hard to grow industry business and bring more clinical trials to Canada for their associated economic benefits, must also be taken into account. Even so, delegation of oversight to industry sponsors for their trials could make sense—even in these challenging circumstances provided that there is some kind of arms length oversight or check.

Unfortunately, and as has been described in more detail elsewhere in this dissertation, there simply is little or nothing in this regard currently in place. There are limited Health Canada inspections, and Health Canada also does of course review the data submitted for New Drug Submissions, which could certainly be argued to constitute a level of oversight. However, as outlined in Chapter 7, there are also compelling reasons (rooted in both conflicts of interest and procedure) to question the effectiveness of such reviews.

Interestingly, the concerns associated with self-regulation by industry sponsors did not feature prominently in the data. One participant who was an auditor and regulatory expert did describe this as an area of concern, and emphasized that it is sponsors who are keeping CROs and sites in commercialized clinical trials “in line”, not the regulator. The issue also came up indirectly, however. As reported in Chapter 6, sites described the pressures they received from sponsors and CROs, which in some cases included instances wherein they felt they were being asked to do things that were inappropriate and not in line with the GCP Guidelines. In this context, some site participants emphasized the importance of taking responsibility for what went on at the site and that sites had to understand the complex factors that could lead to such pressures—including, for example, financial motivations, sloppiness, overworked and/or undertrained staff. The point here is simply to highlight that evidence emerged in this study to

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334 The many diverse efforts that are underway in this regard across the entire country are described in Chapter 2.
support the common sense conclusion that where sponsors are relied upon to self regulate in relation to clinical trials, there needs to be arms length oversight and review. When the CRO presence is added, and oversight duties delegated—responsibility is further fractured and it could certainly be argued that accountability becomes even more difficult making the need for regulatory oversight even more important.

As alluded to under narrative (A) above, the delegation of oversight duties to sponsors in the context of investigator-initiated trials raises an entirely different set of problems. In this context-lack of training and awareness on the part of sponsor-investigators of their responsibilities (and more particularly their sponsor responsibilities) means there is essentially no sponsor oversight in these trials. Moreover, and as explained in Chapter 7, there is reason to believe that there is also even less oversight from Health Canada (in terms of inspections) and REBs for investigator-initiated studies than there is for industry-initiated studies.\(^{335}\) More than a weakness in the system, this constitutes a serious gap that needs to be addressed by the regulator and one that undermines the credibility, safety and assumed quality that investigator-initiated trials tend to enjoy. That being said-it is important to state that there are positive developments being undertaken by many health authorities and at many academic health centres to help support investigators. These include, for example: (1) clinical trial support units established by health authorities to help provide additional support and training to investigators and their staff (Genome B.C. Asset Map, 2010); and (2) research institutions making individual research coordinators available through the institution to support investigators with their trials.\(^{336}\)

As described above, as well as in more detail in Chapter 7, there are a number of problems with Health Canada’s approach to oversight of clinical trials. While the challenges are complex, there are certainly ways to improve the status quo across both industry and investigator-initiated trials. Some options have been described in the context of investigator-initiated trials under Narrative A above. More generally, Health Canada should address shortcomings both in the REB system and its own inspection process. In relation to REBs, the

\(^{335}\) This is not clearly established, though, and constitutes an important question requiring more research. See for example, Klitzman (2013) who calls for more research in this area and Ogilvie (2012) who identifies uncertainty on this point in the Canadian context.

\(^{336}\) This was an initiative described by one of my site based research participants (site manager, August 30th 2010)
many efforts and discussions around developing standards, improving training and establishing accreditation need to materialize into real results. This is complex, has been the subject of much debate and effort (Anderson et al., 2011; McDonald & Cox, 2009; McDonald et al., 2011; Owen et al., 2009; Sampson et al., 2009), and will of course not be easy. However, as the regulator, Health Canada should be taking more of a leadership role than it has to date in relation to this goal (McDonald et al., 2011). Health Canada should also increase resources available for inspections. This would include increased funding and personnel. In addition, and as highlighted by the Auditor General, Health Canada should require sponsors to provide all of the information inspectors require to effectively implement the risk based site selection process (OAG, 2011). In the alternative, Health Canada could decide to cease its inspections, acknowledge that it relies totally on sponsors for this activity and focus its efforts on implementing an effective arm’s length oversight mechanism to ensure transparency and quality of this process.

Recommendation: Health Canada should take more of a leadership role in relation to establishing standards, training and accreditation for Research Ethics Boards and ensuring they have the resources and independence required to fulfill their critical mandate;

Recommendation: Health Canada should increase resources available for clinical trial inspections;

Recommendation: Health Canada should require sponsors to submit all information (including up to date site information) necessary for inspectors to effectively implement the risk-based approach to site selection;

Recommendation: Health Canada should consider eliminating the regulatory inspection for clinical trials and focus its resources and efforts instead on establishing an effective arms length oversight mechanism to improve transparency and ensure quality of sponsor oversight efforts.

While the details on how the above suggestions would be implemented and paid for are no doubt complicated and multifaceted, and while some of them may compromise (at least in the short term) Canada’s efforts to attract commercialized clinical trials, adopting such measures would very likely go a long way towards improving the protection of human subjects in clinical trials in Canada and ensure that Health Canada is meeting its trust based obligations to its citizens. As discussed previously, and as will be discussed again briefly below, the importance of the regulator earning and maintaining the trust of Canadians in this regard is only heightened
by the strong interests and pressures that are so much a part of the global drug development industry.

9.3 **Narrative C: The drugs being developed, tested and approved for the Canadian market typically result in therapeutic benefit for Canadians.**

Clinical trials are inherently risky. Whether they are testing new drugs about which very little is known, or trying new combinations or dosages of established drugs for treating new indications in new populations, clinical trials involve risk and burdens\(^{337}\) for those individuals volunteering as human subjects (Ulrich et al., 2012). For clinical trials to be ethical, they must strike an appropriate balance between the risks to those participating as research subjects and the potential benefits the research may bring to the individual subject, medical science and to society more broadly. This tension goes to the very heart of research ethics as a discipline and to the conduct of ethical research. There are no clear cut, sure fire ways to ensure that the balance is struck right every time and in fact this risk benefit analysis presents real challenges for the REBs who are charged with making this determination as part of their deliberations over whether to approve a study (Emanuel et al., 2000). As described in more detail in Chapter 7, there are real challenges in the adoption of a proportional approach to oversight and ethics review; however, despite those very real challenges and in the absence of any meaningful empirically based approach (McDonald & Cox, 2009), REBs do their best to balance risks and benefits to individuals and society every time they assess a protocol. In some cases, the balance is struck more easily than in others—for example, where the trial presents very little risk or burden to participants, but stands to yield great therapeutic or other benefits. On the flip side, some trials may be easily rejected—where for example, participants would be subjected to great risk for very little potential benefit either to themselves or for society. The Tuskegee Syphilis study would be an example of a protocol that today would be easily rejected by an REB given that its primary purpose was to document the progression of an already well understood disease—at

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\(^{337}\) While the additional follow up often associated with research participation is commonly identified as one of the benefits of participating in a research study, it is also important to recognize there are added costs. Participants will frequently have additional office visits and procedures (including for example, blood draws, biopsies, CT or other scans, infusions, journal keeping etc) that can constitute significant expenditures of time and energy. Costs may also be incurred by subjects in relation to travel, time from work, and child care among others.
great risk and cost to its subjects.\textsuperscript{338} Things get far more difficult in the middle ground. It is tricky, for example, where a protocol offers the prospect of some kind of benefit to individual subjects (perhaps earlier access to tests, or increased medical attention), some benefit to society that is perhaps less compelling than a major medical breakthrough (economic gains), but also involves potentially significant risk and/or cost to participants. In each of the above cases, it seems that while there are a number of factors to consider a key piece of information would be the therapeutic potential of the drug being tested.

