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The Market for Ethics: Human Subjects Research Oversight in the United States and Canada

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The Market for Ethics:
Human Subjects Research Oversight in the United States and Canada

By

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Professor Ann Keller, Chair
Professor Christopher Ansell
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Abstract

The Market for Ethics: Human Subjects Research Oversight in the United States and Canada

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An estimated 2.5 million Americans participate in clinical research annually. Participation exposes human subjects to significant physical risks including death, as it often involves ingesting or introducing drugs and devices to the body that have not yet been proven safe or effective. In the US, a set of policies around the regulation of biomedical research emerged as a politically and contextually contingent result in the post-war years. The centerpiece for oversight of human subjects research was the local, hospital- or university-based IRB. It emerged at the height of organized medicine's political and social power and derived from a logic of professional autonomy.

Much has changed. Today, 80% of clinical research in the US occurs outside the academic medical context, in community settings such as physicians' offices and freestanding research clinics. These research studies are overseen by thousands of IRBs registered with the federal government, some of which are for-profit businesses. The world for which the oversight regime was built – trained clinical researchers submitting their proposed research to the scrutiny of their trained colleagues in a university setting – no longer exists. In spite of the dramatic changes in who is carrying out research and the associated changes in their motivations for doing so, the regulations governing IRBs and clinical research oversight remain stable.

Little empirical scholarship exists regarding how the IRB oversight mechanism is operating now that the research landscape has changed so substantially. Little scholarship empirically charts the entire ecology of IRBs, which now include IRBs in diverse settings such as non-teaching community hospitals, health systems, government facilities, universities and teaching hospitals, as well as independent, central, and commercial IRBs. There exists no full accounting of how many IRBs there are, of which types, in which locations – and few analytical accounts of variations between IRBs based on organizational or environmental factors.

This dissertation reports on the results of an original qualitative research study that involved interviews with IRB members and administrative professionals from commercial IRBs, nonprofit healthcare organization IRBs, academic and government IRBs in the US and Canada. The chapters explore various aspects of the current IRB ecology, in light of drastic changes to the institutional and economic environments in which clinical research occurs over recent decades. After a brief introduction, the second chapter explores IRB professionals' experiences with, and responses to, the legal and regulatory environment in which these professionals and their organizations operate. The third chapter explores variation between types of IRBs, identifying governance gaps and best practices. The fourth chapter explores the attitudes of IRB

professionals toward the commercialization of research ethics review in the United States and Canada. The fifth chapter provides some conclusions and steps for future research.

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CHAPTER 1: INTRODUCTION

This dissertation begins with an observation: since the 1980s, regulatory policy in the United States (and to some extent our peer nations) has generally shifted toward a neoliberal or 'regulatory capitalism' model (Braithwaite 2008; Levi-Faur 2011). Government actors are no longer a one-stop shop for all aspects of regulatory control; instead, government actors have become one node among many within a governance matrix. Namely, government actors are the node that 'steers' the ship, letting the regulated entities do the 'rowing' (Burris 2008). Political scientists, legal scholars, and others have identified this phenomenon across broad swaths of social and economic life, including in health care policy (Trubeck 2008). Defining 'regulation' as a set of (legal) rules designed to constrain the behavior of businesses, professionals, and other large organizations, scholars examining this phenomenon observe that regulation is becoming less state-centered and more hybrid, with responsibilities at all levels of standard-setting, oversight, and enforcement assigned more frequently to non-state actors in nodal relationships with governments and others.

This dissertation explores a particular type of organization that has been subject to a hybrid form of regulation for many decades: the institutional review board (IRB). The papers in this dissertation use IRBs as a case study to explore broad contemporary themes in law, regulation, and governance. While IRBs are used as a case study in these papers, they are themselves subjects very worthy of scholarly examination and critique. These organizations play an essential role in protecting public health and safety, as they serve as ethical gatekeepers for clinical trials in which 2-3 million Americans participate annually. Yet despite their importance, IRBs are quite empirically understudied.

An estimated 2.5 million Americans participate in clinical research annually. Participation exposes human subjects to significant physical risks including death, as it often involves ingesting or introducing drugs and devices to the body that have not yet been proven safe or effective. In the US, a set of policies around the regulation of biomedical research emerged as a politically and contextually contingent result in the post-war years. The centerpiece for oversight of human subjects research was the local, hospital- or university-based IRB. It emerged at the height of organized medicine's political and social power and derived from a logic of professional autonomy.

Much has changed. Today, 80% of clinical research in the US occurs outside the academic medical context, in community settings such as physicians' offices and freestanding research clinics. These research studies are overseen by thousands of IRBs registered with the federal government, some of which are for-profit businesses – commercial IRBs. The world for which the oversight regime was built – trained clinical researchers submitting their proposed research to the scrutiny of their trained colleagues in a university setting – no longer exists. Although their sector has undergone dramatic changes in the past 30 years, the policy regimes to which IRBs are subject have remained stable – a classic case of policy 'drift' in which the formal policies have not been updated to reflect changed conditions in the world.

Outside of the US, many nations have also also adopted the group-review model of research oversight, likely as a result of needing to meet FDA requirements. This is true in Canada, where Research Ethics Boards (REBs) are the functional analog to IRBs in the US. The institutional arrangements, and level of government centralization, vary between the US and Canada. In particular, while commercial IRBs have gained a tremendous amount of market share in the US, this has been less the case in Canada. Indeed, institutions that are part of the

Canadian public healthcare system (including universities and hospitals) cannot use the services of commercial IRBs. Little empirical work has tried to understand the functioning of the IRB mechanism cross-nationally, particularly between the US and Canada, or engaged in analysis of what one nation may learn from the other's experience with adjusting to a shifting institutional environment in which research is increasingly leaving public or institutional settings, in favor of private or community-based settings.

Proceeding from these observations, this dissertation explores a few facets of the current research ethics review environment. Importantly, the dissertation does not offer a fully-formed theory of what would constitute 'good' or 'bad' research oversight. The entire field of bioethics has struggled for decades to do so, and regulatory scholars also struggle with how to assess the 'effectiveness' of one regulatory regime over another, when outcomes are difficult to observe. Instead, this dissertation is concerned with identifying important building blocks to address weaknesses and strengths of the current regime, and to tie this case into broader themes in law, regulation and governance, and comparative political studies.

This dissertation offers empirical and theoretical contributions. The empirical pieces of this dissertation report on data from an original qualitative research study. The theoretical pieces of this dissertation explore the functioning of the current domestic system by drawing from and contributing to the scholarships of law and regulation, legal sociology of organizations, and comparative political studies. The chapters that comprise this dissertation raise questions about the capacity of the system given current realities, as well as questions about whose interests are most served by the current system, and how policy interventions might encourage IRB types and behaviors that more clearly serve the public interest.

CHAPTER 2: IRB PROFESSIONALS' EXPERIENCES WITH, AND RESPONSES TO, LEGAL AND REGULATORY ENVIRONMENT

I. Introduction

Since the 1980s, regulatory policy in the United States has generally shifted toward a neoliberal or 'regulatory capitalism' model (Braithwaite 2008; Levi-Faur 2011), which has been layered on top of older styles of regulation, including command and control. Government actors are no longer a one-stop shop for all aspects of regulatory control; instead, government actors have become one node among many within a governance matrix. Government actors increasingly 'steer' the ship, letting the regulated entities do the 'rowing' (Burris 2008). Political scientists, legal scholars, and others have identified this phenomenon across broad swaths of social and economic life, including in health care policy (Trubeck 2008). Regulation is becoming less state-centered and more hybrid, with responsibilities at all levels of standard-setting, oversight, and enforcement assigned more frequently to non-state actors in nodal relationships with governments and others.

Institutional review boards (IRBs) are a particular type of organization that has been subject to a hybrid form of regulation for many decades. These are organizations that oversee and approve clinical research. Participation in these research projects exposes human subjects to significant physical risks including death, as it often involves ingesting or introducing drugs and devices to the body that have not yet been proven safe or effective.

IRBs play an essential role in protecting public health and safety, as they serve as ethical gatekeepers for clinical trials in which 2-3 million Americans participate annually.[1] Yet despite their importance, IRBs are empirically understudied. Their sector has undergone dramatic changes in the past 30 years. While IRBs were once housed nearly exclusively at universities and teaching hospitals and oversaw research done in-house, IRBs have proliferated in form and venue as the pharmaceutical industry has become the central funder of research and has pushed it from the academy into the community. Most literature on IRBs has focused on academic IRBs, rather than the field more broadly. And no scholarly work has characterized the full ecology or explored how members of these organizations, which are both regulated by agencies and regulators themselves of science and medicine, may experience, behave, and respond to legal and regulatory risks and pressures in their task environment.

This paper interprets the results of empirical research through the lens of IRBs as regulated entities. It applies frameworks related to how organizations understand, construct, and respond to risks, and related to how organizations translate vague laws into action. The paper applies sociolegal and organizational studies frameworks to explore the following broader questions: how do legal and regulatory encounters shape risk perception and firm behavior? Do broader legal and regulatory enforcement strategies, particularly adversarial legalism, apply in this sector? If not, why not? Does an IRB's risk tolerance vary systematically based on endogenous or exogenous factors, and as a result, are some IRBs better equipped than others to carry out its tasks? If so, does this suggest policy interventions to encourage or require certain types of IRBs?

[1] Note that while IRBs also oversee social science research, generally at universities, this paper does not include social science research within the purview of its analysis. This paper is **exclusively** focused on IRBs overseeing biomedical research, principally clinical trials of drugs and devices.

More specifically, the paper offers an exploration of how IRBs experience legal and regulatory risks, adversarial legalism, and how these organizations use professional expertise to filter and navigate the translation of vague law on the books into action. This involves investigating the extent to which IRBs may vary in their approach to risks – including risks to research subjects, and legal and regulatory enforcement risks. The paper hypothesizes that such variation may be systematic, based upon certain organizational and environmental factors, such as whether the IRB is for profit or nonprofit, and the size of the research program it oversees.

To address these questions, I designed a qualitative study intended to provide an in-depth perspective on the ways that IRB professionals across a range of IRB types and venues approach issues related to law and regulation. The objectives of this study were to explore how essential factors varied between IRBs along some key performance axes including legal and regulatory encounters and risk perception, and use of counsel to assist in translating vague laws into action. The paper analyzes the results of that research to consider what we can learn about the motivations and behaviors of organizations that are regulated entities, and that also have delegated regulator functions.

The paper offers empirical and theoretical contributions. First, the paper will evaluate IRBs descriptively, providing a first-ever analysis of IRB empirics (such as how many there are, where they are located). It will also provide qualitative information about how IRB members and senior staff experience regulatory and legal encounters, perceive and respond to such risks, and use counsel.

Second, the paper will offer analytical insights about how professionals from different types of IRBs experience legal and regulatory encounters, how they understand and respond to risks, including legal and regulatory risks, and how this influences behavior. A central finding is that IRB professionals across various types of organizations do not experience significant legal or regulatory encounters of an adversarial kind, and do not perceive legal or regulatory risks as particularly high. This has implications for theories of organizational sociology, and sociolegal studies.

Third, the paper will offer analytical insights about how different IRBs translate 'law on the books' into 'law in action.' A central finding is that, while the laws on the books are vague (by design in this case – it is a feature of management-based regulation, of which IRB oversight is an example), IRBs differ in the frequency with which they call upon legal counsel to assist in translating the vague requirements into practice. Data from this study suggest this variation may be systematic: organizations overseeing large research portfolios tend to use counsel frequently and speak positively about their role, while smaller organizations and independent IRBs tend to use counsel very infrequently and do not tend to report that counsel has much value.

The paper proceeds as follows. Section II provides a brief background about the regulation of biomedical research and IRBs, and the shifts in the institutional environment that have fractured the institutional field, and relocated most IRB activity from academic to non-academic settings. Section III provides a literature review of key texts in sociolegal studies and organizational studies related to legal and regulatory encounters, risk perception, and mechanisms (including use of counsel) organizations use in the translation of law on the books into law in action. Section IV provides the methodology for the original research study. Section V provides key results, and Section VI provides an analysis with particular implications for sociolegal studies and organizational theory. Section VII concludes with limitations of the present study and suggestions for future research.

II. Background: Human Subjects Research and IRBs

In order to understand the issues discussed in this paper, it is first necessary to provide a brief history of human subjects research, its regulatory regime's development, how IRBs fit into the system, and how the enterprise has changed over time.

A. Human Subjects Research

The ethics of involving human subjects in medical research has a long and storied past. What constitutes 'ethical' or 'unethical' research is context-specific, and changes over time. Prior to the mid-20th century, physicians made decisions of research ethics individually, without input from outsiders (Halpern 2008; Rothman 1991; Starr 1982). This settlement reflected the public's trust in doctors, and the political and social power of medicine (Starr 1982; Rothman 1991). Medical research and medical practice were part and parcel of the same set of professional activities, subject to professional self-regulation.

Commercial interests were not prominent in biomedical research until the late 20th century. Early American pharmaceutical interests were not particularly active in clinical research – they were principally manufacturing firms, as most drugs were invented in Europe. As Robert Kagan has noted, government regulation tends to emerge when other legal means (such as litigation) and the market do not result in socially acceptable levels of protection, and the government is willing and able to enact it (Kagan 2000). Up until about the 1950s, clinical research was unregulated because the public did not perceive that other legal means and the market were inadequate to protect people.

A variety of factors caused a shift in this perception. These factors included early efforts by government funders to shield themselves from liability, lawsuits related to governmentally funded medical research, the civil and patients' rights movements, and the rise in suspicion of authority and physicians (Starr 1982; Rothman 1991). These circumstances created the conditions under which prior types of research programs like those at Willowbrook and Tuskegee came to be seen as scandalous. Public values shifted, as did the risk assessment of government funders. Key stakeholders including the public and government funders came to believe that other legal means and the market were no longer producing adequate levels of protection (or legal cover) (see, e.g., Rothman 1991).

The system of government regulation that emerged was a slight ratchet up, from pure self-regulation to a delegated, management-based governance technique. Its centerpiece was the IRB. Its use was mandated by federal law in 1974, although it had been required for federally-funded projects since the 1960s and had been in practice at NIH since the 1950s. The IRB as a mode of governance was premised on the self-regulation of physician-researchers and the peer review mechanism that has long been a feature of professional regulation. It was not a command-and-control mechanism, and was initially only required as a condition of federal funding. The IRB mode of governance left most decision-making up to local actors in peer review, principally in academic settings because that is where the bulk of clinical research occurred. The government's role was to steer at a distance; IRBs themselves would do the 'rowing.'

At the same time, the regulation of pharmaceutical products emerged along a different trajectory. It emerged following a product regulation logic, rather than via a professional self-regulation logic. Regulations requiring IRB oversight of products intended to be submitted to

FDA for marketing approval were not finalized until 1981. Once those regulations were established, the same activity (research oversight) and the same set of organizations (IRBs) came to be overseen by two distinct agencies. FDA oversees IRBs as a part of the regulation of medical products; HHS's Office for Human Research Protections (OHRP) oversees IRBs as part of the agency's duties as a research funder. Both agencies are responsible for enforcement, which involves routine FDA audits and inspections, and OHRP investigations in response to complaints.

Much has changed in the institutional environment in the intervening decades, particularly the rise of the pharmaceutical industry, although the regulatory structures applicable to human subjects research oversight have remained stable.[2] The major shifts can be traced to Reagan's election in 1980, and various policies established during his administration that broadly conform to a neoliberal perspective on the role of government.