However, such information is relevant not only at the REB level, but also for the subject who makes the ultimate decision about whether to participate. Once an REB approves a given protocol (in part based on a preliminary, general assessment of the risk/benefit ratio for potential participants), individual participants have to provide informed consent to participate in research. In this process, participants weigh the risks and potential benefits (including the potential for contributing to the advancement of medicine to help future patients), and make an informed decision about whether participation in a particular clinical trial is in line with their values and interests. Research indicates that people participate in clinical trials for a variety of complex reasons, but two dominant ones are the hope of personal benefit or the possibility of furthering medical science to benefit future patients (Townsend & Cox, in press). Particularly in light of these reasons, the potential of a given clinical trial to yield improved therapeutic benefits over and above those already available would likely be relevant to many participants.

If this assumption is correct—i.e., that both REBs and human subjects make decisions about individual research protocols (whether to approve or participate in, respectively) based at least in part on the potential for advancing medical science, then the fact that most new drugs that are approved for sale in Canada have no therapeutic benefit over existing therapies seems highly relevant, but something that is not necessarily widely known.\textsuperscript{339,340} It has been reported

\textsuperscript{338} That this in fact was done without the subjects’ informed consent is also critical, but is a somewhat separate issue to the risk/benefit of the research itself.

\textsuperscript{339} What is being discussed in this section in particular are clinical trials for new drugs. Such trials are almost invariably of the industry-initiated variety.

\textsuperscript{340} It is of course also worth highlighting that, despite compelling ethical guidance to the contrary (\textit{Declaration of Helsinki}; \textit{TCPS2}), regulators including FDA and Health Canada do not require new drugs to be tested against current therapeutic options; instead, trials of new drugs tend to be
that nearly 4 out of 5 newly patented drugs provide no therapeutic advantage over existing drugs on the Canadian market (Gagnon, 2012). The 2011 annual report of the Canadian Patented Medicines Prices Review Board classified 72 of the 104 newly patented drugs in that year as being of slight or no improvement over existing therapies. Despite this, however, clinical trials are promoted and justified first and foremost in terms of the potential health benefits they bring and their importance for ensuring that Canadians have access to the cutting edge medicines and treatments. Whereas this could be reasonably expected (and is the case) on the part of industry organizations such as Rx&D, the regulator (Health Canada) delivers a similar message. For example, in a recently developed website (May 2013) entitled “Clinical Trials and Drug Safety: It’s Your Health” Health Canada describes clinical trials as giving “Canadians a chance to take part in research that could improve their health” and later states that,

When you take part in a clinical trial, you help others by advancing medical research. If you have a disease, there could be personal benefits. You may get early access to a new promising treatment. The treatment may cure or control your condition. Even if you are not cured, your quality of life might improve. [And/or ]You may get additional access to expert health care because of the time you will spend with the research team involved in the study."

In terms of education and awareness, the webpage does describe the role and kinds of clinical trials in the drug development process, and gives some general information about potential risks and benefits of participation. However, nowhere on this webpage does it describe


341 The author cites the 2010 annual report of the Patented Medicines Prices Review Board (PMPRB).
342 These numbers exclude those drugs that were reported to PMPRB in 2011, but sold prior to introduction of new guidelines in 2010 (the number would then be 77/109). http://www.pmprb-cepmb.gc.ca/english/view.asp?x=1625&all=true
343 For example, the Rx&D claims that “the discovery and development of new medicines and vaccines in Canada makes our communities and our country stronger. It creates jobs and contributes to the sustainability of our healthcare system. But most importantly, new medicines represent some of the most scientifically advanced, safest and most effective treatments available to help Canadians live longer, better and more productive lives.” http://www.canadapharma.org/en/our-industry/industry-facts/saving-lives---transforming-care
344 Ibid.
the economic benefits that come with clinical trials and nowhere does it indicate that 4 out of 5 newly patented drugs will yield little or no increased therapeutic benefits (Gagnon, 2012; PMPRB, 2011). But what of other kinds of benefits? Some have argued that the practice of developing and marketing so called me-too drugs that provide little or no advantage over existing therapies can be justified on the basis that they enhance competition and lower overall drug costs (diMasi & Paquette, 2004; Hollis, 2004). However, there is data indicating that any price reduction is actually quite minimal (Gagnon, 2012; Hollis, 2004 (citing Lu & Comanor, 1998; Ekelund & Persson, 2003); Lexchin, 2006). When one combines this with the fact that development of me-too drugs erodes incentive for innovation by yielding profit to the sponsoring pharmaceutical companies, exposes subjects to the demands and risks (even if minimal) of clinical trials without any potential benefit and the fact that they absorb resources—not just of the sponsor, but of the entire research ethics oversight system (Hollis, 2004)—the economic benefit argument appears strained to say the least. 

Such concerns and debate over the kinds of clinical trials that should be promoted and sought, and the relative importance of health and economic considerations, have also recently been discussed in the United States (Weisfeld et al., 2011). In any event, and by focusing solely on the therapeutic potential of clinical trials, the website arguably acts as a promotional tool more interested in supporting and enhancing industry recruitment efforts (thereby addressing one of the major industry complaints and obstacles to growing clinical trials in Canada), than in educating Canadians about clinical trials in an objective and measured way.

Similar to the website described above, and in stark contrast to efforts in other jurisdictions, Canada’s recently launched (May 2013) and long overdue clinical trials database is also (by Health Canada’s own admission) much more a mechanism by which to inform potential participants of available clinical trials than it is about promoting accountability and

346 For an excellent discussion of these points and additional insights on this question, please see Hollis, (2004). Me-Too Drugs, Is there a Problem? Available at: www.who.int/intellectualproperty/topics/ip/Me-tooDrugs_Hollis1.pdf

347 As reported by Shuchman 2013, “Dr. Pat Stewart, interim senior executive director at Health Canada’s Therapeutic Products Directorate, says the database ‘was meant to be something we could do in an efficient manner that would give enough high-level information, that if a patient was interested in finding out more, they could contact the sponsor and get more information.’”
transparency.\textsuperscript{348} Unlike other established registries that require sponsors to register their trials, the information on Canada’s registry is posted by Health Canada. This has important implications in terms of, for example, the nature of the information that is posted. Canada’s ‘registry’ includes a subset\textsuperscript{349} of the information it collects from sponsors, including the title of the clinical trial protocol, the medical condition being addressed, the drug and population under study, the date Health Canada authorized the trial, and the study’s enrolment status. In contrast, other established registries require sponsors to provide this basic information, but also to include a full list of study sites, investigators and their contact information, information about trial design as well as primary and secondary outcome measures, and in some cases, trial results (Shuchman, 2013). As others have observed, such information is what promotes transparency as “[t]hat more comprehensive information allows academics assessing the risk and benefits of drugs to analyze all new drug studies, not just those that have been published” (Shuchman, 2013). Health Canada’s decision to adopt such a registration system is but one more example of a serious tension between industry and economic interests on the one hand and the health and wellbeing of Canadians on the other—and yet another indication that the former seems to be winning out.\textsuperscript{350}