Chief among these were the Bayh-Dole Act and the Hatch-Waxman Act, which repositioned patent law in a way that led to a meteoric rise in the pharmaceutical industry (Angell 2005). The pharmaceutical industry replaced the federal government as medical research's funder in chief. While academic physician-researchers had once been instrumental in designing clinical studies, including industry-backed studies, this too changed as industry developed its internal research capacities. As the main funder of clinical research, and with its own internal preclinical research capacities, industry grew to need the academy less. Over time, it found it could run trials more quickly and more cheaply in alternative venues and with alternative partners. This led to the rise of a clinical research industry full of ancillary companies that help industry test its products. Indeed, the vast majority of clinical research now occurs in community settings, such as physicians' offices and freestanding research clinics (Fisher 2009, Petryna 2011). The physicians engaged as investigators in this research are not scientists; they are merely contractors implementing industry-written protocols (Fisher 2009). Today, 75% of clinical research now occurs in non-academic settings (Fisher 2009).

IRBs have also evolved. They are also no longer located just in academic or governmental settings. As described in Section IV, there are now approximately 1,250 unique IRB organizations registered to oversee clinical research in the US. Some of these are at universities and academically-affiliated medical centers; but others are located in a variety of other institutional and organizational settings. These include community and health system IRBs (including nonprofit, for-profit, and government health providers), non-profit independent IRBs, IRBs operated by local, state, and federal government divisions and agencies. There are also commercial for-profit IRBs, which are for-profit businesses that review clinical research for a fee. How many of each type remains unknown.[3]

The regulations requiring IRB approval of FDA-regulated products and federally-funded research have remained stable despite these shifts. These organizations remain the ethical gatekeepers for medical products testing. They are still subject to light-touch regulation, based on a legacy of the self-policing powers of the medical profession. But little is known descriptively about these organizations, or empirically about how they operate, particularly now that the research landscape has changed so substantially from when the mechanism was first

[2] See Appendix A for schematics demonstrating changes in primary relationships between sponsors, researchers, and IRBs.
[3] The literature often states that there are more than 3,000 IRBs in the US, although my research shows that there are actually about 1,700 IRB panels, and about 1,275 unique organizations, that are registered as active in good standing on OHRP/NIH's database to oversee FDA-regulated research. The database includes thousands of IRBs in deactivated status, and hundreds not registered to oversee clinical research.

mandated. In C.K. Gunsalus's assessment, "virtually no scientific evidence is brought to bear on any aspect of the debate about how IRBs function. Unrealistic and untested assertions abound" (Gunsalus et al 2007).

Further, little scholarship tries to describe or interrogate the entire ecology of IRBs. Some empirical work looks at academic IRBs, and there is quite a bit of non-empirical complaint about academic IRBs, particularly those overseeing social science research. There is also some scholarship about clinical research more broadly that touches upon the existence of commercial IRBs, but little empirical research has looked at the totality of these organizations, which now include IRBs in diverse settings such as non-teaching community hospitals, health systems, government facilities, universities and teaching hospitals, as well as independent, central, and commercial IRBs. There exists no full accounting of how many IRBs there are, of which types, in which locations – and few analytical accounts of variations between IRBs based on organizational or environmental factors. The existing relevant literatures are reviewed just below.

a. Empirical Variability

An extensive literature demonstrates that IRBs display a significant range of variability in their decisions – both between different IRBs, and within the same IRB over time. In 2011, Christine Grady and Lura Abbott published a literature review of the empirical IRB scholarship. The authors reviewed 43 empirical studies evaluating US IRBs, and reported that the studies show IRBs differ in their application of federal regulations, in the time they take to review protocols, the decisions they make, and in the committees' structures and processes (Abbott and Grady 2011). Despite the volume of this literature, the authors note that more research is necessary, to investigate what issues IRBs themselves find important and to offer an analytical framework for assessing the organizations, rather than simply descriptions. Relevantly, none of the studies in the Abbott and Grady article, and none identified since, have focused explicitly on non-academic IRBs. Some may include non-academic IRBs (generally non-teaching hospitals) in surveys or discussion, but this is uncommon. The overwhelming majority of work is related to university IRBs and IRBs at academically affiliated teaching hospitals.

Many studies identify variation in IRB practices, and inconsistencies within and among IRBs (Emanuel, Wood, Fleischman, Bowen, Getz, Grady 2004; Wood, Grady & Emanuel 2004; Abbott and Grady 2011; Klitzman 2011). Some focus on variation between IRBs reviewing multicenter studies (Greene and Geiger 2006; Stark 2010; Menikoff 2010). Some address differences in who participates at meetings (Lidz 2012; Rothstein and Phoung 2007). Some look at how IRBs and their leaders approach industry-funded research (Klitzman 2013) and financial conflicts of interest (Weinfurt 2009). Of particular interest are older articles, which can provide interesting historical detail and context, useful in considering how IRBs and their processes have changed over time (Veatch 1982; Meslin 1994; Cowan 1974; Brown 1979; Heath 1979).

In addition to articles, a few scholars have published books that include empirical accounts of IRBs and their variation. These include Laura Stark's 2011 book Behind Closed Doors, and Robert Klitzman's Ethics Police? (2015). Klitzman's book reports on a qualitative project based upon interviews with IRB leaders and members from top NIH grantee universities and academically affiliated research institutions (n=46 individuals from 34 IRBs). Klitzman's chapters provide insight into how IRBs weigh risks and benefits, define research and how good it needs to be in order to approve, and how they decide what to tell subjects. He also explores

IRBs' relationships and encounters with regulators, importantly noting (anecdotally) that legal and regulatory pressures have led some IRBs to "become more formal" and "risk averse" (Klitzman 2015, 182; 224; 232).

Klitzman's study is important as the first larger-scale empirical project that tries to understand how and why IRBs behave as they do. However, its design leaves room for additional research. First, his study only includes IRBs from high-performing, highly ranked NIH grantee institutions. By excluding so many other types of IRBs, his results are not generalizable to the population of IRBs overall. Second, Klitzman's study does not address legal or regulatory concerns or experiences as a focus or a framework for understanding IRB behavior. Third, his study is almost entirely atheoretical, and does not tie research governance to broader themes in regulation and governance, political science, or sociology. Finally, the work is expositive but not analytical – he does not offer causal or correlational claims between IRB behavior and any particular features either exogenous or endogenous to the organizations themselves, and states directly that he does not believe IRBs vary "systematically in any one clear direction. IRBs do not differ according to fixed…categories." (Klitzman 2015, 353).

b. IRB Ecology

A related literature addresses the variety of IRBs by organization and type. As discussed above, most literature focuses on academic IRBs. Other types of IRBs include independent IRBs and commercial IRBs (these are sometimes defined synonymously, but not always). Mirowski & Van Horn discuss the rise of CROs and independent IRBs (Mirowski & Van Horn 2005). Comparing local (generally academic) IRBs to independent/commercial IRBs, the authors note that, among other factors, independent IRBs review protocols faster, and are subject to less regulation (just FDA regulations, as opposed to also NIH and OHRP regulations (Mirowski & Van Horn 2005).

Legal scholars and commentators have also written about the movement of research from academic to community settings, and the changing role of the IRB and its organizational location. Of note, David Forster, then Director of Regulatory Affairs at Western IRB, the largest commercial IRB in the country, set out the historical origins of commercial IRBs and addressed some criticisms of its operations including that commercial IRBs have an inherent financial conflict of interest and that they promote IRB shopping in the event that one IRB disapproves a protocol (Forster 2001). Although the use of commercial IRBs has accelerated, FDA has long acknowledged the existence and regulatory validity of commercial IRB review (Nightingale 1983).

Fisher's Medical Research for Hire (2009) and Elliott's White Coat, Black Hat (2010) both include short treatments of commercial IRBs. Fisher situates these organizations within the broader outsourcing and fragmentation of clinical trials. She mentions that the more than 40 for-profit IRBs in the US collected more than $60 million in 2002; Western IRB alone holds 50% of the market share (Fisher 2009, 11).

Elliott discusses the GAO's 2009 sting of commercial IRBs, in which an egregiously scientifically and ethically inappropriate protocol was sent to three commercial IRBs for approval.[4] While two turned it down quickly, Coast IRB approved it. Later, it was discovered that Coast had only turned down a single protocol of the several hundred it had approved in 5

[4] The protocol described pouring potentially toxic liquid into open cavities during surgery. Post-scandal, Coast went out of business.

years, and had revenue of close to $10 million a year (Elliott 2010, 159). Despite the blip of bad press, commercial IRBs are a growing industry – Chesapeake IRB was named by Deloitte as one of the fastest growing 'tech' companies in the US, and in 2007, a major stake in Western IRB was sold to private equity firm Boston Ventures (which also owns majority interests in NASCAR and Six Flags) (Elliott 2010, 166). His efforts to interview Western IRB professionals were mostly thwarted, because the firm is so protective of its proprietary property – including its methods of reviewing protocols. He argues that commercial IRBs have no incentive for other IRBs to do a good job, because their business activities are in competition with other IRBs. The implication (currently unsupported by empirical data) is that leaving this activity to the market may be detrimental to the public's health.

In addition, a few scholars have raised normative concerns about certain IRB types, particularly commercial IRBs. Some treatments question whether IRBs should be able to operate as for-profit companies at all (Emanuel 2006; Shamoo & Woeckner 2006; Lemmens and Friedman 2000; Lemmens and Thompson 2001). Others explore how independent different types of IRBs actually are (Macklin 2008). Yet others have explored the operation of central IRBs (Christian 2002; Wagner 2010). Finally, in 2009 the Government Accountability Office (GAO) undertook a sting operation of IRBs, particularly of commercial IRBs.[5]

c. Fragmentation of Clinical Trial Enterprise

In recent years, a number of scholars have published books (and some key articles) that explore the clinical research enterprise in the US. These works are largely empirical accounts based on qualitative research.

Jill Fisher's 2009 book "Medical Research for Hire" is an ethnographic study observing that, in the past two decades, the US pharmaceutical industry has completely reorganized the clinical testing of its products, moving from academic medical settings into the community. Currently, about 75% of clinical trials in the US are conducted in the private sector, by nonacademic, non-scientist physicians, who contract to oversee pharmaceutical trial protocols as 'site investigators,' recruiting their own patients or local community members. Fisher then explores the experiences of independent physicians and their staff in performing contracted research services for pharmaceutical companies.

Fisher surfaces systems-level insights. Chief among these is the insight that the replacement of academic medical centers by a 'proliferation of ancillary companies' (CROs, commercial IRBs, private practices, dedicated for-profit research centers) is congruent with the rise of corporate outsourcing and delegation overall (See also: Monahan's concept of delegating responsibility as a neoliberal strategy of 'fragmented centralization' 2005). This in turn is a reflection of neoliberal trends in the organization and management of corporate pursuits. She also ties these developments to broader instantiations of neoliberalism in US policy, in which the state has retreated from active involvement in managing risks, transferring responsibility to citizens to provide for themselves as individual and empowered 'consumers.' In this reading, individual citizen consumer-patient-subjects are given the 'choice' to participate in clinical research, with the risks to be assumed at the individual level. Of course, this neoliberal spin

[5] This operation produced a 2009 report and statement to Congress entitled "Human Subjects Research: Undercover Tests Show the IRB System is Vulnerable to Unethical Manipulation," and the transcript from the 2009 Senate Hearing, "Institutional Review Boards that Oversee Experimental Human Testing For Profit."

obscures the information asymmetries between patient-subjects and their health care providers, and their unequal power and economic positions.

Abadie's 2010 book The Professional Guinea Pig notes that while most early testing of drugs occurred in prison populations until the 1970s, since then, the industry has turned to the open market to find test subjects. While this shift was borne out of the desire to protect incarcerated people, over time it has harmonized with a broader neoliberal logic under which the state's ability (and obligation) to protect the public has declined, while commodification of the human body has increased. In this regime, individuals "feel that they are making their own choices and…take responsibility for their own actions, in particular actions that may place them at risk" (Abadie 2010, 160).

Many scholars have noted the decline of academic-sited research and the rise of alternative sites. Until recently, academic investigators were "key players" in the design, recruitment, and interpretation of data in clinical trials (Davidoff 2001). Into the late 1990s, most pharmaceutical companies didn't have in-house expertise to design protocols (Falit 2006). But firms have increasingly exercised control over protocol design, have hired top-level research physicians to work in-house on protocols (Falit 2006), and clinical trials have largely moved from academic settings into community settings (Fisher 2009). As of 2005, commercial sponsors provided 70% of funding for clinical drug trials in the US (Falit 2006, citing Mello 2005). That number has gone up, and more recent estimates are that 80% of clinical research is industry funded (Fisher 2009).

Others have explored the growth of contract research organizations (CROs) over the past 20 years. These businesses have "gradually taken over much of academia's traditional role in drug development" (Shuchman 2007, 1365). The industry has grown quickly (Rettig 2000). In 2001, CROs had $7 billion in revenue; by 2007, it was up to $17.8 billion. In 2004, just the top ten CROs enrolled 640,000 subjects that year (Shuchman 2007). CROs have been described as "data-production sweatshops" (Shuchman 2007, 1367). They're cheaper in part because they employ young, less experienced personnel (Fisher 2009). Philip Mirowski has written about the rise of CROs as a 'paradigm of privatized science' (Mirowski & Van Horn 2005).

III. Literature Review – Theoretical Frameworks

A. Organizational Sociology and Risk Studies/Regulated Behavior

This paper uses qualitative interviews with IRB professionals from IRBs across the ecology to explore how IRBs, as an example of an entity that is both regulator and regulated, experiences legal and regulatory risks, adversarial legalism, and how these organizations use professional expertise to filter and navigate the translation of vague law on the books into action.

Part of this involves exploration of the extent to which IRBs may vary in their approach to risks – including risks to research subjects, and legal and regulatory enforcement risks. The paper hypothesizes that such variation may be systematic, based upon certain organizational and environmental factors, such as whether the IRB is for profit or nonprofit, and the size of the research program it oversees. Halpern's study in Lesser Harms indicates such systematic variation may occur, while other scholars, including Klitzman, think otherwise. The paper will then explore the implications of this variation in light of the literature in organizational sociology and organizational approaches to risk. Some of these works cross over between organizational

sociology, legal sociology, and governance studies (Silbey 2011; Heimer 2005; Heimer 2008; Halpern 2008).

Sydney Halpern's book Lesser Harms (2004) is also a critical work on organizations and the management of technological risks and hazards. Halpern articulates the conditions under which certain organizations may be more or less risk adverse. She explores how different sponsors of vaccine trials in roughly 1920-1960 approached the risks posed by testing vaccine drugs in human subjects. Halpern shows that some sponsors were risk adverse, and others tolerant when confronting similar hazards (Halpern 2004, 15). She also identifies endogenous and exogenous factors that influenced their risk preference. She draws from two themes in the sociology of organizations. The first is that interactions with the environment affect organizational behavior (Scott 1998; Scott 2000). The second is that organizations tend to import legitimacy-conferring models from the law and the professions. This phenomenon is perhaps most commonly articulated with reference to DiMaggio and Powell's concepts of isomorphism (DiMaggio & Powell 1983), and to Meyer and Rowan's notion that adoption of institutional forms can be purely symbolic and kept separate from the organization's 'technical core' (Meyer & Rowan 1977).

She argues that several organizational dynamics affected a sponsor's willingness to sponsor in risky human subjects research (defined as studies that the medical community considered particularly hazardous). These include the sponsor's knowledge about the science underlying the study, the sponsor's experience with research controversy, and the sponsor's incentives for undertaking or for avoiding risk. The first, she notes, is a factor concerning the processes internal to organizations; the second and third involve organizations' relations with their environment (Halpern 2004).