\textsuperscript{348} The website links to Health Canada’s clinical trials registry, with the statement that, We also give Canadians information about clinical trials so that they can make informed decisions about their health. Our website lists all the phase I, II, and III drug patient clinical trials in Canada. The list is updated each night, and has information like:
\begin{itemize}
\item the sponsor and title of the study
\item the drug being tested
\item the start and end dates
\item the type of volunteers needed (age range, sex, medical condition, etc.)
\end{itemize}
(http://www.hc-sc.gc.ca/hl-vs/iyh-vsv/med/clinical_trials-essais_cliniques-eng.php)

\textsuperscript{349} As Shuchman (2013) notes, Health Canada in fact has more information it could post (including the sites and PI contact information) but has opted not to do so. http://www.cmaj.ca/site/earlyreleases/19june13_Health_Canadas_new_clinical_trials_database_should.xhtml

\textsuperscript{350} While not directly relevant to the discussion on clinical trials, the erosion of the Therapeutics Initiative (based at the University of British Columbia) is another important development that suggests industry interests may be being prioritized over the health and wellbeing of Canadians. The Therapeutics Initiative is a group of independent scientists who scrutinize the safety and efficiency (that is, the value relative to other available treatments) of the medications available to B.C. residents through the provincial drug program (Pharmacare). More information may be found at:
Recommendation: Health Canada should present a more balanced message about the potential of clinical trials to benefit the health of Canadians. This will help ensure that Canadians are better informed both in relation to clinical trial participation, but also in terms of the drug development and approval process more generally.

Recommendation: Health Canada should revise its trial registry system so that clinical trials sponsors are required to post sufficient information (including results) so as to allow for real transparency and meaningful accountability.

9.4 Encouraging Findings Emerging From This Study

While this study has focused primarily on the challenges and areas of concern in regards to both the relationship between investigative sites and CROs, and clinical trial oversight in Canada more generally, it is also important to restate here a number of positive findings that emerged through the course of this study. A critical aspect in this regard is first and foremost the dedication and commitment of those working in this field, as exemplified by each and every one of my participants. What the rules and standards are or should be in relation to clinical trials is no doubt important; however, rules and standards are of little value if those implementing them at each stage of the clinical trial process are not sensitive to the complexities of their position and committed to ensuring both the safety and wellbeing of trial participants and the quality and integrity of the studies being performed. The willingness of my participants to discuss the challenges and concerns they had in relation to their work, the insightful and thoughtful suggestions they had in relation to addressing many of these issues and their clear passion and commitment to both clinical trial participants and the quality and integrity of the trials they worked on were all extremely inspiring and reassuring. As suggested throughout this dissertation, there are a number of areas where action and improvements are required—for example in relation to additional training, support, infrastructure and guidance for those working at the front lines of clinical trials. This study suggests that those on the ground are at once engaged and both willing and able to provide extremely valuable insights and contributions on future initiatives in these and related areas.

More specifically in relation to investigative sites and their interactions with CROs, there was an acknowledgement that CROs tend to be more responsive to site queries than industry

http://www.vancouversun.com/health/Pharma+team+kill+drug+safety+watchdog/8654735/story.html
sponsors, even if ultimately communications take longer as described in Chapter 6. Moreover, site and CRO participants alike suggested that CROs are often more aware of the realities sites face in conducting clinical trials and that some CROs take proactive steps to develop useful tools and forms that are designed to help investigative sites in their day-to-day clinical trial tasks. While no doubt motivated in large part by the need of CROs to ensure that the clinical trial sites they recruit are successful (i.e., in order to satisfy their sponsor clients), this nonetheless has important and positive implications for investigative sites. Site and CRO participants also suggested that, at least in theory if less often in practice, CROs are well situated to act as a buffer through which sponsor demands may be filtered and in rare cases may act as advocates for sites in making requests for additional support from industry sponsors. Finally, it is important to highlight that, especially as compared to smaller or less well established industry sponsors, CROs may well be more knowledgeable about regulatory and other requirements. Additional reflection on these recognized strengths and advantages will be an important step in helping improve overall relationship between sites and CROs, but also could have significant implications for the overall quality and integrity of clinical trials.

This study also highlighted a number of other promising initiatives and developments. For example, as part of the many initiatives underway in Canada to attract more clinical trials, there has been a recognition that additional support is required for sites including additional training for both investigators and staff (see Chapters 4 and 5). While the motivation for this is to make sites more attractive to industry sponsors, such developments will also benefit human subjects and Canadians more generally by helping to improve the quality and integrity of clinical trials. Recent and ongoing hearings by the Standing Senate Committee on Social Affairs, Science and Technology into various aspects of clinical trials also suggest that increased attention is being brought to this important subject. Moreover, that the Auditor General also recently highlighted a number of problems related to site inspection, including the site selection process, will hopefully lead to such issues receiving some much needed attention. Finally, though on a less optimistic note, while Health Canada’s recent clinical trials registry could have been an important positive development, it falls far short of international standards in terms of promoting transparency and is notable only in terms of being a significant disappointment.
9.5 Closing Comments

This study has presented a series of findings relating to the challenges and concerns that arise at the frontlines of clinical trials. It provides Canadian evidence on some of the challenges research staff face within their own sites, as well as in relation to their interactions with CROs and (to a lesser degree) sponsors. Drawing on these findings, this study then critically assesses the legal and policy frameworks governing clinical trials in Canada to identify areas where improvement might be necessary.

Many of the issues that emerged from the data have potentially serious implications for the integrity of clinical trials, subject safety or both. Although some of the issues discussed by my participants in both commercialized and investigator-initiated trials have been described to varying degrees in the academic (nursing, medical, bioethics, health law) literature, industry literature or both—there has been very little academic empirical research exploring these issues in a specifically Canadian context. This study has taken this step and has identified a number of weaknesses in Canada’s regulatory and policy frameworks that could have important implications at the frontlines. It has also demonstrated how these weaknesses are exacerbated by current trends, efforts and initiatives being undertaken across the country. Finally, and in light of the findings and analysis conducted, a series of recommendations are made, both in Chapters 7 and 9, to start to address some of the key areas of concern. These are listed again (in point form) below under the “Contributions” section.

Although the dissertation has focused on areas of concern in relation to clinical trials in Canada, it in no way undermines the critical importance of this industry and the potential benefits—both in therapeutic and economic terms—that it generates for this country. What it does do, I hope, in the midst of so many intense efforts currently underway to grow Canada’s clinical trial business, is to serve as a cautionary reminder: a reminder that our regulatory and oversight frameworks are not infallible, and that they have weaknesses that need to be addressed if the health and well-being of Canadians are to be assured. It also serves as a reminder that to fail in this regard not only potentially exposes human subjects and Canadians (as future drug consumers) to greater drug related risks, it also threatens to undermine public trust and support for research—that is, the very foundation upon which all research is realized.
9.6  Contributions And Recommendations Emerging From This Research

In general terms, this study provides empirical support for the need to provide clearer, more effective oversight of clinical trials in Canada. This relates to both industry-initiated trials and investigator-initiated trials. This study has highlighted some areas of common concern as well as unique issues that need to be considered in relation to each domain. Recommendations to improve transparency and accountability, as well as the overall quality of clinical trials, have been made both in this and an earlier Chapter (Chapter 7). These recommendations are listed again in point form below. Where they relate directly to one of the narratives addressed in this Chapter, this is identified. Other recommendations that emerged from Chapter 7, and that don’t necessarily relate to one of the three themes, are listed under “Additional Recommendations.”

9.6.1  Recommendations Narrative A (Golden Age Of Investigator-Initiated Trials)

Recommendation 1: Increase oversight for investigator-initiated trials by strengthening current mechanisms and implementing additional public sector oversight.

Recommendation 2: *ICH-GCP* standards should continue to apply to both industry and investigator-initiated trials. *GCP* training should be made mandatory for both investigators and their staff. A mechanism similar to the *TCPS 2* tutorial should be considered. Health Canada should provide clear guidance as to what is required in terms of training to be qualified.

Recommendation 3: Health Canada should ensure REBs and Inspectors provide effective oversight of investigator-initiated trials and do not reduce their scrutiny of such trials based on unfounded assumptions of high quality (e.g., appropriate standards are being met) and reduced risk (e.g., no conflicts of interest).

Recommendation 4: Health Canada should require those funding investigator-initiated trials to provide budgets sufficient to support GCP compliance.

Recommendation 5: Health Regions and institutions should work to improve on site mechanisms to support research staff in bringing research related concerns forward to investigators. The development of networking opportunities for research site staff and mentoring programs is also
encouraged. Additional research may be required to identify barriers and develop practical solutions.

9.6.2 Recommendations Narrative B (Health Canada’s Key Role In Oversight)

Recommendation 6: Health Canada should take more of a leadership role in relation to establishing standards, training and accreditation for Research Ethics Boards and ensuring they have the resources and independence required to fulfill their critical mandate.

Recommendation 7: Health Canada should establish clear jurisdiction over not only the sponsor, but also over other key parties including CRO, investigator and REB. This could be done, for example, by directly incorporating the relevant provisions of the ICH-GCP Guidelines into the Division 5 Regulations under the Food and Drugs Act.

Recommendation 8: Health Canada should increase resources available for clinical trial inspections.

Recommendation 9: Health Canada should require sponsors to submit all information (including up to date site information) necessary for inspectors to effectively implement the risk based approach to site selection.

Recommendation 10: Health Canada could consider eliminating the regulatory inspection for commercialized clinical trials and focus its resources and efforts instead on establishing an effective arms length oversight mechanism to improve transparency and ensure quality of industry oversight efforts.

9.6.3 Recommendations Narrative C (New Drugs Yield Therapeutic Benefit)

Recommendation 11: Health Canada should present a more balanced message about the potential of clinical trials to benefit the health of Canadians. This will help ensure that Canadians are better informed both in relation to clinical trial participation, but also in terms of the drug development and approval process more generally.
Recommendation 12: Health Canada should revise its trial registry system so that clinical trials sponsors are required to post sufficient information (including results) so as to allow for real transparency and meaningful accountability.

9.6.4  **Additional Recommendations (Legal & Policy Framework (Chapter 7))**

Recommendation 13: Clearly articulate roles and limitations of each party involved in oversight (regulator; REB; and sponsor).

Recommendation 14: Health Canada and REBs should adopt an evidence based proportionate approach to their oversight and protocol review activities.

Recommendation 15: Penalties levied under the User Fee Act when the regulator is late in its reviews of New Drug Submissions should be eliminated.

9.7  **Limitations Of The Research**

This research has a number of limitations. First, while I adopt a site-based perspective, I did not interview any investigators in the course of this study. Instead, I focus on the voice of the coordinators. This was done for a couple of reasons. First, the available literature suggests that coordinators are in fact the key contact point between CRO and investigative sites and handle the day to day running of the trial. As such, and given that my goal was to explore the challenges that arise at this interface, this main point of contact seemed a reasonable focus. The second reason was related to access. Investigators are notoriously difficult to recruit (Fisher, 2009) and I would likely have had to access this population largely through their research coordinators. This process could have compromised the frankness with which coordinators and research staff spoke to me about their on-site challenges. That being said, the problem remains that on these and other issues I only hear the coordinator or staff view, and do not have the benefit of the investigator’s rebuttal or perspective.

Second, I only conducted 24 interviews, with most of those (12) being in the site category. However, the small number of interviews and in particular the fact that categories of sponsor and CRO were lightly populated is mitigated in part by the fact that so many of my participants had a lot of experience across multiple categories. So for example, a participant may
have been a coordinator at the time of the interview but also often brought experience working as a monitor for a CRO from past positions. This enriched the data by having more informed participants, but also meant I was able to reach saturation in categories where that might have been less likely looking solely at numbers of participants in a given category. Participants are categorized in terms of their position at the time of their interview. Participants are listed in Tables 3.1, and their relevant backgrounds are listed in Table 3.2.

A third limitation is that while I interviewed three participants with experience working in community based sites, I only interviewed one person actually working in that setting at the time of the interview. This participant was located in a large, established community based research unit. As such, I really have very little data relating to community sites and have not addressed at all the range of community sites conducting clinical trials. It would have been preferable to have had a stronger representation from the community based sites. However, on the question of site-CRO interactions, I was able to get some sense of the relationship between site and CRO across these two domains because some site participants had worked in community based sites previously. Moreover, sponsors and CROs also provided insights into the issues they encountered in the community versus the academic realm.

Fourth, these interviews were conducted in 2010 and early 2011. It is now the end of 2013. The long delay in a rapidly progressing field—especially in relation to all the efforts that are underway to improve and enhance Canada’s clinical trial business—means that some of the data is almost certainly now out of date. However, it does present a snapshot of how things were at the time and given that many of the efforts are still in the early stages of development, it is likely that many of the issues and challenges persist.

Fifth, while I describe this as a Canadian study the vast majority of my participants were located in B.C. That being said, participants in the consultant and sponsor categories did tend to speak from a more Canadian perspective; that is, they had frequently conducted business across Canada and often internationally as well. However, and particularly in relation to the site data, this study has a profoundly B.C. bent. As such, it may well not be an accurate reflection of site experiences across the country and particularly in those jurisdictions (Ontario and Quebec) where vastly more clinical trials are conducted.
Finally, while one of my participants had rich expertise in the regulation of clinical trials in both Canada and internationally, I did not speak to the regulator (Health Canada). As such, I have no high level perspective that could have provided insights into why the frameworks are as they are, or what the legislative priorities might be seen to be right now (among other things). I also did not have the opportunity to explore how Health Canada might have responded to the gap identified in terms of investigator-initiated research. That being said, I did have the benefit of the transcript evidence from the 2012 hearings of the Standing Senate Committee on Social Affairs, Science and Technology exploring “the process to approve prescription pharmaceuticals with a particular focus on clinical trials.” (Ogilvie, 2012). Health Canada representatives testified on numerous occasions at these hearings. Some of this evidence has been incorporated into this study (see Chapter 7), and certainly helped inform my thinking in the critical legal and policy analysis.