She specifies a continuum of attitudes toward risk in three parts: risk avoidance, risk containment, and risk delegation. She then offers fascinating empirical evidence of this risk framework in action. Critically, she shows that among sponsors with high technical knowledge, those that were motivated principally by commercial incentives or "scientific commercialism" (pharmaceutical sponsors) tended to have higher risk tolerance than did sponsors motivated principally by other (academic and professional prestige) incentives (Halpern 2004, 85-87). She argues that corporate managers were undertaking a "huge financial gamble" in investing funds toward a vaccine, and therefore were willing to take bigger risks with regard to danger to human subjects. As she concludes, "perceptions of their relations with the regulatory and resource environments may have rendered some commercial enterprises more willing than other types of research sponsors to pursue hazardous vaccine experiments" (Halpern 2004, 86).

B. Sociolegal Studies

Sociolegal scholars depict the law as a culturally and structurally embedded institution within society. Accepting the inherent ambiguity of the "law-on-the-books," this scholarship focuses instead on the mechanisms by which those uncertain formal rules are translated into "law-in-action" by organizations (Suchman & Edelman 1996; Heimer 2012).

Organizations act as "filtering agents" between formal doctrine and the reality of organizational life because laws are often vague, and set forth broad, ambiguous principles instead of specific tasks to perform (Edelman, Petterson, Chambliss & Erlanger 1991; Edelman 1992). In performing this translation, organizations construct 'rational myths' about how to appropriately respond to law (Edelman, Uggen & Erlanger 1999). Importantly, in this

mythmaking translation, legal sociologists have demonstrated a disparity between the actual legal risks organizations face and the (inflated) legal threat constructed by organizational personnel and lawyers (Edelman 1992).

C. New Institutionalism

This paper conceptualizes IRBs as actors influenced by other organizations and factors in their environment. New institutionalism in organizational studies thus offers a complimentary view, in which organizations are complex social actors whose behavior is shaped by endogenous logics, technical goal requirements and maximizing calculations, as well as broader contextual factors. Often, organizations must negotiate between competing institutional logics, such as when business logics of efficiency and rationality compete with legal logics of justice and protection (Edelman, Fuller, & Mara-Drita 2001), and relevantly, between legal logics and medical professionalism (Heimer 1999; Rothman 1991; Starr 1982). The wider environmental context, including legal risk, shapes organizations' behaviors, at times leading them to perform symbolic compliance gestures in addition to their substantive efforts. These symbolic activities are isomorphically transmitted to similar organizations within the organizational field, lending legitimacy to the symbols that they have helped create (Suchman & Edelman 1996; DiMaggio & Powell 1983).

Drawing on these traditions, some scholars have applied these frameworks to the specific case of IRB governance. This literature is almost universally critical of IRBs, and tends to be aimed at IRBs overseeing social sciences research rather than biomedical research (Feeley 2007; Stark 2011). These critiques are largely uninformed by empirical research.

Building on the tradition of studying the gap between law on the books and law in action, IRBs have been characterized as a type of extralegal organization that acts as a "filtering agent" between vague law-on-the-books and law-in-action (Heimer & Petty 2010). American research oversight rules are ambiguous and weakly enforced, and IRBs struggle to produce clear answers. Over time, IRBs cope by showing compliance through formalistic, symbolic rule-following and vigilant documentation. This result is what neo-institutionalists such as DiMaggio & Powell might expect – IRB organizations have created intricate procedures to indicate to those on the outside that they are vigilantly enforcing ethics and human subjects protection. They are, as some critics described, an example of the archetypal Weberian "iron cage" (Bledsoe et al 2007). Of particular relevance to this study, scholars have suggested, without empirical support, that this symbolic compliance is motivated by a desire to protect their institutions from legal and regulatory enforcement risk (Heimer 2010; Annas 1991; Gunsalus et al. 2007).

It is important to note that almost all of the scholarship criticizing IRBs for rigidity is focused on IRB oversight of *social science* research. Scholars have not yet charted the entire ecology of IRBs and their behaviors, and thus there exists no synthesis from which to draw generalizable conclusions.

Legal scholars and bioethicists looking specifically at *biomedical* IRBs have expressed deep anxiety over the rise commercial IRBs, where protocol approval is simply for sale. Scholars in this tradition are apprehensive that the profit motive may drive these IRBs to exhibit inappropriate laxity, approving risky protocols that may be ethically and scientifically improper (Lemmens & Freedman 2000; Emanuel, Lemmens & Elliot 2006; Elliot 2010). Little empirical work informs this conversation.

Halpern also draws from new institutionalism in Lesser Harms. In particular, she uses this framework to explain why, as she argues, sponsors converged around risk containment approach to human subjects research risks in the middle of the 20th century. She draws from sociological and sociolegal studies that have found modern organizations tend to adopt rationalized structures, policies, and procedures, influenced in large measure by other organizations in their environment. She argues that clinical research sponsors adopted the use of consent documents, insurance to cover research problems, and scientific-panel oversight of research protocols as such rationalized organizational processes (Halpern 2004, 95). However, in keeping with new institutionalist accounts of organizational behavior, these rationalized processes of risk management were often in form more than in substance. Sponsors adopted the strategies of their peers to symbolize conformity to the expectations of the community and society, but the processes often had little to do with how the organization actually operated (Halpern 2004, 110). Halpern cannot, however, demonstrate that these rationalized processes in fact produced more or less harms than did organizations without such processes.

IV. Methods

A. Study Design and Sample

a. Total IRB Universe

The author first undertook to characterize the entire population of IRBs in the United States that are registered to oversee biomedical research. IRBs are not required to be accredited or approved by any governmental or non-governmental agency or organization in order to oversee biomedical research. Instead, IRBs are simply required to submit a short form to the appropriate federal agency with basic information about the IRB. FDA/OHRP then list the name and location of each such registered IRB online at a publicly available website. See Section IV.B.a below for discussion of use of this dataset in this study.

b. Qualitative Study

The author then undertook a qualitative study, based on open-ended interviews conducted with current and former IRB members and administrators, each from US-based, OHRP/FDA-registered IRBs. Interviews occurred during site visits and remotely from November 2015 – May 2018. The qualitative approach was chosen for several reasons. First, with few exceptions, few studies have investigated the full range of IRB types (by ownership status, size of research program, academic affiliation). Qualitative research is particularly well suited for exploratory studies for which previous literature is limited (Crabtree and Miller 1999). Such studies are useful for generating hypotheses that can later be tested with quantitative data (Crabtree and Miller 1999; Glaser and Strauss 1967). In addition, the author anticipated that some factors, such as legal and regulatory risk perception, were complex and challenging to measure. Qualitative research provides a method to describe the diverse facets and dimensions of such factors. Further, another goal of the interviews was to inform development of a survey that might be used in future research to characterize a larger sample of IRBs. Qualitative research is a useful early step in service of survey instrument development (Bradley et al. 2001; Miles et al 1994).

As is standard in qualitative research (Bradley et al 2001), the author chose sites and interviewees using purposeful sampling to ensure that diverse set of IRBs and IRB professionals were included. Study IRBs were selected to reflect a range of geographical locations, size, ownership type; study interviewees were selected to reflect a range of roles within the IRB and related organization. Additional IRBs and interviewees were recruited through snowball sampling, including through the author's professional networks and professional associations. Additional interviews were conducted until no new concepts were identified, in other words, until the point of theoretical saturation. This occurred after 19 interviews. The characteristics of the study IRBs and interviewees are displayed in Tables 1 and 2.

Eligible interviewees were current or former IRB members, administrators, or counsel, from eligible IRBs in the United States, defined as those IRBs with active registration to conduct FDA-regulated human subjects research on the FDA/OHRP database as of the interview date.

B. Data Collection

a. Total IRB Universe

A search for all US-based IRBs registered in active standing on the OHRP/FDA database to review biomedical research on April 26, 2017 yielded 1712 IRB panels. This search excluded IRBs registered to review *social science research only*. It included only those IRBs either registered to review FDA research only (27), or registered to review FDA and OHRP research (1685).

Of the 1712 total active IRB panels, there were 1274 unique IRB entities. The remainder are multiple IRB panels at the same organizations. For instance, VA Greater Los Angeles Health Care System has 3 IRB panels separately registered on the OHRP/FDA database, but is counted as 1 unique IRB entity. The methodology to determine if multiple IRB panels were part of a single unique entity was to assess if the IRB entry had the same name and was in the same city as another IRB entry. If the name or city were different, the two entries were considered to constitute two unique IRB entities. If the name and city were the same, the two were considered as one unique IRB entity. See **Table 1** for list of IRBs.

b. Qualitative Study

In-depth, open-ended interviews were conducted in person and via teleconference with study interviewees. 19 interviews were conducted with interviewees at 19 IRBs, for a total number of 19 key respondents interviewed from 19 IRBs. See **Table 2** and **Table 3.** These included 12 IRB members and 13 IRB administrators (note, some respondents had both an administrative role and membership on their IRB).

The author conducted each interview with a single participant. Interviews took place in person (8) or on the phone (11). Interviews were each one to three hours in length. All interviews were audio-recorded and transcribed by independent researchers and professional transcriptionists.

Interviews were conducted using an interview guide instrument (provided at **Appendix B**). For each question, interviewees were encouraged to provide specific examples and details from their experiences. All qualitative interview procedures, interview guides, and recruitment plan were approved by the UC Berkeley institutional review board.

C. Data Analysis

Transcribed interviews were analyzed using coding techniques common to qualitative data analysis (Bradley et al 2001). Coding of the data was accomplished through a series of steps. An initial code list was generated based upon the interview instrument, and was then refined during review and analysis of the transcribed interviews. The process of iterating the code structure involved adding and redefining codes as new insights emerged, as well as identifying relationships within code categories. A total of 19 specific codes organized within 6 broad themes ultimately served as the basis for final transcript review and data organization.

Using this final version of the code structure, the author and a research assistant independently coded the transcripts and recorded the data using Excel to capture recurrent themes, links between themes, and quotations of interest.

Techniques were used to maximize the systematicness and verifiability of data analysis. These included consistent use of the interview guide instrument, audio recording, independent transcription, and consistent use of the coding structure in data analysis by two individuals for intercoder reliability.

V. Results

A. Descriptive Statistics

a. IRB Ecology

Table 1
Descriptive statistics of US-based IRBs registered in active standing to review biomedical research as of April 26, 2017

State	# of Unique IRB Entities	Percent of Total
Alabama	24	1.88
Alaska	1	0.08
Arizona	23	1.81
Arkansas	10	0.78
California	115	9.03
Colorado	22	1.73
Connecticut	25	1.96
Delaware	7	0.55
Florida	57	4.47
Georgia	37	2.90
Hawaii	8	0.63
Idaho	7	0.55
Illinois	50	3.92
Indiana	27	2.12
Iowa	14	1.10
Kansas	10	0.78
Kentucky	16	1.26
Louisiana	17	1.33
Maine	8	0.63

Maryland	46	3.61
Massachusetts	57	4.47
Michigan	37	2.90
Minnesota	17	1.33
Mississippi	12	0.94
Missouri	30	2.35
Montana	6	0.47
Nebraska	8	0.63
Nevada	7	0.55
New Hampshire	13	1.02
New Jersey	37	2.90
New Mexico	6	0.47
New York	91	7.14
North Carolina	32	2.51
North Dakota	6	0.47
Ohio	50	3.92
Oklahoma	14	1.10
Oregon	19	1.49
Pennsylvania	75	5.89
Rhode Island	12	0.94
South Carolina	16	1.26
South Dakota	3	0.24
Tennessee	25	1.96
Texas	68	5.34
Utah	6	0.47
Vermont	2	0.16
Virginia	37	2.90
Washington	22	1.73
Washington DC	11	0.86
West Virginia	6	0.47
Wisconsin	25	1.96
Total	**1,274**	**100.00**

b. IRBs and IRB Professionals in the Study

Table 2
Descriptive statistics of IRBs in the study (n=19)

	n
Ownership Type	
For-profit	3
Non-profit	9
Government	7
Org Type	
Healthcare	15
Commercial IRB	3
Public Agency	1

Size of Research Program (Active)*	
1-100 protocols	4
100-500 protocols	8
>500 protocols	5
Location	
California	4
Massachusetts	4
Washington	2
Arizona	1
Connecticut	1
Ohio	1
New Mexico	1
Oregon	1
North Carolina	1
Pennsylvania	1
Texas	1
Minnesota	1

* Two commercial IRBs declined to provide this data.

Table 3
Descriptive statistics of IRB professionals interviewed in the study (n=19)

Role*	
Administrator	13
Member (Scientific)	8
Member (Lay)	4
Gender	
Male	10
Female	9
Tenure in HSR	
<10 years	4
>10 years	15

***** Some respondents have more than one current role.

B. Legal and Regulatory Findings

After review of the interview data, respondents' comments were organized into 4 broad factors that formed the basis for the taxonomy of legal and regulatory issues. Of these, two broad factors describe legal encounters and legal risk perception (see Table 4) and regulatory encounters and regulatory risk perception (see Table 5), one factor describes complaints encountered by respondents (see Tables 6 and 7), and 2 factors that describe variation in the role of counsel in the research oversight process (see Table 8).

a. Legal and Regulatory Risk Perception

Two broad factors characterize variation in IRB respondents' perception of legal and regulatory risks, attitudes which may impact the committee's capacity to carry out its central mission of protecting human subjects in research. These broad factors are: (1) legal encounters and perception of legal risk; (2) regulatory encounters and perception of regulatory risk.

i. Legal Encounters & Legal Risk.

Zero respondents (0/19) reported significant concern with legal risk posed by human subjects research. There is little to no variation. Some IRB members offer that they believe their institution's insurance policy would cover them, individually, if they were ever sued, and this question does come up from time to time among members. One respondent reported sitting on an IRB that was sued several years ago, which affected reviews "for the next year or two." One respondent from a small portfolio commercial IRB expressed surprise that IRBs are not sued more often. But few respondents have firsthand knowledge of any lawsuits, even the marquee litigations that have stirred the bioethics community, including the Markingson v. University of Minnesota case.

Respondents who are IRB administrators sometimes say that they see it is part of their job to "shield" the IRB from having to think about legal risk. Respondents with experience on social science IRBs sometimes suggest that social science IRBs do not understand what "real" risks are, and are conservative in their review based on risks they perceive, but biomedical IRBs are not. Respondents at health care institutions that have risk managers report that these individuals are not typically involved in research review. A few respondents report that, while not concerned about litigation, they do occasionally consider the public relations implications of their work. See **Table 4** for quotations illustrating legal encounters and attitudes toward legal risk.

Table 4
Quotations Illustrating Legal Encounters and Attitudes Toward Legal Risk

Surprise About Lack of Lawsuits
I'm shocked that we in the commercial sector haven't had more [lawsuits] because in an institution, you can control the break line, a little. You can control actions; you have the faculty and the medical staff. We don't have all of that. We don't have the infrastructure to control what happens locally (Small portfolio commercial IRB administrator)
Not Concerned About Lawsuits
We have a policy about the liability. It basically says that IRB members are covered under the hospital, they're indemnified. So that policy is there. The ethicist that recently joined asked to see that; he's the only person that asked. Nobody on staff has really brought any concerns about that and when I do orientations for the community members, I do mention that. But I don't think it's realistic, they don't have any examples that hits home to them of things like "oh, this could happen to me." (Small portfolio nonprofit hospital IRB administrator)

I think that although it is not litigation fear, it is a fear that we will be perceived as anything other than doing our utmost to protect the subject... I just don't perceive them as thinking about legal things (Mid-sized portfolio government hospital IRB administrator)
PR, Not Lawsuits
I don't think so....I don't think we have ever done something because of concerns of litigation. I can think of one or two examples where it wasn't the only reason for sure but we have certainly thought about our action from a reputational point of view. Not worried about what would happen inside the courtroom but I little concerned about what might happen in the newspaper (Mid-sized portfolio nonprofit hospital IRB scientific member / Administrator)
I cannot let litigation drive anything that we do. But I will say this: I do think twice about how, if something goes wrong, how it would play out in the newspaper. Not worried about litigation (Large portfolio academic IRB administrator)
Experience with Lawsuits
We were sued. My panel was sued…We were sued and it did influence the reviews for the next year or two (Large portfolio academic nonprofit hospital IRB chair)

ii. Regulatory Encounters & Regulatory Risk.