9.8 Areas For Future Research

As I reflect on my findings and the experience of conducting this research, a number of areas appear ripe for future research. For example, while the insights provided by the coordinator and other research staff at the investigative sites was I think a rich and appropriate starting point, additional research targeting the investigator perspective on many of the issues raised in this report is needed. Understanding the investigator perspective on the importance of early engagement of the research team, their satisfaction with their level of training and knowledge in relation to their research roles (particularly sponsor-investigators), and their views on what might facilitate their oversight responsibilities are just some of the many areas that would be important to explore.

While the investigator perspective will be critical to include in future research, and while there is an established and growing literature on the coordinator position, more empirical work around the coordinator role is still required. Further exploration could be done, for example, into how best to address or support research coordinators to ensure they have the resources and ability to bring their research related concerns forward. Coordinators are the ones primarily interacting with subjects and CROs. Asking them how they could be better supported to address the ethical and other issues that arise be they in relation to CROs, sponsors or even their own investigators could have profound implications for improving human subject protections.
The above research areas should target both public and private sites, with perhaps an increased focus on community sites. This study provided some insights in this regard; however, the dominant perspective was that of academic affiliated sites. While this study yielded some important findings in relation to investigator-initiated trials, the fact that most industry-initiated clinical trials are in fact conducted in the community certainly suggests more research in that arena is necessary. Questions could include, among others, how such sites raise their concerns with sponsors and CROs, what kind of support or infrastructure they might find helpful to support them in this regard and what kind of networking or other capacity building efforts could be useful. Another area to explore might involve possible obstacles to collaboration between community based research units and academic or public sites, and how these could be addressed in order to facilitate a more seamless research infrastructure and increase overall capacity in the research community.

As mentioned in the previous section on limitations, while this study provides insight into the challenges sites face in B.C., future research is also needed in order to compare the findings from the present study with research done with investigative sites across Canada, and particularly in the major clinical trial hubs of Ontario and Quebec.

In the context of furthering the development of an evidence-based research ethics oversight framework (Anderson et al., 2011; Cox et al., 2009; McDonald et al., 2008; McDonald & Cox, 2009; McDonald, Cox & Townsend, 2013; Owen et al., 2009) it will be important to explore the participant perspective on these issues. Specific questions in this regard might include among a myriad of others (a) How do participants experience investigator versus industry-initiated trials? (b) Do they have more confidence in one over the other, and why? (c) Does their level of confidence change through their participation? (d) Are participants aware of a CRO when it is involved? If so, how do they become aware? (e) What does the CRO involvement mean for participant experience in the trial? (f) How concerned are participants about issues that come up—for example, when a monitor takes their information off site, even though the consent form indicated all identifying information would remain onsite? (g) How concerned are participants when investigators deviate from protocol without checking with the industry sponsor? (h) What kind of GCP breaches tend to be of most concern for participants in investigator vs industry-initiated clinical trials? Is there a difference? (i) Do the kinds of things
addressed by GCP address the main areas of concern raised by clinical trial participants? Where are there areas of divergence and convergence? Insights gained from such research would go along way to addressing the well recognized shortcomings of proportional approaches to research review described earlier, and would generally support the development of an oversight system that is responsive to the needs and priorities of those it is intended to protect.

Finally, and as called for by Klitzman (2013), further research into whether and how research ethics boards bring greater or less scrutiny to investigator-initiated trials as opposed to industry-initiated trials is an important next step. Assessing reasons why this happens, if it does, will help inform discussion on whether level of scrutiny should vary on this basis. Similar questions could also helpfully be asked of Health Canada’s Health Product and Foods Branch Inspectorate. It would also be informative to explore how regulators and sponsors respond to these findings and analyses, and to explore the obstacles that exist to incorporating some or all of the recommendations made in this study.
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Appendices

Appendix A: Interview Protocols (Site; CRO; Sponsor; Consultant)

A.1 Investigative Site Interview Schedule
Check participant has had time to read consent form.
Review essential aspects (i.e., purpose of study, what is being asked, confidentiality, how I will handle any concerns, risk and agreement to maintain data for longer than normal)
Ask if there are any questions or concerns.
Double check that all required boxes are checked and that participant has a signed copy of the consent form for their records.

(a) General
1. Please tell me a bit about your current role and responsibilities.
   a. How long have you been in your current position?
   b. Where were you before this?
   c. Have you ever worked for, been employed by a CRO or pharmaceutical sponsor? If so, how did that compare with your current experience?
   d. How many clinical trials are currently ongoing at this site?
   e. How many involve CROs? How many CROs are involved?
   f. What is your role in each CT?

(b) CRO-Investigative Sites
2. What has been your experience generally interacting with CROs?
   a. Could you describe generally how those interactions work?
      i. What tends to go well? What tends to be challenging?
      ii. Who is involved?
   b. How many different CROs do you currently interact with? (ie how many CROs have contracted with this particular site?)
   c. Do CROs tend to be involved with specific kinds of trials? If so, what kinds?
3. What, in your view, makes a CRO good or challenging to work with? (more of one kind than the other?)
   a. When a relationship with a CRO or monitor is particularly good-is there an underlying reason? Eg-would a CRO put more effort or higher skilled people on bigger trials, for example?
   b. Have you ever asked (sponsor) that a CRO be changed? Or Monitor?
      i. Would you have concerns doing this?
      ii. What factors would you consider in deciding whether or not to do this?
      iii. Would you feel like you could in certain circumstances?
      iv. What kind of situation would that be
   c. IF you have raised complaints or asked for new monitor/CRO-what has been the fallout of this (relationship with sponsor? CRO? Monitor? Time delay in research process etc?)
      i. Would you do it again? Why/Why not?
4. Please describe the process from the time you are approached by a CRO as a potential site, through to being enrolled and through to the trial’s conclusion.
   a. Who is primary contact?
   b. Who negotiates terms of interaction?
c. How are expectations (on both sides) expressed and addressed?
d. If and when problems, disagreements arise—how are these handled?

5. In what ways (if any) does the involvement of a CRO change the research process or pre/post research processes?
   a. Is there any impact on, for example, the ethics review application process? (Board used, documents submitted, process? Etc)
   b. Are there additional pressures or demands?
   c. Are these different from dealing directly with sponsors? How?
   d. How does your site handle such pressures?
   e. Have you ever been aware of tensions that have arisen between CRO and Sponsor?

6. What, from your perspective, are the biggest challenges/concerns that arise in general terms, when working with a CRO? How are these addressed at your site?
   a. Does it make a difference when the PI is more involved or aware of the issues? Why or why not?

7. Have you ever been in a situation where you feel what is being required or asked of you by the CRO is in tension or conflict with what you feel your obligations are to either the subjects or to the data? If so:
   a. What kind of situation?
   b. How was it handled?
   c. Who, if anyone, did you raise your concerns with?
   d. Would you handle it the same way again?

8. I am doing my work coming out of the Centre for Applied Ethics—and wondering if there are any ethical issues in your area that you think are important or would like to raise?

9. What documents (if any) do you look to for guidance for your ethical & legal responsibilities in clinical trials?
   a. Are these helpful? Problematic?
   b. Sufficient? Are there gaps you would like addressed?
   c. Suggestions?

(c) Academic Investigative Sites & Community Investigative Sites

10. I want to better understand the similarities, differences and relationships between academic and community based investigative sites. Can you describe-based on your experience-generally the major similarities and differences between how these kinds of sites function?
   a. Differences in staffing?
   b. Kinds of trials conducted at each kind of site?
c. Are there overlaps in staffing? That is, do some individuals work in both contexts simultaneously? If so—what are the advantages/disadvantages of such a setup?

(d) Concluding Questions
11. Is there anything we have not talked about that you think is important?
12. Are there particular areas you would recommend that I pursue?

It would be helpful to hear your thoughts on this study.

- Why did you decide to participate in this study?
- What do you hope I will learn from this study?
- Do you have any other comments, suggestions or perhaps questions you think I should ask of other participants?
A.2 CRO Interview Schedule
- Check participant has had time to read consent form.
- Review essential aspects (i.e., purpose of study, what is being asked, confidentiality, how I will handle any concerns, risk and agreement to maintain data for longer than normal)
- Ask if there are any questions or concerns.
- Double check that all required boxes are checked and that participant has a signed copy of the consent form for their records.

a) **General: Background and CRO related experience**

1. Please tell me a little about your experience working directly and indirectly with CROs.
   a. Have you ever worked for, been employed by a CRO? Pharmaceutical sponsor (depending on current position)? [If both, how did those experiences differ?]
   b. Have you ever worked as a researcher or research worker at either a community or academic investigative site?
   c. What kind of training or courses have you taken for your position?

2. Could you please tell me about your current position (if relevant)?
   a. How would you define your role/responsibilities?
   b. How long have you been in your current position?
   c. Where were you before this?
   d. How many clinical trials are you currently involved with? What kinds of trials?
   e. How many Academic sites involved? How many community sites involved?

b) **CRO-Investigative Sites**

3. I am particularly interested in the ways in which CROs and IS interact.
   a. Could you describe generally how those interactions work?
      i. What tends to go well? What tends to be challenging?
      ii. Who is involved?
      iii. How do things differ when you are interacting with an academic vs. a community based site?
   b. Do CROs tend to be involved with specific kinds of trials? If so, what kinds?

4. Please describe the process from the time you are looking to recruit a site, through to enrollment of the site and PI, through to the trial’s conclusion.
   a. What are the key qualities you look for in an investigative site?
   b. Under what circumstances would you seek out a community site over an academic site? Vice versa? Why?
   c. Who is primary contact in CRO/site interactions?
   d. Who negotiates terms of interaction?
   e. How are expectations (on both sides) expressed and addressed?
   f. If and when problems, disagreements arise—how are these handled?
5. In what ways (if any) do you think CRO involvement changes or impacts the research process or pre/post research processes (differently than just with sponsor)?
   a. Is there any impact on, for example, the ethics review application process? (Board used, documents submitted, process? Etc)
   b. Are there additional pressures or demands?
   c. Are these different from dealing directly with sponsors? How?

6. *Taking a step back, would you say that there are factors working at this interface that can tend to lead people to act more or less ethically? If so-what might these be and why?*

7. What, from your perspective, are the biggest challenges/concerns that arise in general terms, when working with an investigative site? How do these differ between an academic vs. community based site? How are these addressed? What documents or materials do you turn to for guidance/clarification (if any)?

8. What documents (if any) do you look to for guidance for your ethical & legal responsibilities in clinical trials?
   a. Are these helpful? Problematic?
   b. Sufficient? Are there gaps you would like addressed?
   c. Suggestions?

c) **Academic Investigative Sites & Community Investigative Sites**

9. I want to better understand the similarities, differences and relationships between academic and community based investigative sites. Can you describe—based on your experience—generally the major similarities and differences between how these kinds of sites function?
   a. Differences in staffing?
   b. Kinds of trials conducted at each kind of site? Different? If so-why?
   c. Are there overlaps in staffing? That is, do some individuals work in both contexts simultaneously? If so—what are the advantages/disadvantages of such a setup?

d) **Concluding Questions**

10. Is there anything we have not talked about that you think is important?
11. Are there particular areas you would recommend that I pursue?

**It would be helpful to hear your thoughts on this study.**

- Why did you decide to participate in this study?
- What do you hope I will learn from this study?
- Do you have any other comments, suggestions or perhaps questions you think I should ask of other participants?

**Thank you for your generous participation in my study.**
A.3 Sponsor Interview Schedule
- Check participant has had time to read consent form.
- Review essential aspects (i.e., purpose of study, what is being asked, confidentiality, how I will handle any concerns, risk and agreement to maintain data for longer than normal)
- Ask if there are any questions or concerns.
- Double check that all required boxes are checked and that participant has a signed copy of the consent form for their records.

**a) General: Background and industry related experience**

1. Could you please tell me about your current position?
   a. How would you define your role/responsibilities?
   b. What kind of training or professional background led you to this role?
   c. Do you deal with CROs in your current role?
   d. How long have you been in your current position?
   e. Where were you before this?
   f. *How many clinical trials are you currently involved with? What kinds of trials?*
      i. *How many Academic sites involved? How many community sites involved?*

2. Please tell me a little about your background and experience working directly and indirectly with CROs.
   a. Have you ever worked for, or been employed by a CRO? Pharmaceutical sponsor (depending on current position)? [If both, how did those experiences differ?]
   b. Have you ever been employed by either a community or academic investigative site? If yes—follow up with questions re sites later in the interview.

**b) Sponsor-CRO relationship**

3. Could you tell me a bit about what, from your perspective, seem to be the current trends in CRO-Sponsor relationships?
   a. Is there a move towards closer partnerships? Or a tendency to diversify across a number of CROs?

4. Could you tell me about how you go about selecting a CRO?
   i. In person visits important? Why/why not? Do they happen?
   ii. What do you look for when hiring a CRO?
   iii. Who do you primarily deal with at the CRO during the selection process?

5. Do you have experience (from sponsor perspective) of working with both ACROs and non ACROs? Could you describe some of the key differences from sponsor perspective?
   a. When would you choose to work with an Academic Contract Research Organizations (eg JSS Medical Research based in Montréal-affiliated with McGill, Laval and U de M); For specific kinds of trials?
b. Do ACROs tend to have access to different kinds of sites than non-academic CROs?
c. More common to work with CROs or ACROs?

6. What would you describe as some of the main advantages/disadvantages of working with an academic CRO vs a non-academic CRO?

7. What, from your perspective, are the biggest challenges/concerns that arise in general terms, when working with a CRO?

8. Can you describe for me how agreements between CRO and sponsor are negotiated?
   a. A great deal of detail, or “we are hiring you to manage this project…”
   b. Has there been a shift in the kind of work being delegated to CROs?
      i. For example-I have heard from other interviews that there may be a growing trend for pharma sponsors to delegate hiring of staff (eg CRAs) to CROs—so the staff are actually employed by CROs but are then working solely with one sponsor on a few of their trials. Has this been your experience? Probe both if yes and no; (advantages/disadvantages)

9. I have a couple of questions about CRAs-
   i. Clarification point: CRA & Monitor? Term seems interchangeable in the literature, but have spoken to some people that have drawn a distinction (CRA-more of a project manager and Monitor-more dealing with site specific issues)—your take? (Not needed)
   ii. Would you say CRAs tend to be independent contractors, CRO employees or Sponsor employees? Adv/disadv from sponsor perspective to each of these?