Respondents uniformly report that regulatory encounters are routine and generally unconcerning to the IRB. The IRB does not handle the inspections and is typically detached from the process entirely. Inspections are handled by the administrative side. Respondents report more worry about OHRP inspections than FDA, but OHRP's inspections are very rare and most respondents have never been part of an IRB inspected or investigated by OHRP.

Several respondents report a desire for FDA to take more of a 'friendly audit' or 'educational' approach to inspections, rather than the agency's perceived focus on 'paper compliance.' But few respondents have negative comments about FDA auditors.

Regulatory agencies including FDA, OHRP, HHS, and NIH put out volumes of guidance materials. Most respondents believe these materials to be voluntary, but often indicate that they adhere to them anyway ("It'd be foolish not to avail yourself of it"). Small portfolio healthcare IRBs appear more likely to be reluctant to diverge from agency guidance than larger portfolio organizations. Administrators are more familiar with agency guidance documents than IRB members, who often report not using these materials in research review. See **Table 5** for quotations illustrating regulatory encounters and attitudes toward regulatory risk.

Table 5

Quotations Illustrating Regulatory Encounters and Attitudes Toward Regulatory Risk

Regulatory Encounters
We're privileged here because our HRPP is headed up by somebody who's, like, on a first-name-basis with HHS and FDA ethicists. So we sort of have the ability to like, just ask for advice… So I think we find them easy to work with, in general… I think, you know, they have a culture, and we have a culture and our cultures mix well together—that might not be the same for other places. We try to be pretty transparent and they want to look inside, so that works (Large portfolio academic nonprofit hospital IRB administrator).

We have never had any problems... They're [FDA auditors] very nice… The first time our mentor was there with me and he said, 'Remember, they're not the enemy. They're here to help you, to help become a better IRB.' So we went from that premise and the two subsequent times when we were audited… we just followed through with that, and I think in the notes that they make they say that we were cooperative and pleasant, and we didn't yell and scream and fuss. I think they appreciate that too because they're not in a very user-friendly job. People always think auditors, you think IRS and audits and all that and it just puts an unpleasant taste in your mouth (Small portfolio commercial IRB administrator)
It should be a collegial peer review process where you can learn from them. But they're [FDA auditors] not there to teach you; they're there to find whether you're in compliance (Mid-sized portfolio nonprofit hospital IRB member [non-scientific])
All that we have is sticks. There's no carrots anywhere in the system. There needs to be some sort of system of carrots. There needs to be some sort of system where there's positive reinforcement and positive messages [from regulators to IRBs] (Small commercial IRB administrator)
They're [FDA auditors] okay. They know their job. It's very regulatory. They don't care about ethics; they don't care about safety; they don't care about anything but compliance. So if you did the right thing, but didn't document it, you're going to get dinged. So what do I think about FDA? It's the same thing I think about lawyers: it's compliance; it doesn't matter if it's right or wrong (Small portfolio commercial IRB administrator)
"It [regulatory enforcement] is a big deal. It comes fairly regularly to our institution. We have a lot of investigator-held INDs. Whenever something bad happens, we write the letter to OHRP. The panel is very unaware of the relationship with OHRP and letters that have to be written. Because they're not really involved… And I don't think the panel even sees those letters... Sometimes the FDA is the worst thing in the world; sometimes they're really helpful to us. We don't run scared around here, except when we do (large portfolio academic nonprofit hospital IRB member [scientific])
We've had no problem with the FDA. Realize that these people who come and look at the IRB, the next day could be at a meat-packing plant. So … they've got a checklist (large portfolio academic hospital IRB member [scientific])
Agency Guidance - Usefulness
We abide by the OHRP and the FDA [guidance]. When we have questions, we go to the websites. A couple of times, I've called and actually spoken to a human and said, "This is my problem, where do you suggest I find the answer?" or, "Where do I go from here?" and they've been very helpful, so we've not had any complaints from them and I think of them as a huge resource library. You can go and find your answers and find what you need (Small commercial IRB administrator)
I don't think that the members are familiar with [agency guidance]. I think the coordinator is more (mid-sized portfolio nonprofit hospital IRB member [non-scientific])
Agency Guidance - Voluntariness

So, the guidance. I think of it as voluntary but I think it'd be foolish not to avail of it, especially the research that falls under [that agency's] jurisdiction (Large portfolio academic nonprofit hospital IRB administrator)
Unless I can think of a good reason not to - I'm going to follow the guidance (Mid-sized portfolio nonprofit hospital IRB member [scientific] and administrator)
Voluntary. And I've been known to challenge [them] (Small portfolio commercial IRB administrator)
I know they always say they're voluntary but are they truly voluntary - I guess that's really the question. So I guess we look upon it as "semi-mandatory" (small nonprofit hospital IRB member [scientific])

b. Complaints and Opinions

i. Complaints.

Respondents uniformly report very low rates of complaints among research participants, including over long periods of time. The few complaints respondents recall typically involve research participants who have trouble accessing payments for participation. Less common are complaints about the recruitment process. For instance, a wife or parent who receives a recruitment letter in the mail for a relative who died at the recruiting hospital. Very occasionally, an unusual complaint will arise. For instance, a family member complained when the deceased's tissue was not collected for donation within the required window, as the deceased had wished. These infrequent complaints are typically unrelated to physical or psychological risks involved in study participation that might give rise to any legal or regulatory concerns. Respondents report very little variation in the volume of complaints. Even at very large institutions, which oversee thousands of research protocols, respondents report only a handful of complaints a year, at most. Some report none over the course of 10+ years. See **Table 6** for frequency of most common complaints encountered by respondents over the lifetime of their careers.

Table 6
Complaints Encountered by IRBs

Complaint	Number of Respondents Who Have Ever Encountered this Complaint over Career Lifetime (n=19)
Failure to receive payments/billing	10
Recruitment Complaints	3
Access to Research	1
Other (non-risk)	3

ii. Factors Explaining Low Volume of Complaints.

Respondents are given a puzzle: litigation and complaints are extremely prevalent in medical practice, but quite infrequent in the context of clinical research. Respondents offer a range of factors that may account for this phenomenon (see Table 7).

Table 7
Potential Factors Explaining Low Rates of Litigation and Complaints in Research

Factor
Research team seen as more allied with family / participant than general medical care
Presence of research team as opposed to individual clinician interaction only
Research receives more advance scrutiny than general medical practice
Participants get more or at least more consistent care than in medical encounters
Causation may be difficult to show in research, at least with ill participants
Use of a protocol may lead to less errors by staff
The informed consent process may lead to educated participants who accept risk
Documentation is better in the context of research than general medical practice
There is far less research than medical care – less potential complainers
Complaints are dealt with elsewhere in the organization, rather than by the IRB[6]
Self-selection – people who participate in research are different from the general patient population
Participants "vote with their feet" – if they're not happy with the study, they just drop out

c. Role of Counsel

Two broad factors characterize variation in the role of legal counsel in the research oversight process, which may impact the committee's capacity to carry out its central mission of protecting human subjects in research. These broad factors are: (1) variation in role of counsel for the organization at IRB meetings; and (2) variation in the role of counsel as a resource for IRB professionals. See **Table 8** for quotations illustrating presence of counsel at meetings and attitudes toward counsel as a resource.

i. Counsel at Meetings.

Some respondents are emphatic in their belief that it would be inappropriate for legal counsel for the IRB's home organization to either sit on the IRB or even attend meetings. These individuals report the concern that legal counsel would have a conflict of interest between their role as counsel for the organization and any role they might play in protecting human subjects in research at the IRB. Other respondents report that legal counsel for the organization sits ex-officio at IRB meetings. There is often a lawyer from the community on the IRB, who is unaffiliated with the IRB's host institution.

ii. Counsel as Resource.

Data here suggest systematic variation regarding the frequency of interaction with counsel and usefulness of counsel as a resource for resolving issues related to research. Some respondents, particularly those at independent IRBs and small portfolio healthcare organizations, report infrequent if any contact with their organization's legal counsel, and tend to report that they do not see much use for counsel. Large portfolio organizations often report frequent (even

[6] One respondent from a large academic IRB reported awareness that several large university systems are self-insured for research-related injuries.

daily) contact with in-house counsel, which members and administrators find quite helpful in the research review process.

Table 8

Quotations Illustrating Regulatory Encounters and Attitudes Toward Regulatory Risk

Counsel at Meetings
There's usually a representative from the office of general counsel who is sort of assigned to research issues who is typically an ex-officio member of the board and comes to the majority of the IRB meetings (Large portfolio academic nonprofit hospital IRB administrator)
The lawyer hasn't been showing up as often as when I started [on the IRB], we had a house lawyer who was always there… Then they got a law firm and we would get various lawyers coming on. Sometimes…this one guy in particular was just…he would just pick on the most obscure, obtuse things, and we'd all just roll our eyes. It's like, "Really?"… I think it's really not useful for them to be there. There's really no need for the lawyer; the lawyer's never been a voting member (Mid-sized portfolio nonprofit hospital IRB member [non-scientific])
The general medical [IRB] has the lawyer … on the IRB; the oncology one doesn't because so many of them were cooperative group studies so there weren't a lot of legal things to be concerned about (Mid-sized portfolio nonprofit hospital IRB member [scientific] and administrator)
Oh, I cannot have an institutional lawyer. I would object to that because they got a conflict of mission (Small portfolio commercial IRB administrator)
Well, having a lawyer on the IRB could probably be a conflict of interest but when I first joined the IRB in the 1980's up to about 2008/9, there was a [n in-house] lawyer who attended the IRB meetings and I despised the practice (large portfolio academic hospital IRB member [scientific])
Counsel as a Resource
There's usually a representative from the office of general counsel who is sort of assigned to research issues who … is also available to, and consulted by, the IRB office on a regular basis if not daily… If anything, a lot of times they bring inside knowledge from other conversations that they've had, other perspectives, other dealings with the researchers. Sometimes they add things to the conversations that people aren't aware of from what's presented by their researcher and sometimes that allays concerns that are raised and sometimes it raises new ones, but it's usually a collaborative process between us and [the lawyer] (Large portfolio academic nonprofit hospital IRB administrator)
I also have access to the [university attorney] and so I'm on with her a lot trying to get advice... Lawyers are good (Large portfolio academic hospital IRB administrator)
You know what, I don't really feel like I need to utilize it. I mean, yeah we have access to the legal department… [but] there really hasn't been a need on my end (small portfolio nonprofit hospital IRB administrator)
We do have 1 or 2 lawyers at the Office of General Counsel who serve us, and we use them all the time (large portfolio academic hospital IRB member [scientific])

Of course, there is a conflict of interest there because [attorney], as a member of the Office General of Counsel, is there to protect the institution. And my job is-- it is also to protect the institution but my primary responsibility is to protect human subjects and also, secondarily, to support researchers. But what I like about this place is the lawyers are nice, really nice, really helpful (large portfolio academic hospital IRB administrator)
Our team attorney is very involved in the contracts part of things, research agreements, but … I can't remember the last time I contacted her about something that was under IRB review (Mid-sized portfolio government hospital IRB administrator)

VI. Analysis

A. Central Finding 1: Low Variation in Legal and Regulatory Encounters and Risk Perception

A hypothesis was that risk perception and tolerance would vary, for instance, that as size of research program increases, risk tolerance would increase. The central finding here is that there is little variation in the perception of research oversight as posing significant legal or regulatory risks to IRB members or institutions. Legal and regulatory risk perception is uniformly low across respondents in various roles at all types of IRBs.

Another hypothesis was that organizations with prior litigation or negative regulatory encounters would be more risk averse or have a higher perception of legal or regulatory risk. The central finding here is that infrequency of litigation or particularly negative regulatory encounters makes assessing this hypothesis difficult. But the evidence from this study does not provide any support for the hypothesis. One respondent reported a protracted negative encounter with FDA, and another respondent reported having been sued as a member of an IRB. Neither reported these encounters having a lasting impact on IRB operations.

This finding has a few sub-findings and important implications, discussed below.

i. Why Is Risk Perception So Low?

There is an interesting question as to why individuals who oversee biomedical research are not particularly concerned about lawsuits or regulatory enforcement.

With regard to litigation, one explanation is that that there simply isn't a lot of litigation or complaints to be worried about. Litigation by research subjects, while once expected to increase (e.g. Mello), largely has not. It may also be that the volume of complaints is, in reality, low (see below). If we consider litigation as a policy tool, because we are so reticent to shape policy through legislative/regulatory means (Kagan, Adversarial Legalism), then policy is not being shaped much by litigation or adversarial legalism. Whether and why litigation and complaints are low is discussed below in subsection B.

Another reason these individuals do not perceive legal risks may be that IRB members are insulated from risk to the organization and believe themselves to not be personally liable. Because they believe themselves to be personally insulated, they are not particularly attuned to the risks the organization may face.

A third possible explanation is that the IRB is unaware of legal or regulatory issues because, while these issues do in fact arise, they are handled elsewhere in the organization.

Regarding regulatory risk, some respondents report that the IRB does not handle regulatory inspections or audits and is detached from the process. This indicates that research oversight functions at some organizations are only loosely coupled to other important internal processes (e.g. compliance). Regarding legal risk too, there is the possibility that IRB members and administrators are not aware of complaints or lawsuits because these issues are dealt with elsewhere in the organization. This suggests that perhaps IRBs' perceptions of legal and regulatory risks as low are not actually in line with reality. These committees may be operating with a rosier or distorted understanding of legal risks and harms encountered by participants, which may in turn affect their behavior and decision-making.

A fourth potential explanation is that some IRBs may not be concerned about legal and regulatory risks because they do not have the information or expertise to assess the riskiness of the research their committees oversee. Halpern's work describes conditions under which certain organizations may be more or less risk adverse and identifies endogenous and exogenous factors that influenced their risk preference. She argues that several organizational dynamics affected a sponsor's willingness to sponsor in risky human subjects research (defined as studies that the medical community considered particularly hazardous). These include the sponsor's *knowledgeability about the science underlying the study*, the sponsor's experience with research controversy, and the sponsor's incentives for undertaking or for avoiding risk. The first, she notes, is a factor concerning the processes internal to organizations; the second and third involve organizations' relations with their environment (Halpern 2004).

She specifies a continuum of attitudes toward risk in three parts: risk avoidance, risk containment, and risk delegation. She then offers fascinating empirical evidence of this risk framework in action. Critically, she shows that among sponsors with high technical knowledge, those that were motivated principally by commercial incentives or "scientific commercialism" (pharmaceutical sponsors) tended to have higher risk tolerance than did sponsors motivated principally by other (academic and professional prestige) incentives (Halpern 2004, 85-87). She argues that corporate managers were undertaking a "huge financial gamble" in investing funds toward a vaccine, and therefore were willing to take bigger risks with regard to danger to human subjects. As she concludes, "perceptions of their relations with the regulatory and resource environments may have rendered some commercial enterprises more willing than other types of research sponsors to pursue hazardous vaccine experiments" (Halpern 2004, 86).