10. Could you tell me a bit about the site selection process, and how often CROs are involved with this, vs how often sponsors take care of this themselves?

11. Do you have experience working with both academic and non-academic sites? (Here draw out the different kinds of sites—get her take on the distinctions);
   a. Main advantages/disadvantages of each?
      i. Training levels of staff?
      ii. Speed?
      iii. Efficiency?
   b. When would you work with an Academic site vs. non-A site?
   c. Kinds of trials conducted at each kind of site? Different? If so-why?
   d. Are there overlaps in staffing? That is, do some individuals work in both contexts simultaneously? If so—what are the advantages/disadvantages of such a setup?
12. How aware are sponsors of the kinds of demands/requirements CROs make of the sites they are managing? How much oversight does the sponsor typically have of this relationship?

13. Do you think CROs place different pressures (kinds or degrees) on sites than do sponsors?

14. In what ways (if any) do you think CRO involvement changes or impacts the research process (differently than just with sponsor)?
   a. In terms of how things happen at the site?
      i. Ethics review
      ii. Recruitment;
      iii. Consent;
      iv. Data collection
      v. Researcher/human subject interaction generally

15. From your perspective, what are some of the most common difficulties/challenges/disagreements that arise between CROs and Sites? (Note here: if CRO as middleman and CRA being gone around etc doesn’t come up----raise this and ask whether sponsor perceives this to be a problem and how addressed?)
   a. How often do sponsors hear about these problems/tensions/disagreements?
   b. Typically from whom?
   c. What steps can the sponsor take in these cases? Does sponsor tend to intervene?

16. In general terms, what kinds of things would lead you to fire a CRO?
   a. Site performance an issue?
   b. Once a CRO has been fired, what is the likelihood of establishing another working relationship with that company?

17. Taking a step back, would you say that there are factors working at the Sponsor-CRO interface that can lead to ethical challenges (for CRO)? At the site level? If so—what might these be and why?

18. What, from your perspective, are the biggest challenges/concerns that arise in general terms, when working with an investigative site? How do these differ between an academic vs. community based site? How are these addressed?

19. What documents (if any) do you look to for guidance for your ethical & legal responsibilities in clinical trials?
   a. Ever refer to TCPS?
   b. Are these helpful? Problematic?
   c. Sufficient? Are there gaps you would like addressed?
   d. Suggestions?
d) **Concluding Questions**
   20. Is there anything we have not talked about that you think is important?
   21. Are there particular areas you would recommend that I pursue?

**It would be helpful to hear your thoughts on this study.**

a) Why did you decide to participate in this study?
b) What do you hope I will learn from this study?

**Thank you for your generous participation in my study.**
A.4 Consultant Interview Schedule
• Check participant has had time to read consent form.
• Review essential aspects (i.e., purpose of study, what is being asked, confidentiality, how I will handle any concerns, risk and agreement to maintain data for longer than normal)
• Ask if there are any questions or concerns.
• Double check that all required boxes are checked and that participant has a signed copy of the consent form for their records.

A. General
1. Please tell me a bit about your current role and responsibilities.
   a. How long have you been in your current position?
   b. Where were you before this?
   c. Have you ever worked for, been employed by a CRO or pharmaceutical sponsor (depending on current position)? If so, how does that knowledge and experience inform your current role?
   d. Have you ever worked as a researcher at either a community or academic investigative site?
   e. Do you know roughly how many clinical trials involving CROs are currently ongoing in Canada?
   f. How would you define your role/responsibilities in relation to these trials?

B. CROs & sites in Canada
2. What, from your perspective, are the key strengths of the current Canadian regulatory & ethics oversight frameworks in relation to clinical trials in Canada involving CROs? Weaknesses?
3. How are CROs and their activities regulated in Canada?
   a. What are the main documents outlining legal obligations and ethical responsibilities of CROs?
   b. In what ways are CROs considered separately from Sponsors?
   c. What are CRO reporting requirements? For example, if a CRO gets a report of some significant problem (SAE or serious protocol violation, for example) at one of its sites, does it meet its reporting obligations by bringing this to the Sponsor’s attention? Or must it make sure the information is received by the regulator (either directly, or indirectly through the sponsor)?
   d. What contact, if any, does Health Canada have with CROs in Canada? How does this take place? (Ie primarily through Rx&D? Other bodies?)
   e. Do you know—Roughly how many CROs in Canada? What resources would you look to as a reliable source for this kind of statistical information in Canada?
4. In what ways (if any) do you think CRO involvement may change or impact the research process or pre/post research processes?
   a. Is there any impact on, for example, the ethics review application process? (Board used, documents submitted, process? Etc)
   b. Are there additional pressures or demands?
   c. Are these different from dealing directly with sponsors? How?
d. What implications (if any) do you think CRO involvement has for the wellbeing of subjects?

5. What, from your perspective, are the biggest challenges/concerns that arise in general terms, in clinical trials involving CROs? How are these addressed?
   a. Do any of these concerns arise at, or impact the investigative site directly?

6. I am doing my work coming out of the Centre for Applied Ethics—and wondering if there are any ethical issues in your area that you think are important or would like to raise?

C. Investigative sites reporting requirements:
   7. Could you please describe the reporting requirements of the IS?
      a. For example, if something occurs at a site (eg SAE), does site meet its reporting obligations by bringing this to the CRO’s attention? Or must it make sure the information is received by the Sponsor? Regulator?
      b. What about if coordinator concerned that something not being done appropriately by PI—endangering the subject’s safety—what should be done?

D. Academic Investigative Sites & Community Investigative Sites
   8. I want to better understand the similarities, differences and relationships between academic and community based investigative sites. Can you describe—based on your experience—generally the major similarities and differences between how these kinds of sites function?
      a. Differences in staffing?
      b. Kinds of trials conducted at each kind of site?
      c. Are there overlaps in staffing? That is, do some individuals work in both contexts simultaneously? If so—what are the advantages/disadvantages of such a setup?

E. Concluding Questions
   9. Is there anything we have not talked about that you think is important?
   10. Are there particular areas you would recommend that I pursue?

It would be helpful to hear your thoughts on this study.

- Why did you decide to participate in this study?
- What do you hope I will learn from this study?
- Do you have any other comments, suggestions or perhaps questions you think I should ask of other participants?

Thank you for your generous participation in my study.
Appendix B: Initial Codes in NVIVO after 8 interviews coded (all categories)

Figure B.1: NVIVO Codes Part 1_Screenshot
Tree Nodes

- Predictions of future trends
- Previous work experience
- Prioritizing the subject
- Reasons for participating in my study
- Recruiting
- Retaining accountability and responsibility
- Sponsor-CRO outsourcing
  - Being a smaller sponsor
  - Factors influencing outsourcing decision
  - Hiring and Staffing
  - Taking Ownership
- Suggestions
- Technology troubles
- The cost of doing business
- Training
- Working across physical and cultural barriers
- Working with CROs
  - Changing CROs
  - Communicating & negotiating through and around CROs
- Working with sponsors
  - Working with smaller sponsors

Figure B.2: NVIVO Codes Part 2_Screenshot
Appendix C: List of 34 themes as distributed on Venn Diagram

<table>
<thead>
<tr>
<th>All:</th>
<th>Middleman</th>
<th>Lack of sufficient infrastructure at sites</th>
<th>Protocol deviations</th>
<th>Pressures to recruit faster</th>
<th>Insufficiently involved PI</th>
<th>Training and staff issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRO/Site</td>
<td>Sites treating CRO differently than sponsor (less responsive)</td>
<td>Expectations from the top to do more with less and the impact this has on each of CRO and Site</td>
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<tr>
<td></td>
<td></td>
<td>Shrinking budgets (this actually probably reported by all)</td>
<td>Pressure to change the data/massaging reporting</td>
<td>Frustrations around lack of ability to give answers to site</td>
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</tr>
<tr>
<td>CRO/Sponsor</td>
<td>Sites inappropriately deviating from protocol</td>
<td>CRO using sponsor as a stick (CRO admit it; sponsor frustrated by it)</td>
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<tr>
<td>Sponsor/site</td>
<td>Payment issues and challenges when CRO involved with payment</td>
<td>CROs trying to cut corners—on a budget and trying to make a profit</td>
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<td></td>
<td>CRO disrupts ability to develop relationship between site and sponsor</td>
<td>High staff turnover and poor training and burnout</td>
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<td></td>
<td>Lack of dedication and knowledge of product/protocol—“not their baby”</td>
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<tr>
<td>Site:</td>
<td>Coordination of academic site departments is tough and not appreciated as a potential obstacle by CROs and sponsors;</td>
<td>Sponsor not spending money on EDC systems that will facilitate functions at site</td>
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<td></td>
<td>Privacy breaches and data security concerns (pre-screening and removal of data)</td>
<td>Protocol not fitting with research realities</td>
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<td></td>
<td>Happens both sponsor and grant studies—in latter seems to depend on how involved/present the PI is at the site</td>
<td>Sponsor not appreciating the tension between clinic and research—denying access to drug for patient;</td>
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<tr>
<td></td>
<td>Protocol design concerns</td>
<td>RH not talking to left hand in organization</td>
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<td></td>
<td>Inconsistency between teams of how things are done in the institution—both sponsor and CRO</td>
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<tr>
<td>Sponsor</td>
<td>Monitors lying about monitoring</td>
<td>Scope creep when contracting with CRO</td>
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<tr>
<td></td>
<td>Academic CROs going beyond what they do well</td>
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<tr>
<td>CRO</td>
<td>Insufficient backing by Sponsor</td>
<td>Having sites go around to sponsor</td>
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<td></td>
<td>Coordinators falsifying consent</td>
<td>Being pushed by sponsor to recruit sites they don’t want to enroll or don’t have confidence in.</td>
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</tbody>
</table>
## Appendix D: Summary of Main Issues Discussed by Participants in Chapter 6

### Table D.1: Summary Table for Chapter 6

<table>
<thead>
<tr>
<th>Issue</th>
<th>Investigative Site</th>
<th>CRO</th>
<th>SPONSOR</th>
<th>CONSULTANT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Increased pressure</strong></td>
<td>Ambivalent: Mixed Response.</td>
<td>Recognized risk; cause: sponsors expectations too high and unrealistic Sponsors want us to get things done ASAP, and hire us to exert more pressure on site so they don’t have to;</td>
<td>Recognized risk: CROs promise more than they can deliver CROs want to beat the timelines to decrease cost and increase profit-add more pressure than sponsor would on same timeline</td>
<td>Recognized risk: Tightening budgets + no regulatory oversight; + sponsor oversight decrease in tight times=CROs try to see what they can get away with</td>
</tr>
<tr>
<td><strong>Privacy /data security: Recruitment</strong></td>
<td>Inappropriate “pre-screening” and other recruitment methods Especially if US CRO/Sponsor;</td>
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<tr>
<td><strong>Privacy /data security: Data monitoring</strong></td>
<td>Patient information leaving site;</td>
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<td></td>
<td>Major area of concern; Lack of knowledge across all parties;</td>
</tr>
<tr>
<td><strong>GCP Interpretation</strong></td>
<td>Grey areas cause concern; Draw on REB to validate and support their position;</td>
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<tr>
<td><strong>CRO: MIDDLEMAN</strong></td>
<td>Delayed responses; Misinterpretations of site questions by CRO;</td>
<td>Lack of sufficient information and decision making authority;</td>
<td>Recognized Site and CRO concerns;</td>
<td>Sensitive to the issues raised by site and CRO</td>
</tr>
<tr>
<td><strong>Frustrated Communication</strong></td>
<td>Increased workload</td>
<td>Above leads to more work and therefore cost implications;</td>
<td>Expressed some awareness of implications this has for sites in terms of workload/cost;</td>
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</tr>
<tr>
<td><strong>Disrupted relationship</strong></td>
<td>CROs alienate site from sponsor; sponsors not sufficiently aware of site needs/realities or CRO related cost implications; Makes it harder to resolve issues;</td>
<td>Sponsor goes around CRO, erodes credibility;</td>
<td>Agrees CROs disrupt the relationship but on most points this is something that can be sacrificed; Leads to loss of potentially valuable insights &amp; can damage important sponsor-site relationship; Aware of CRO issues, but not area of concern;</td>
<td>Sensitive to issues-particularly from Sponsor perspective;</td>
</tr>
<tr>
<td><strong>Payment</strong></td>
<td>Prefer to deal with sponsors, even though problems with both</td>
<td></td>
<td>Know this is an issue for sites;</td>
<td>This is a major area of concern for sites and sponsors should be more aware;</td>
</tr>
<tr>
<td>Issue</td>
<td>Investigative Site</td>
<td>CRO</td>
<td>SPONSOR</td>
<td>CONSULTANT</td>
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<td>--------------------------</td>
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<tr>
<td>Form over substance</td>
<td>CROs don’t solve problems; Not their baby; cookbook or check list approach; narrow focus on tasks;</td>
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<td>Less driven to identify and address problems;</td>
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<td>(checklist)</td>
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<tr>
<td>Training: General</td>
<td>CRO staff less well trained than sponsor; spread too thin; however problems arise across both sponsor and CRO staff-depends on individual;</td>
<td>Recognized problem: Inexperienced staff work independently too early; CRAs not supported sufficiently by CROs</td>
<td>CRO staff less experienced than sponsor staff and more overworked;</td>
<td>Echoed this concern, but also noted problems can arise in both CRO/Sponsor;</td>
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<tr>
<td>Competency</td>
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<tr>
<td>Staff Turnover</td>
<td>Big problem with CROs; Major disruption to work; major increase in cost that site expected to absorb; Poor transition; Emotional cost as relationship severed;</td>
<td></td>
<td>Know this is a concern in terms of cost and time;</td>
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</tr>
<tr>
<td>Organizational Elements</td>
<td>Too many people involved and too little internal communication;</td>
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<td>Recognized organizational issues can present challenges for sites;</td>
</tr>
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<td></td>
<td>Too much variation between teams in a given CRO;</td>
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<tr>
<td>Advantages [for sites]</td>
<td>More responsive; more attuned to site realities than sponsor; potential to be advocate and buffer for site; More knowledgeable than some small biotechs;</td>
<td></td>
<td>Stressed they can be better organized and more responsive to sites needs; Create tools to facilitate processes at sites;</td>
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<tr>
<td>of working with CROs</td>
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*Note: Italics means these points were made in the data, but only to a very limited extent; that is, they were only touched on by one participant and in a very limited way.*