While developed to explain the behavior and attitudes of research sponsors rather than research oversight committees, this framework suggests a possible explanation for our finding: some IRBs may lack the knowledgeability about the science underlying the study. This may be because of lack of internal expertise on the board, or because the board is not given sufficient information from research sponsors (largely pharmaceutical industry) to accurately assess risk to participants and in turn organizational risk. Future research will need to evaluate these four possible explanations.

ii. No Defensive Behavior

The central finding that legal and regulatory risk perception is low is also contrary to existing literature on IRB behavior, which suggests (without empirical support) that IRBs behave conservatively and in a risk-averse manner because they are engaged in defensive behavior motivated by a desire to protect their institutions from legal and regulatory enforcement risk (Heimer 2010; Annas 1991; Gunsalus et al. 2007). This study finds no support for this. Some

respondents suggested that social science IRBs may behave this way, because of an impoverished understanding of real risk to participants, but not biomedical IRBs. The IRBs our respondents represent very rarely disapprove research protocols, some less than 5 disapprovals over 10+ years. And none express particular concern about litigation, complaints, or negative regulatory enforcement activity.

iii. Commercial IRBs Aren't Different In Terms of Approval Rates and Complaints

The finding also has implications for the legal and bioethics literature that has expressed concern that commercial IRBs may exhibit inappropriate laxity, approving risky protocols that may be ethically or scientifically improper (Lemmens & Freedman 2000; Emanuel, Lemmens & Elliot 2006; Elliot 2010). The respondents in this study behave similarly in regards to their approval habits – almost all protocols are approved, very few are disapproved, by all types of IRBs. The respondents also all have similar experiences in regards to low levels of litigation, complaints, and negative regulatory enforcement.

iv. Agency Guidance

Agencies produce volumes of regulatory guidance. This study finds evidence of systematic variation among IRB professionals' attitudes about whether such guidance is voluntary or mandatory, based on the size of the organization. IRB professionals from larger healthcare and university institutions are more likely to indicate a willingness to disregard regulatory guidance and establish their own standards. This has potential implications for repeat players, discussed below.

Empirically, scholars have found significant compliance variation at the organizational level (Thornton, Kagan & Gunningham 2008; Gunningham, Kagan & Thornton 2004, Vogel 2009). For instance, Vogel has found that some firms go 'beyond compliance' and push to 'trade up' regulatory standards when doing so confers a competitive business advantage (Vogel 2009). Kagan and collaborators in particular have identified a number of factors in the task environment that come together with regulation to help explain firm behavior. Regulation operates as a 'coordinate mechanism' interacting with market, social, and corporate pressures within an organization. Importantly, work in this vein has identified instances in which business firms' behavior is influenced by fear of legal punishment, fear of social consequences, and internalized sense of duty (Kagan, Gunningham & Thornton 2011). In other words, legal pressure is just one variable that influences firm behavior, and its influence varies firm to firm based on the mix of other variable signals of importance to the firm.

Bardach and Kagan noted decades ago the increasing proliferation of nonbinding agency guidelines or soft regulation, noting that "a risk with this approach is that such guidance, while technically nonbinding, will in practice come to be viewed as binding, and thus firms might effectively lose the flexibility they are legally afforded" (Bardach & Kagan 1982:237). Assuming that certain smaller organizations and firms may believe that disregarding guidance will be akin to noncompliance in the eyes of regulators, one can conceive of agency guidance as a legal vehicle that may influence firm behavior.

Thornton, Kagan and collaborators did not posit *systematic* variation in how much the legal variable matters to a firm. However, work by Marc Galanter may provide tangential

support for the notion that variation may be systematic. His classic work on why the "haves" come out ahead in court provides support for the idea that larger, more established firms hire better and more lawyers, and have closer and longer relations with them, leading to better legal strategy (Galanter 1974). This leads 'repeat player' firms to 'come out ahead' more often in court. This work hasn't been extended to regulatory compliance rather than litigation, but it is ripe for further analysis.

This finding in general also suggests a link between larger expertise or capacity and the ability of an organization to establish its own standards for compliance. Evidence from this study indicates that larger, better resourced organizations are in a better position to establish their own standards.

This is important, as more organizations are given the task of 'rowing' as delegated regulators, with the government 'steering' from afar. If smaller less resourced organizations are less willing (or able) to craft solutions locally and look to extralegal guidance as law, it may, at a minimum, give unelected regulators undemocratic power, as nonbinding guidance does not go through notice and comment under the Administrative Procedures Act.

B. Central Finding 2: No Variation in Litigation / Complaints Volume; Variety of Suggestions as to Why

Individuals who oversee biomedical research report a consistently low volume of complaints from participants, including over long periods of time.

These front-line individuals provide a variety of opinions as to why this may be the case. Some possible explanations indicate loose coupling (e.g., there may be more settlements than they know about because these are handled in other parts of the organization); others suggest factors endogenous to the research task (e.g., use of a research protocol leads to less errors); while yet others suggest factors exogenous in the task environment (e.g., legal causation may be difficult to show in the context of a study where the participant was already ill).

Beyond those offered by IRB professionals in this study, additional factors may also be relevant. For instance, different types of research and phases of research may have different explanations for why litigation and complaints are low. For instance, Phase I trials may involve poorer individuals who may have trouble accessing the justice system. On the other hand, cancer studies typically involve wealthier participants who are very sick to begin with.

These potential explanations to the riddle open multiple areas for future inquiry. They may also suggest some leanings for general medical practice, which experiences quite high levels of adversarial legalism, malpractice litigation, and complaints.

C. Central Finding 4: Variation in Role of Counsel

There is evidence of systematic variation in the use and usefulness of counsel. Larger organizations report frequent (sometimes daily) contact with legal counsel, which tends to be positive. Organizations overseeing smaller research portfolios report infrequent to no contact with counsel about research oversight, and tend to report that contact with counsel is not needed or helpful.

Edelman and others have shown how organizations act as "filtering agents" between formal doctrine and the reality of organizational life because laws are often vague, and set forth broad, ambiguous principles instead of specific tasks to perform (Edelman, Petterson, Chambliss

& Erlanger 1991; Edelman 1992). In performing this translation, organizations construct 'rational myths' about how to appropriately respond to law (Edelman, Uggen & Erlanger 1999). Importantly, in this mythmaking translation, legal sociologists have demonstrated a disparity between the actual legal risks organizations face and the (inflated) legal threat constructed by organizational personnel and lawyers (Edelman 1992). Here, that inflated legal threat is not observed. The findings here suggest that perhaps smaller organizations do not see an inflated legal threat because they are not interacting with counsel. The riddle remains for larger organizations, which do interact with counsel frequently. Future research will need to evaluate this more specifically.

VII. Conclusion and Implications

It might be suggested that, given the low disapproval rate and low complaint volume, the regulatory framework is doing a good job of minimizing risk in the first place. There are reasons to believe this is not so. First, many subjects may not have access to the legal system to pursue complaints, and causation may be difficult to show. Second, we know that FDA is moving toward quicker drug approval up front and more post-marketing surveillance of new drugs and devices. This means that more studies, particularly industry-sponsored clinical trials, will be based on less preclinical work and expose participants (and patients after approval) to more risk.

Beyond those factors, it is important to recognize numerous instances of negative or unreliable data from clinical trials being discovered in litigation after drug approval and injury. This indicates that pharmaceutical sponsors have a pattern of keeping clinical trials of drugs going long after the sponsor knows the drug is unsafe. This is prima facie evidence that many clinical trials are in fact quite risky to participants.

For instance, AstraZeneca paid $520 million to settle a Department of Justice investigation into its marketing of Seroquel. Among others, the Department found that the company had paid doctors to put their names on articles reporting on clinical trials that had in fact been ghostwritten by medical literature companies, and in which those 'authoring' physicians had never taken part. Then the company used those studies and articles as the basis for promoting unapproved uses of the drug (DOJ, 2010).

Further, in discovery, internal correspondence revealed discussions by the company about how to conceal or finesse clinical trials that were going poorly or had negative results. In the words of an AstraZeneca publication manager, "Thus far, we have buried trials 15, 31, 54… The larger issue is how do we face the outside world when they begin to criticize us for suppressing data" (Elliott 2010). About Trial 15, a senior AstraZeneca official praised a company physician for doing "a great 'smoke-and-mirrors' job" to "put a positive spin (in terms of safety) on this cursed study" (Elliott 2010).

These internal communiques indicate clearly that the company knew it was running studies that were likely harmful '(in terms of safety)' to participants, and kept going anyway.

That would be bad enough. But the company also designed clinical trials specifically as a concealed way to market the drug it knew was harmful. For instance, documents from litigation reveal that the Sales and Marketing department, rather than the Research and Development department, was responsible for funding Seroquel research. And another set of internal documents show that other Seroquel studies were described internally as having a "regulatory" purpose as well as a "commercial" purpose – to "generate commercially attractive messages" about a drug the company knew to be dangerous to humans (Elliott 2010).

These activities show that the company was knowingly subjecting clinical trial participants to dangerous drugs. AstraZeneca is not the only one. In litigation related to Eli Lilly's drug Zyprexa, internal documents surfaced showing that Lilly had buried a whopping 16% of participants in Lilly's Zyprexa clinical trials gained more than 66 lbs after a year on the drug, a figure far higher than the company had disclosed to physicians. Trials continued after it was clear the negative effects were extreme –including trials with children (Healy 2002). A final settlement was reached, with Lilly agreeing to pay more than $1.2 billion to 28,500 people injured by the drug (Berenson 2007).

Finally, litigation related to Merck's drug Vioxx demonstrated clearly that the company knew the drug caused cardiovascular problems early on in clinical trials – well before the drug was marketed. The company continued VIOXX clinical trials with the flawed drug, using a data safety monitoring board (DSMB) whose members were not independent of the company. In fact, the head of the DSMB for the VIGOR study was awarded a 2 year consulting agreement with Merck during the study, and owned more than $70,000 worth of Merck stock. The board allowed the study to continue even after learning that participants had a whopping 79% greater risk of death or serious cardiovascular event (Krumholz 2007).

These episodes indicate prima facie that clinical trials can involve significant risks to participants, and that industry has a pattern of failing to provide relevant safety information to participants, physicians, and others. This pattern indicates that there are good reasons to suspect that the regulatory oversight system is not catching these risks or providing adequate opportunities to access redress.

The questions then are, why do IRB professionals overseeing these studies not perceive them to raise legal or regulatory risks? Why are these risks invisible to the people who are tasked with overseeing these studies? Is it because of factors endogenous to the organization, like expertise, or exogenous, like a lack of information being provided from sponsors to reviewers? Are the legal and regulatory risk perceptions of professionals in other management-based or light-touch regulatory regimes similarly low, which might suggest something about the nature of the regulatory model? Does this particular delegated regulatory system need to be reformed, given changes in the institutional environment? Should policy encourage research oversight at larger, better resourced institutions that seem better able to use counsel and craft solutions, or should policy interventions provide more resources to smaller organizations? This study is the first to explore these puzzles and questions. Future research will need to follow these routes of exploration further.

CHAPTER 3: TRADEOFFS IN DELEGATED REGULATION: ASSESSING IRBS – VARIATION, GOVERNANCE GAPS, AND BEST PRACTICES

I. Introduction

Much has been written about the tectonic shifts in regulation and governance that have occurred during the past few decades across wide swaths of social and economic life. The more recent scholarly focus on 'new governance' techniques emerged in response to the concern that a focus on traditional state-centered, top-down systems of regulation was both overly simplistic, given the range of mechanisms available to regulators (Carrigan & Coglianese 2011), and increasingly outmoded, given the progressively nodal nature of institutional reality. Such concern has, in turn, been situated within a broader context of the ascendency of global capitalism and its frequent preference for less regulation when possible, and more flexible regulation when necessary (Burris *et al*. 2008).[7] A less normative (but not mutually exclusive) analysis would also note that, simply, it is hard to regulate certain activities; firms may be better equipped with the means and information to meet regulatory requirements in their own ways, and thus flexible regulation may be better suited to tackle complicated problems than more proscriptive approaches.

The interest in 'new governance' reflected a broad cross-sector trend toward the conviction that policy solutions would need to incorporate additional tools to more effectively and efficiently produce socially valued behavior by regulated entities. Accordingly, a variety of more flexible, less state-centered regulatory instruments emerged. These include information disclosure requirements, tradeable permits, industry self-regulation, third-party accreditation and certification programs, and management-based and principles-based regulation. These forms of regulation have been implemented in areas of environmental regulation, food safety, toxic chemical use and release, industrial safety and renewable energy, among others.

Institutional review boards (IRBs) are a particular type of organization that has been subject to a hybrid form of regulation for many decades. These are organizations that oversee and approve clinical research. Participation in these research projects exposes human subjects to significant physical risks including death, as it often involves ingesting or introducing drugs and devices to the body that have not yet been proven safe or effective. The use of a non-governmental committee oversight mechanism, the IRB, is an old case of management-based regulation owing to the legacy of professional self-regulation, which has in this particular case been inherited increasingly by industry and other non-professionals as clinical research has become more of a corporate, business activity and less of a professional medical activity.

IRBs play an essential role in protecting public health and safety, as they serve as ethical gatekeepers for clinical trials in which 2-3 million Americans participate annually.[8] Yet despite their importance, IRBs are empirically understudied. Their sector has undergone dramatic changes in the past 30 years. While most clinical research was once performed and overseen at universities and teaching hospitals, over the past few decades this research has increasing shifted

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[7] Certainly, the corporate preference for deregulation is not universal. For instance, when stricter regulation is economically advantageous, firms may push to 'trade up' regulatory standards. For instance, see: Vogel, David. *Trading up: Consumer and environmental regulation in a global economy*. Harvard University Press, 2009.

[8] Note that while IRBs also oversee social science research, generally at universities, this paper does not include social science research within the purview of its analysis. This paper is **exclusively** focused on IRBs overseeing biomedical research, principally clinical trials of drugs and devices.

to other venues, overseen by non-local IRBs, including commercial IRBs. The scant literature on IRBs has focused on academic IRBs, and little work has been undertaken to characterize their ecology and explore how this particular management-based, light touch regime is operating 'at the shop floor' and systematically across organizations.

Indeed, by design, management-based regulation delegates to regulated firms much ability to set standards, oversee, and enforce broad regulatory requirements. It is expected that this will lead to some variation 'at the shop floor,' as different firms devise slightly different ways to meet the regulations. This variation may be a 'feature' of the regulatory system (when the variation is responsive to local conditions), or a 'bug' (where the variation is detrimental or unresponsive to local context). Understanding the quality of the variation that results 'at the shop floor' from flexible regulation can help shed light upon whether the regulatory approach is capable of, and is in fact, producing the beneficial outcomes intended by the regulation.

This paper interprets the results of empirical research through the lens of IRBs as delegated regulators under a management-based regulatory system. The paper applies frameworks related to regulation and governance to explore the following broader questions: are there internal or external features of IRBs that vary in terms of their capacity to do a good job? Are these variations systematic based upon the size, location, or ownership type of the IRB and its housing organization, and as a result, are some IRBs better equipped than others to carry out its tasks? If so, does this suggest policy interventions to encourage or require certain types of IRBs?

To address these questions, I designed a qualitative study intended to provide an in-depth perspective on the ways that IRB professionals across a range of IRB types and venues approach issues related to regulation and governance, particularly as the system moves toward increasing reliance on external IRBs (commercial and non-commercial). The objectives of this study were to explore how essential factors varied between IRBs along some key performance axes including internal organizational features and external factors. This paper evaluates IRBs as a mechanism of governance, positing variation among different IRBs and probing the benefits and drawbacks of 'delegated governance.' Regulatory scholars explore the ways in which regulatory (usually defined as secondary legal) rules and the institutional design of regulatory systems shape the behavior of firms, other organizations, and professionals. Drawing from these frameworks, the paper analyzes the results of the qualitative research to consider what we can learn about the capacity, behavior, and experiences of organizations that are delegated regulators under light touch regulatory regimes, which are increasingly contracting out their functions to external actors.

The paper offers empirical and theoretical contributions. First, the paper evaluates IRBs descriptively, providing a first-ever analysis of IRB empirics (such as how many there are, where they are located). It also provides qualitative information about how IRBs vary in terms of internal organizational factors, external features of the task environment, and other environmental factors.

Second, the paper offers analytical insights about the nature of variation among IRBs. Scholars admit there is a dearth of empirical research about the functioning of light touch regulatory regimes. This paper reports on extensive qualitative research with professionals in the IRB space. It reports on a few findings that have significant implications for understanding the functioning of this particular instance of light touch regulation, as well as insights into conditions under which this form of regulation (increasing in frequency), in which regulated entities do

much of the steering (instead of government agencies) may fail to achieve its public health and safety purposes in other domains.

The paper has two central findings. The first is a finding of significant variation "on the shop floor" in terms of how these delegated regulators function. This includes variation in internal features and external factors that may influence IRB expertise and capacity. This variation is a consequence of management-based regulation as a form, because the management-based approach is designed to afford regulated entities the ability to craft individual solutions. This variation may be a 'feature' of this regulatory system (when the variation is responsive to local conditions), or a 'bug' (where the variation is detrimental in terms of health and safety).

The variation reported herein is troubling because they indicate that shifts in the broader institutional landscape (including the shift toward centralized and non-local research review) has produced organizations that do not all have similar levels of capacity and sophistication.

Interestingly, the findings suggest that at least some of this variation is systematic, based on the size or ownership status of the organization housing the IRB. This in turn has implications in terms of the likely quality of the research ethics services that IRBs provide. This has implications in terms of the types of organizations we might like to encourage, and others we might like to discourage, through public policy (and, as consumers and patients, by voting with our wallets in terms of where we seek care). The finding of systematic variation challenges existing literature asserting that variation in IRB behavior is not systematic.

The second central finding is that, in particular, there is significant variation among IRB-housing organizations with regard to larger compliance capacities. This too appears at least somewhat systematic. Whether the IRB is part of a larger research compliance function, or is tied back to compliance functions at the local level (for non-local IRB reviews) is critically important. This is particularly true in the case of reliance relationships, where local research sites rely on an external IRB to review and oversee research. This is increasingly common and will essentially be mandated by new federal regulations for multi-center research studies.

A larger implication is that flexible regulation without a clear set of baseline standards as a floor, and a weak enforcement system (a weak "stick", in the forms of regulatory enforcement and litigation), is not producing uniformly capable organizations (IRBs). This type of significant heterogeneity is of concern in the context of an important public health and safety function. There is evidence of gaps in oversight, which raises the risk of insufficient research oversight and the potential for harms to research participants. The finding lends itself to policy interventions to create a stronger baseline at the IRB level and the research organization level.

Another implication and finding is that research is increasingly been 'overseen' by IRBs that are not at the site where research is taking place, and that the movement towards using external IRBs to review research, which may actually be performed thousands of miles away at sites the IRB has never seen, also creates potential gaps in oversight, and misalignment of financial and business incentives. This too suggests that it may be time to update the management-based regulations that govern research oversight to provide more a baseline set of requirements, given the new world of non-local research review.

In short, this paper provides evidence of variation, some but not all of which is to be expected in a management-based regulatory regime; evidence of gaps in oversight and capacity 'on the shop floor'; and a few emergent best practices and suggestions for policy updates. The paper proceeds as follows. Section II provides a literature review of key texts in regulation and governance, particularly with regard to management-based regulation. Section III provides a brief background about the regulation of biomedical research and IRBs, and the shifts in the

institutional environment that have fractured the institutional field, and shifted the location of most IRB activity from academic to non-academic settings. Section IV provides the methodology for the original research study. Section V provides key results, and Section VI provides an analysis with particular implications for regulation and governance theory, including a set of best practices that have emerged from the study data. Section VII concludes with limitations of the present study and suggestions for future research.

II. Literature Review – Regulation & Governance

1. 'New Governance'

New governance literature focuses on the interplay between regulators and regulated entities, and often analyzes the menu of regulatory instruments available to steer and row business behavior. This scholarship is particularly interested in evaluating 'flexible' alternatives to command and control regulation, in pursuit of the 'responsive law' ideal that finds a balance between discretion and rules (Nonet & Selznick 1978; Burris 2008). David Levi-Faur and others link the rise of 'new governance' techniques to the ascendancy of neoliberalism and "regulatory capitalism," in which the state continues to devolve governance to the regulated firms themselves, with light 'steering' from the state (Levi-Faur 2011; Braithwaite 2008). Such flexible regulatory regimes allow organizations to adapt regulations to their individual circumstances, while holding them accountable in some legal way for their behavior. These are often instances of 'process-oriented regulation,' sometimes called meta-regulation when there is indeed some overarching set of governmental regulatory requirements, albeit in the distance, and government regulators and regulatees have limited understanding of what good outcomes look like (Gilad 2010). Scholars have theorized that specific characteristics of firms including cultures and management attitudes may predict the effectiveness of a new governance regime, but have admitted that few studies have demonstrated the effects of different types of regulation with empirical evidence (Carrigan & Coglianese 2011). It is important to note that regulation of the professions has long involved a lighter touch, but the trend toward new governance has expanded into corporate and business regulation.

A few narratives often explain the rise of interest in 'new governance.' First, scholars anchor their interest in the functional fact that 'traditional' approaches to regulation are often, and perhaps increasingly, ill-suited to deal with the complex and dynamic problems that regulations aim to address. Second, scholars point to dramatic changes in technology and the global nature of the economy that have led to a fragmentation of traditional state-based modes of power. Governments are no longer the only 'regulators' in any given substantive space, and they now compete or collaborate with other social actors for power and influence. Among others, non-governmental organizations, public-private partnerships, and corporations now form a regulatory matrix along with governments, in which each is a 'node' in a distributed network of power (Levi-Faur 2011; Burris et al. 2008).

These empirical or external 'push factors' in the broader political economy developed alongside important internal developments within legal and democratic theory. These include the decline of unified theories, a rejection of binary dichotomies, and dissatisfaction with fragmented schools of thought (Lobel 2004). Such legal scholars explore the limitations of traditional regulatory approaches and are critical of a dichotomy between regulation and deregulation,

exploring instead a world of gradients and alternatives between those two poles (Karkkainen 2004), including experimentalist governance (Dorf & Sabel 1998; Sturm 2001).

Given these empirical phenomena and intellectual energy, regulatory scholars in the legal academy and political science and policy studies turned their analytical gaze beyond classical state-centered, highly prescriptive 'command and control' regulation, towards alternative methods of shaping the behavior of regulated entities to achieve social goals. Traditional tools took two main forms – means-based regulation, in which government mandates required all regulated entities to take the same actions or use the same technologies; and performance-based regulation, in which government mandates required regulated entities to hit certain targets or goals, without specifying how to meet the target (Carrigan & Coglianese 2011). Over time, command and control regulation came to be viewed as blunt, costly, and rigid. In addition, these tools required vigilant monitoring by government regulators, which became more difficult as many economies and agencies faced strident calls for smaller government and forced austerity.

Thus, the rise of 'new governance' scholarship is situated within this confluence of energy around empirical and intellectual developments. The scholarship acknowledges an awareness that policy solutions would need to incorporate additional tools to induce compliance with socially valued behavior, and a number of more flexible, less state-centered regulatory instruments were identified in theory and practice. Among others, these include self-regulation, information disclosure requirements, audit mandates, and as will be discussed in more detail shortly, management-based and principles-based regulatory regimes. These tools differ in the mechanisms through which they aim to control the behavior of regulated targets. But they share a general perspective about a shift in the role of government from a one-stop shop for all aspects of regulatory control, including standard-setting, monitoring, and enforcement, to one node among many within a governance matrix – namely, the node that should 'steer' the ship, with regulated entities or other nodes like industry groups doing the 'rowing' (Burris *et al*. 2008).

Some new governance literature is more functional or descriptive, often identifying instances of new governance empirically and considering the conditions under which such regimes may be more or less successful in producing social goods (Coglianese & Lazer 2003). Other work is animated by a more overtly normative concern that distributed governance is already or will be hijacked by better resourced actors, particularly those representing global capitalist enterprise (Braithwaite 2006), and that by focusing on traditional state-centered forms of regulation, we are missing the opportunity to identify governance models that can lead to more effective results (Burris *et al*. 2008; Levi-Faur 2011).

Another strand of scholarship, principally within legal scholarship, explores the theoretical limitations of top-down regulation and the potential (and sometimes realized) possibilities for experimentalist governance (Dorf & Sabel 1998). Overall, scholars have identified new governance approaches in practice in public policy domains in the US including environmental protection (Bennear & Coglianese 2013), environmental health and safety systems (Huising & Silbey 2013), and workplace discrimination (Sturm 2001). Such approaches have also been identified in the European Union, particularly with regard to the EU's Open Method of Coordination (de Búrca 2003).

2. A Specific Type of New Governance: Management-Based Regulation

Management-based regulation is one of several alternatives to command and control in the arsenal of new governance tools available to policy-makers. The central mechanism by which management-based regulations aim to achieve their goal of shaping behavior is by requiring that regulated firms engage in a process to plan how best to achieve public goals (Coglianese & Lazer 2003). Unlike command and control regulations that either intervene at an organization's acting stage (namely through 'technology-based' regulation) or output stage (through 'performance-based' regulation), management-based regulation intervenes at the organization's *planning* stage. By setting broad framework goals, management-based regulations leave the specific technologies to be used and outputs to be achieved up to regulated entities.

Instances of this regulatory approach vary in the level of specificity required of firms' plans. Some management-based regulations require that firms submit their plans to regulators for approval; others require that firms merely verify compliance publicly or to the government via a written assurance. Yet other variations require that regulated firms remain subject to government or third-party inspection and/or compliance audits.

Management-based regulations also vary with regard to the specificity of criteria required of plans. For instance, some management-based regulations specify particular elements that each plan should or must have, including identification of risks, mitigation activities, procedures for monitoring and enforcement, and measures for updating the plan (Coglianese & Lazer 2003). Other regulations may be more general. The commonality that all variations share is that firms are required to generate their own plans for how to comply with general criteria set by the government, with the purpose of achieving a specified social goal. Often, regulators will provide regulated entities with soft law guidance documents in order to assist firms in meeting management-based regulatory requirements (Coglianese and Lazer 2003).[9]

New governance scholars have identified a number of management-based regulatory regimes in the US, particularly in food safety, environmental and industrial safety, and pollution prevention. Some scholars have also evaluated the merits of this regulatory tool, noting that management-based approaches may be more effective than command and control regimes when: 1) regulated firms are heterogeneous; 2) regulating outputs is difficult; and 3) there is a high degree of uncertainty about the nature of the risk being regulated (Coglianese and Lazer 2003; Bennear 2007; Bennear and Coglianese 2013). Others have tempered optimism with an acknowledgement of the limits of management-based regulation, particularly with regard to the role of organizational trust within a firm, and the fact that divided loyalties and mistrust within a firm can derail even the best-intentioned planning processes (Gunningham and Sinclair 2009).

3. Research Oversight as Management-Based Regulation

Some new governance scholars have characterized IRB oversight of research as a failed attempt at responsive new governance. In this view, IRBs' institutional design departed from

[9] Citing an earlier insight on this point by Bardach and Kagan (1982: 237), Coglianese and Lazer note that a risk of publishing soft law is that it will in practice come to be viewed as binding, thus limiting willingness of firms to take alternative approaches. This is certainly a concern in the biomedical research context, though beyond the scope of the current analysis.

command-and-control instruments (Halpern 2008), and in theory appears to have the trappings of responsive capacity, including the ability for IRBs to develop constitutive and normatively generated governance mechanisms in which community stakeholders fashion local norms beneath the distant and supportive gaze of the state (Burris 2008). However, in this account, IRBs are in reality ill equipped to make substantive ethical decisions; they spend too much time and energy on the minutiae of informed consent documents instead of engaging in participant risk assessment, and the process is costly. As a result, the IRB model more closely resembles the 'autonomous law' of a classic bureaucracy than the responsive ideal-type.

Earlier work has also described various features of the domestic biomedical research regulatory oversight system as management-based (Goldstein 2017). Federal research regulations related to oversight of human research, animal research, conflicts of interest in research and research misconduct are all instances of management-based regulation. Each is governed by a set of federal regulations that specify the planning and internal rulemaking efforts that regulated organizations must engage in to achieve the social goals of conducting ethical research. The regulations do not specify the technologies to be used, or the outputs to be achieved. Instead, organizations have the flexibility to design their own research ethics programs, policies, and processes – all within broad framework criteria set forth in the regulations. Decisions regarding particular projects or problems and the ongoing management of such are devolved to local, private sector actors (often committees), rather than through command and control-style edicts or centralized, governmental decision-making.

Dan Carpenter addresses IRBs briefly in Reputation and Power (2011). While he does not discuss the type of regulatory regime, he provides evidence for the assertion that IRBs are a delegated regulator. In assessing the division of labor between FDA and IRBs when it comes to overseeing clinical research, he argues that the proliferation of IRBs "became a (partially unintended) mode of more thoroughly and efficiently regulating pharmaceutical development" (556). "The Administration might, in 1969, have chosen to review and inspect each and every research protocol itself, both for human subjects issues and for research quality issues." But by delegating this task to the IRB, the "resource-poor agency" was able to "effect a vast expansion in its governance of medical research while effecting minimal direct intrusion into clinical settings." Whether IRBs can in fact do a good job is "beside the point." For him, the important piece of the IRB story is that IRBs are a means by which FDA "profoundly" expands its regulatory reach (568). In addition, the IRB keeps the FDA out of (and, in his words, "symbolically 'above'") the day-to-day of protocol approval and study monitoring. The "satellite regulators not only do most of the work, but they also bear much of the brunt of criticism" (568).

III. Background: Human Subjects Research and IRBs

Below is a history of human subjects research, its regulatory regime's development, how IRBs fit into the system, and how the enterprise has changed over time.

A. Human Subjects Research

The ethics of involving human subjects in medical research has a long and storied past. What constitutes 'ethical' or 'unethical' research is context-specific, and changes over time. Prior to the mid-20th century, physicians made decisions of research ethics without input from outsiders (Halpern 2008; Rothman 1991; Starr 1982). This settlement reflected the public's trust

in doctors, and the political and social power of medicine (Starr 1982; Rothman 1991). Medical research and medical practice were part and parcel of the same set of professional activities, subject to professional self-regulation.

Commercial interests were not prominent in biomedical research until the late 20th century. Early American pharmaceutical interests were not particularly active in clinical research – they were principally manufacturing firms, as most drugs were invented in Europe. As Robert Kagan has noted, government regulation tends to emerge when other legal means (such as litigation) and the market do not result in socially acceptable levels of protection, and the government is willing and able to enact it (Kagan 2000). Up until about the 1950s, clinical research was unregulated because the public did not perceive that other legal means and the market were inadequate to protect people.

A variety of factors caused a shift in this perception. These factors included early efforts by government funders to shield themselves from liability, lawsuits related to governmentally funded medical research, the civil and patients rights movements, and the rise in suspicion of authority and physicians (Starr 1982; Rothman 1991). These circumstances created the conditions under which prior types of research programs like those at Willowbrook and Tuskegee came to be seen as scandalous. Public values shifted, as did the risk assessment of government funders. Key stakeholders including the public and government funders came to believe that other legal means and the market were no longer producing adequate levels of protection (or legal cover) (see, e.g., Rothman 1991).

The system of government regulation that emerged was a slight ratchet up, from pure self-regulation to a delegated, management-based governance technique. Its centerpiece was the IRB. Its use was mandated by federal law in 1974, although it had been required for federally-funded projects since the 1960s and had been in practice at NIH since the 1950s. The IRB as a mode of governance was premised on the self-regulation of physician-researchers and the peer review mechanism that has long been a feature of professional regulation. It was not a command-and-control mechanism, and was initially only required as a condition of federal funding. The IRB mode of governance left most decision-making up to local actors in peer review, principally in academic settings. The government's role was to steer at a distance; IRBs themselves would do the 'rowing.'

At the same time, the regulation of pharmaceutical products emerged along a different trajectory. It emerged following a product regulation logic, rather than via a professional self-regulation logic. Regulations requiring IRB oversight of products intended to be submitted to FDA for marketing approval were not finalized until 1981. Once those regulations were established, the same activity (research oversight) and the same set of organizations (IRBs) came to be overseen by two distinct agencies: FDA oversees IRBs as a part of the regulation of medical products, while HHS's Office for Human Research Protections (OHRP) oversees IRBs as part of the agency's duties as a research funder. Both agencies are responsible for enforcement, which involves routine FDA audits and inspections, and OHRP investigations in response to complaints.

Much has changed in the institutional environment in the intervening decades, particularly the rise of the pharmaceutical industry, although the regulatory structures applicable to human subjects research oversight have remained stable.[10] The major shifts can be traced to

[10] See Appendix A for schematics demonstrating changes in primary relationships between sponsors, researchers, and IRBs.

Reagan's election in 1980, and various policies established during his administration that broadly conform to a neoliberal perspective on the role of government.

Chief among these were the Bayh-Dole Act and the Hatch-Waxman Act, which repositioned patent law in a way that led to a meteoric rise in the pharmaceutical industry (Angell 2005). The pharmaceutical industry replaced the federal government as medical research's funder in chief. While academic physician-researchers had once been instrumental in designing clinical studies, including industry-backed studies, this too changed as industry developed its internal research capacities. As the main funder of clinical research, and with its own internal preclinical research capacities, industry grew to need the academy less. Over time, it found it could run trials more quickly and more cheaply in alternative venues and with alternative partners. This led to the rise of a clinical research industry full of ancillary companies that help industry test its products. Indeed, the vast majority of clinical research now occurs in community settings, such as physicians' offices and freestanding research clinics (Fisher 2009, Petryna 2009). The physicians engaged as investigators in this research are not scientists; they are merely contractors implementing industry-written protocols (Fisher 2009). Today, 75% of clinical research now occurs in non-academic settings (Fisher 2009).

IRBs have also evolved. They are also no longer located just in academic or governmental settings. As described in Section IV, there are now approximately 1,250 unique IRB organizations registered to oversee clinical research in the US. Some of these are at universities and academically-affiliated medical centers; but others are located in a variety of other institutional and organizational settings. These include community and health system IRBs (including nonprofit, for-profit, and government health providers), non-profit independent IRBs, IRBs operated by local, state, and federal government divisions and agencies. There are also commercial for-profit IRBs, which are for-profit businesses that review clinical research for a fee. How many of each type remains unknown.[11]

The regulations requiring IRB approval of FDA-regulated products and federally-funded research have remained stable despite these shifts. These organizations remain the ethical gatekeepers for medical products testing. They are still subject to light-touch regulation, based on a legacy of the self-policing powers of the medical profession. But little is known descriptively about these organizations, or empirically about how they operate, particularly now that the research landscape has changed so substantially from when the mechanism was first mandated. In C.K. Gunsalus's assessment, "virtually no scientific evidence is brought to bear on any aspect of the debate about how IRBs function. Unrealistic and untested assertions abound" (Gunsalus et al 2007).

Further, no scholarship empirically charts the entire ecology of IRBs. Some empirical work looks at academic IRBs, and there is quite a bit of non-empirical complaint about academic IRBs, particularly those overseeing social science research. There is also some scholarship about clinical research more broadly that touches upon the existence of commercial IRBs, but little empirical research has looked at the totality of these organizations, which now include IRBs in diverse settings such as non-teaching community hospitals, health systems, government facilities, universities and teaching hospitals, as well as independent, central, and commercial IRBs. There exists no full accounting of how many IRBs there are, of which types, in which

[11] The literature often states that there are more than 3,000 IRBs in the US, although my research shows that there are actually about 1,700 IRB panels, and about 1,275 unique organizations, that are registered as active in good standing on OHRP/NIH's database to oversee FDA-regulated research. The database includes thousands of IRBs in deactivated status, and hundreds not registered to oversee clinical research.

locations – and few analytical accounts of variations between IRBs based on organizational or environmental factors. The existing relevant literatures are reviewed just below.

a. Empirical Variability

An extensive literature demonstrates that IRBs display a significant range of variability in their decisions – both between different IRBs, and within the same IRB over time. In 2011, Christine Grady and Lura Abbott published a literature review of the empirical IRB scholarship. The authors reviewed 43 empirical studies evaluating US IRBs, and reported that the studies show IRBs differ in their application of federal regulations, in the time they take to review protocols, the decisions they make, and in the committees' structures and processes (Abbott and Grady 2011). Despite the volume of this literature, the authors note that more research is necessary, to investigate what issues IRBs themselves find important and to offer an analytical framework for assessing the organizations, rather than simply descriptions. Relevantly, none of the studies in the Abbott and Grady article, and none identified since, have focused explicitly on non-academic IRBs. Some may include non-academic IRBs (generally non-teaching hospitals) in surveys or discussion, but this is uncommon. The overwhelming majority of work is related to university IRBs and IRBs at academically affiliated teaching hospitals.

Many studies identify variation in IRB practices, and inconsistencies within and among IRBs (Emanuel, Wood, Fleischman, Bowen, Getz, Grady 2004; Wood, Grady & Emanuel 2004; Abbott and Grady 2011; Klitzman 2012). Some focus on variation between IRBs reviewing multicenter studies (Greene and Geiger 2006; Stark 2010; Menikoff 2010). Some address differences in who participates at meetings (Lidz 2012; Rothstein and Phoung 2007). Some look at how IRBs and their leaders approach industry-funded research (Klitzman 2013) and financial conflicts of interest (Weinfurt 2009). Of particular interest are older articles, which can provide interesting historical detail and context, useful in considering how IRBs and their processes have changed over time (Veatch 1982; Meslin 1994; Cowan 1974; Brown 1979; Heath 1979).

In addition to articles, a few scholars have published books that include empirical accounts of IRBs and their variation. These include Laura Stark's 2011 book Behind Closed Doors, and most relevantly, Robert Klitzman's Ethics Police? (2015). This is a qualitative project based upon interviews with IRB leaders and members from top NIH grantee universities and academically affiliated research institutions (n=46 individuals from 34 IRBs).

Klitzman's chapters provide insight into how IRBs weigh risks and benefits, define research and how good it needs to be in order to approve, and how they decide what to tell subjects. He also explores IRBs' relationships and encounters with regulators, importantly noting (anecdotally) that legal and regulatory pressures have led some IRBs to "become more formal" and "risk averse" (Klitzman 2015, 182; 224; 232).

His last chapters consider reforms to the current regime, noting that the then-proposed changes, and now enacted changes, to the research oversight regulations envision an expanded use of central IRBs. All of his interviewees were aware of central IRBs (which he does not define), but all favored local over centralized reviews. He mentions commercial IRBs in passing, stating that almost all of his interviewees were "strongly wary or critical of for-profit boards, fearing lower standards among these for-profit competitors, and often an implicit threat" (Klitzman 2015, 335). Of course, he doesn't include any commercial or central IRB members in his study, so he cannot offer any evidence of their inferiority to academic IRBs or even difference between the attitudes or behaviors of them and his interviewees.

Klitzman's study is important as the first larger-scale empirical project that tries to understand how and why IRBs behave as they do. However, its design leaves room for additional research. His study only includes IRBs from high-performing, highly ranked NIH grantee institutions. By excluding so many other types of IRBs, his results are not generalizable to the population of IRBs overall. And the work is expositive but not analytical – he does not offer causal or correlational claims between IRB behavior and any particular features either exogenous or endogenous to the organizations themselves, and states directly that he does not believe IRBs vary "systematically in any one clear direction. IRBs do not differ according to fixed…categories." (Klitzman 2015, 353).

b. IRB Ecology

A related literature addresses the variety of IRBs by organization and type, although none offers a full typology or ecology of all IRBs. As discussed above, most literature focuses on academic IRBs. Other types of IRBs include independent IRBs and commercial IRBs (these are sometimes defined synonymously, but not always). Mirowski & Van Horn discuss the rise of CROs and independent IRBs (Mirowski & Van Horn 2005). Comparing local (generally academic) IRBs to independent/commercial IRBs, the authors note that, among other factors, independent IRBs review protocols faster, are subject to less regulation (just FDA regulations, as opposed to also NIH and OHRP regulations (Mirowski & Van Horn 2005).

Legal scholars and commentators have also written about the movement of research from academic to community settings, and the changing role of the IRB and its organizational location. Of note, David Forster, then Director of Regulatory Affairs at Western IRB, the largest commercial IRB in the country, set out the historical origins of commercial IRBs and addressed some criticisms of its operations including that commercial IRBs have an inherent financial conflict of interest and that they promote IRB shopping in the event that one IRB disapproves a protocol (Forster 2002). Although the use of commercial IRBs has accelerated, FDA has long acknowledged the existence and regulatory validity of commercial IRB review (Nightingale 1983).

Fisher's Medical Research for Hire (2009) and Elliott's White Coat, Black Hat (2011) both include short treatments of commercial IRBs. Fisher situates these organizations within the broader outsourcing and fragmentation of clinical trials. She mentions that the more than 40 for-profit IRBs in the US collected more than $60 million in 2002; Western IRB alone holds 50% of the market share (Fisher 2009, 11).

Elliott discusses the GAO's 2009 sting of commercial IRBs, in which an egregiously scientifically and ethically inappropriate protocol was sent to three commercial IRBs for approval.[12] While two turned it down quickly, Coast IRB approved it. Later, it was discovered that Coast had only turned down a single protocol of the several hundred it had approved in 5 years, and had revenue of close to $10 million a year (Elliott 2010, 159). Despite the blip of bad press, commercial IRBs are a growing industry – Chesapeake IRB was named by Deloitte as one of the fastest growing 'tech' companies in the US, and in 2007, a major stake in Western IRB was sold to private equity firm Boston Ventures (which also owns majority interests in NASCAR and Six Flags) (Elliott 2010, 166). His efforts to interview Western IRB professionals were mostly thwarted, because the firm is so protective of its proprietary property – including its

[12] The protocol described pouring potentially toxic liquid into open cavities during surgery. Post-scandal, Coast went out of business.

methods of reviewing protocols. He argues that commercial IRBs have no incentive for other IRBs to do a good job, because their business activities are in competition with other IRBs. The implication (currently unsupported by empirical data) is that leaving this activity to the market may be detrimental to the public's health.

In addition, a few scholars have raised normative concerns about certain IRB types, particularly commercial IRBs. Some treatments question whether IRBs should be able to operate as for-profit companies at all (Emanuel 2006; Shamoo & Woeckner 2006; Lemmens and Friedman 2000; Lemmens and Thompson 2001). Others explore how independent different types of IRBs actually are (Macklin 2008). Yet others have explored the operation of central IRBs (Christian 2002; Wagner 2010). Finally, in 2009 the Government Accountability Office (GAO) undertook a sting operation of IRBs, particularly of commercial IRBs.[13]

c. Fragmentation of Clinical Trial Enterprise

In recent years, a number of scholars have published books (and some key articles) that explore the clinical research enterprise in the US. These works are largely empirical accounts based on qualitative research.

Jill Fisher's 2009 book "Medical Research for Hire" is an ethnographic study observing that, in the past two decades, the US pharmaceutical industry has completely reorganized the clinical testing of its products, moving from academic medical settings into the community. Currently, about 75% of clinical trials in the US are conducted in the private sector, by nonacademic, non-scientist physicians, who contract to oversee pharmaceutical trial protocols as 'site investigators,' recruiting their own patients or local community members. Fisher then explores the experiences of independent physicians and their staff in performing contracted research services for pharmaceutical companies.

Fisher surfaces systems-level insights. Chief among these is the insight that the replacement of academic medical centers by a 'proliferation of ancillary companies' (CROs, commercial IRBs, private practices, dedicated for-profit research centers) is congruent with the rise of corporate outsourcing and delegation overall (See also: Monahan's concept of delegating responsibility as a neoliberal strategy of 'fragmented centralization' 2005). This in turn is a reflection of neoliberal trends in the organization and management of corporate pursuits. She also ties these developments to broader instantiations of neoliberalism in US policy, in which the state has retreated from active involvement in managing risks, transferring responsibility to citizens to provide for themselves as individual and empowered 'consumers.' In this reading, individual citizen consumer-patient-subjects are given the 'choice' to participate in clinical research, with the risks to be assumed at the individual level. Of course, this neoliberal spin obscures the information asymmetries between patient-subjects and their health care providers, and their unequal power and economic positions.

Abadie's study notes that while most early testing of drugs occurred in prison populations until the 1970s, since then, the industry has turned to the open market to find test subjects. While this shift was borne out of the desire to protect incarcerated people, over time it has harmonized with a broader neoliberal logic under which the state's ability (and obligation) to protect the public has declined, while commodification of the human body has increased. In this regime,

[13] This operation produced a 2009 report and statement to Congress entitled "Human Subjects Research: Undercover Tests Show the IRB System is Vulnerable to Unethical Manipulation," and the transcript from the 2009 Senate Hearing, "Institutional Review Boards that Oversee Experimental Human Testing For Profit."

individuals "feel that they are making their own choices and…take responsibility for their own actions, in particular actions that may place them at risk" (Abadie 2010, 160).

Of particular value to this paper are Abadie's observations about the IRB of a community-based HIV center in whose trials several of his 'professional guinea pig' interviewees participate. The IRB is of interest because it is not an academic IRB – a rarity in the literature. His treatment of the IRB and its behavior is not a centerpiece of the book (related discussions appear on perhaps 15 pages overall). However, several empirical observations are important. Chief among these is the deep level at which this IRB reviews the scientific value of the proposed protocol (even before considering the risks and benefits of the intervention). Unlike IRBs that are criticized for following a "formalistic, legalistic approach to informed consent, members at CBTO engage in a discussion that goes beyond formal issues…lay and professional members alike engage in a discussion about the validity of the trial, attempting to distinguish between scientific merit and marketing claims" (Abadie 2010, 151).

Many scholars have noted the decline of academic-sited research and the rise of alternative sites. Until recently, academic investigators were "key players" in the design, recruitment, and interpretation of data in clinical trials (Davidoff 2001). Into the late 1990s, most pharmaceutical companies didn't have in-house expertise to design protocols (Falit 2006). But firms have increasingly exercised control over protocol design, have hired top-level research physicians to work in-house on protocols (Falit 2006), and clinical trials have largely moved from academic settings into community settings (Fisher 2009). As of 2005, commercial sponsors provided 70% of funding for clinical drug trials in the US (Falit 2006, citing Mello 2005). That number has gone up, and more recent estimates are that 80% of clinical research is industry funded (Fisher 2009).

Others have explored the growth of contract research organizations (CROs) over the past 20 years. These businesses have "gradually taken over much of academia's traditional role in drug development" (Shuchman 2007, 1365). The industry has grown quickly (Rettig 2000). In 2001, CROs had $7 billion in revenue; by 2007, it was up to $17.8 billion. In 2004, just the top ten CROs enrolled 640,000 subjects that year (Shuchman 2007). CROs have been described as "data-production sweatshops" (Shuchman 2007, 1367). They are cheaper in part because they employ young, less experienced personnel (Fisher 2009). Philip Mirowski has written about the rise of CROs as a 'paradigm of privatized science' (Mirowski & Van Horn 2005).

IV. Methods

A. Study Design and Sample

a. Total IRB Universe

I first undertook to characterize the entire population of IRBs in the United States that are registered to oversee biomedical research. IRBs are not required to be accredited or approved by any governmental or non-governmental agency or organization in order to oversee biomedical research. Instead, IRBs are simply required to submit a short form to the appropriate federal agency with basic information about the IRB. FDA/OHRP then list the name and location of each such registered IRB online at a publicly available website. See Section IV.B.a below for discussion of use of this dataset.

b. Qualitative Study

I then undertook a qualitative study, based on 19 open-ended interviews conducted with current and former IRB members, administrators, and counsel, each from US-based, OHRP/FDA-registered IRBs. Interviews occurred during site visits and remotely from November 2015 – May 2018. The qualitative approach was chosen for several reasons. First, with few exceptions, few studies have investigated the full range of IRB types (by ownership status, size of research program, academic affiliation). Qualitative research is particularly well suited for exploratory studies for which previous literature is limited (Crabtree and Miller 1999). Such studies are useful for generating hypotheses that can later be tested with quantitative data (Crabtree and Miller 1999; Glaser and Strauss 1967). In addition, I anticipated that some factors, such as experiences with commercial and central IRBs, were complex and challenging to measure. Further, another goal of the interviews was to inform development of a survey that might be used in future research to characterize a larger sample of IRBs. Qualitative research provides a method to describe the diverse facets and dimensions of such factors, which in turn is useful for survey instrument development (Bradley et al. 2001; Miles et al 1994).

As is standard in qualitative research (Bradley et al 2001), I chose sites and interviewees using purposeful sampling to ensure that I included a diverse set of IRBs and IRB professionals. Study IRBs were selected to reflect a range of geographical locations, size, ownership type; study interviewees were selected to reflect a range of roles within the IRB and related organization. Additional IRBs and interviewees were recruited through snowball sampling, including through the author's professional networks and professional associations. Additional interviews were conducted until no new concepts were identified, in other words, until the point of theoretical saturation. This occurred after 19 interviews. The characteristics of the study IRBs and interviewees are displayed in Tables 1 and 2.

Eligible interviewees were current or former IRB members, administrators, or counsel, from eligible IRBs in the United States, defined as those IRBs with active registration to conduct FDA-regulated human subjects research on the FDA/OHRP database as of the interview date.

B. Data Collection

a. Total IRB Universe

A search for all US-based IRBs registered in active standing on the OHRP/FDA database to review biomedical research on April 26, 2017 yielded 1712 IRB panels. This search excluded IRBs registered to review *social science research only*. It included only those IRBs either registered to review FDA research only (27), or registered to review FDA and OHRP research (1685).

Of the 1712 total active IRB panels, there were 1274 unique IRB entities. The remainder are multiple IRB panels at the same organizations. For instance, VA Greater Los Angeles Health Care System has 3 IRB panels separately registered on the OHRP/FDA database, but is counted as 1 unique IRB entity in this study. The methodology to determine if multiple IRB panels were part of a single unique entity was to assess if the IRB entry had the same name and was in the same city as another IRB entry. If the name or city were different, the two entries were considered to constitute two unique IRB entities. If the name and city were the same, the two were considered as one unique IRB entity. See **Table 1**.

b. Qualitative Study

In-depth, open-ended interviews were conducted in person and via teleconference with study interviewees. 19 interviews were conducted with interviewees at 19 IRBs, for a total number of 19 key respondents interviewed with experience at 21 IRBs. See **Table 2** and **Table 3**. These included 12 IRB members and 13 IRB administrators (note, some respondents had both an administrative role and membership on their IRB).

The author conducted each interview with a single participant. Interviews took place in person (8) or on the phone (11). Interviews were each one to three hours in length. All interviews were audio-recorded and transcribed by independent researchers and professional transcriptionists.

Interviews were conducted using an interview guide instrument (provided at **Appendix B**). For each question, interviewees were encouraged to provide specific examples and details from their experiences. All qualitative interview procedures, interview guides, and recruitment plan were approved by the UC Berkeley institutional review board.

C. Data Analysis

Transcribed interviews were analyzed using coding techniques common to qualitative data analysis (Bradley et al 2001). Coding of the data was accomplished through a series of steps. An initial code list was generated based upon the interview instrument, and was then refined during review and analysis of the transcribed interviews. The process of iterating the code structure involved adding and redefining codes as new insights emerged, as well as identifying relationships within code categories.

Using this final version of the code structure, the author and a research assistant independently coded the transcripts and recorded the data using Excel to capture recurrent themes, links between themes, and quotations of interest.

Techniques were used to maximize the systematicness and verifiability of data analysis. These included consistent use of the interview guide instrument, audio recording, independent transcription, and consistent use of the coding structure in data analysis by two individuals for intercoder reliability.

V. Results

1. Descriptive Statistics

1.1 IRB Ecology

Table 1
Descriptive statistics of US-based IRBs registered in active standing to review biomedical research as of April 26, 2017

State	# of Unique IRB Entities	Percent of Total
Alabama	24	1.88
Alaska	1	0.08
Arizona	23	1.81
Arkansas	10	0.78
California	115	9.03
Colorado	22	1.73
Connecticut	25	1.96
Delaware	7	0.55
Florida	57	4.47
Georgia	37	2.90
Hawaii	8	0.63
Idaho	7	0.55
Illinois	50	3.92
Indiana	27	2.12
Iowa	14	1.10
Kansas	10	0.78
Kentucky	16	1.26
Louisiana	17	1.33
Maine	8	0.63
Maryland	46	3.61
Massachusetts	57	4.47
Michigan	37	2.90
Minnesota	17	1.33
Mississippi	12	0.94
Missouri	30	2.35
Montana	6	0.47
Nebraska	8	0.63
Nevada	7	0.55
New Hampshire	13	1.02
New Jersey	37	2.90
New Mexico	6	0.47
New York	91	7.14
North Carolina	32	2.51
North Dakota	6	0.47
Ohio	50	3.92
Oklahoma	14	1.10
Oregon	19	1.49
Pennsylvania	75	5.89
Rhode Island	12	0.94
South Carolina	16	1.26
South Dakota	3	0.24
Tennessee	25	1.96
Texas	68	5.34
Utah	6	0.47
Vermont	2	0.16

Virginia	37	2.90
Washington	22	1.73
Washington DC	11	0.86
West Virginia	6	0.47
Wisconsin	25	1.96
Total	**1,274**	**100.00**

1.2 IRBs and IRB Professionals in the Study

Table 2
Descriptive statistics of IRBs in the study (n=21^)

	n
Ownership Type	
For-profit	3
Non-profit	9
Government	7
Org Type	
Healthcare	15
Commercial IRB	5
Public Agency	1
Size of Research Program (Active)*	
1-100 protocols	4
100-500 protocols	8
>500 protocols	5
Location	
California	4
Massachusetts	4
Washington	2
Arizona	1
Connecticut	1
Ohio	1
New Mexico	1
Oregon	1
North Carolina	1
Pennsylvania	1
Texas	1
Minnesota	1

^ Two respondents were interviewed about their service on 2 separate IRBs.
* Two commercial IRBs declined to provide this data. In analysis, they are identified as "Small/Medium-sized research portfolio commercial IRBs"

Table 3
Descriptive statistics of IRB professionals interviewed in the study (n=19)

	n
Role*	
Administrator	13
Member (Scientific)	8
Member (Lay)	4
Gender	
Male	10
Female	9
Tenure in HSR	
<10 years	4
>10 years	15

* Some respondents have more than one current role.

2. Findings - Internal Factors: Structural Features

After review of the interview data, respondents' comments were organized into three broad factors that formed the basis for the taxonomy of internal structural factors, which may influence IRB expertise and capacity. These factors are: (1) variation in the presence of an active researcher on the IRB; (2) variation in the use of a separate scientific review committee to vet protocols; (3) variation in the ability of IRBs to ensure that a relevant medical specialist reviews appropriate protocols; and (4) variation in whether the IRB sits within a larger human research protection program or otherwise within larger compliance functions within the organization. See **Tables 4-7** for quotations illustrating variation in these factors.

2.1.1 Active Researchers

Respondents vary systematically regarding whether their IRB has one or more active clinical researchers who are voting members. Most respondents (14/19) report having at least one active researcher on the IRB. However, small research portfolio healthcare organizations and independent / commercial IRBs were more likely to report not having at least one active clinical researcher on the board. Of the 4 respondents who reported not having at least one active researcher on the IRB, 2 were from small portfolio commercial IRBs, and 2 were from small/mid portfolio healthcare organizations.

Table 4
Internal Factors: Variation in Structural Features – Active Researchers

Active Researchers
We prefer to have all of them [IRB members] be active researchers. Sometimes because of grants or other position responsibilities they're not actively doing research at the time. But we definitely prefer that they be active researchers (mid-sized research portfolio government health care organization)
No Active Researchers
There's no one that's an active researcher that's a member, no. I mean, we have one cardiac surgeon that's doing a medical record review kind of study, but not any of the other clinical trials (small research portfolio nonprofit healthcare organization)

2.1.2 Separate Scientific Review

Respondents vary regarding whether their IRB has a scientific review process that evaluates the scientific merits of research proposals separate from the IRB's oversight and approval. About half of the respondents in whose interviews this question came up (12) reported having a separate scientific review process (6).

At some healthcare organizations, scientific review happens at the departmental level before a protocol is sent to the IRB; at others, there is an entirely separate committee and process for scientific review.

Small healthcare organizations and independent / commercial IRBs are less likely to have a separate scientific review process. However, some very large healthcare organizations do not have a SRC and are adamantly against them. Respondents from these organizations take the position that scientific issues cannot be separated from ethics, and that the IRB needs to consider both sides of the coin. Other respondents disagree, believing that the IRB affirmatively should not be analyzing the scientific validity of the studies it reviews.

Table 5
Internal Factors: Variation in Structural Features – Separate Scientific Review

Separate Scientific Review
So here we have 20-some different scientific review committees. Each department has their own process. When they were established, we provided them certain guidelines of what was expected, types of questions they were supposed to address, and some of them—they've all evolved in separate ways. Some of the departments do great scientific review and some don't. I think certain disciplines align themselves to a more rigorous sort of review…for example, cardiology has a very tight review—they require the bias of that physician to be involved on every scientific review of every project. (Large portfolio nonprofit healthcare organization)
Yes. The ones for the oncology site has to go through the cancer committee's protocol sub-committee. So they get reviewed scientifically there and then basically, if the physicians think there's enough interest or they have patients that would benefit from that trial, then they'll move it on to the IRB. (Midsized research portfolio nonprofit healthcare organization)
[Having SRC] also benefits your ability to go through the IRB… more smoothly. They don't raise these embarrassing questions about the science. So I am a big fan of scientific review done right. The worst thing that can happen however, is for you to tell me you have a scientific review process and what it is it's

the department chair getting it and saying, "Okay. Yeah…. It's okay with me" … Or have some overworked resident look at it and not take it seriously… Now some departments automatically do scientific reviews, so oncology, all the oncology studies undergo a Protocol Review Committee, which looks at both feasibility and science… Other departments, I do not know what is happening. So as a consequence we get some good things and we get a lot of crap. (Large research portfolio nonprofit government healthcare organization)
Yes. Typically people will submit the protocol to R&D [scientific review committee] and IRB at essentially the same time, and IRB staff starts a prescreening—goes through everything, makes sure everything's, like all the paperwork that they need to submit has been submitted, it's all been filled out—and then they send some prescreening questions back to the investigator to see if they find anything they need clarification or correction on. Meanwhile the R&D committee's doing their thing and meanwhile the privacy officer's reviewing the thing, and the information security officer's reviewing the thing. (Mid-sized research portfolio government healthcare organization)
No Separate Scientific Review
No. We don't believe in it. We're very strong about that. We believe that the risk-benefit is intimately tied into the scientific questions. So our IRB panels have the scientific expertise, and we would never defer that to another group… I don't know who we'd get to do an additional scientific review (Large research portfolio nonprofit healthcare organization)
We do not have one of those [SRC]. Our committee members take note of funding and… if it is NIH, they do not.. look at the science and say, "We better re-review the science that NIH reviewed."... So essentially the IRB acts as a scientific review as well, with the exception of, like, NCI or things like that. (Mid-sized research portfolio government healthcare organization)

2.1.3 Relevant Specialists

Respondents report variation in whether their IRB requires each study to be reviewed by a specialist in the particular medical area and/or patient population. Smaller healthcare organizations and independent / commercial IRBs are less likely to report ensuring that a relevant specialist reviews studies.

For example, at an IRB that only has an oncologist on the board, a cardiology study may be reviewed by this oncologist and may not be reviewed by a cardiologist. At other IRBs, if the board does not have a cardiologist, it will ask a cardiologist to review as a guest reviewer or consultation.

Table 6
Internal Factors: Variation in Structural Features – Relevant Specialists

Expertise Ensured
We've occasionally brought in some expertise and yes, I think there's always something that a reviewer might not totally understand and we will ask for an outside reviewer. (Small/Mid-sized research portfolio commercial IRB)
Yes… at [IRB], it was very common that we would bring in an outside consultant (Large research portfolio commercial IRB)
As needed, we'll bring on guest reviewers, because sometimes we just don't have the expertise. For example, research that involves children. We do so little of it that we don't have any members on the

committee who have experience in research with children. (Mid-sized research portfolio government healthcare organization)
Expertise Not Ensured
I mean I don't believe we have a cardiologist on the board. We do a lot of cardiology studies. But the PI's come, so they can be quizzed and we've got an ER doc, we've got an oncologist, we've got an internist, we've got a pathologist. But usually the ER doc, the internist, and the oncologist…they know enough medicine to be able to figure this out. (Mid-sized research portfolio nonprofit healthcare organization)
We don't have a cardiologist there when a cardiology protocol is being discussed. But I also feel comfortable with that in the sense that these are all pharmaceuticals. I feel like they've been pretty well vetted, I mean they usually have their INDs or they're device studies. And I feel like once they get to this point, the companies want the protocols to succeed so they're not going to create something that doesn't make sense, doesn't have good study design and we do have that medical expertise of the other physicians. (Small research portfolio nonprofit healthcare organization)

2.1.4 Larger Compliance Function

Respondents vary in regard to whether their IRB is connected to a larger compliance function within the institution where it is housed. This has a few parts.

2.1.4.1 Facilitating/Coordinating Mechanism

Respondents vary in terms of whether the IRB and its office serve as a 'facilitating' or coordinating mechanism for other research-related functions within the organization. IRBs housed in large healthcare organizations tend to report that the IRB is just one component of research evaluation and approval processes. Sometimes the IRB serves as the coordinating mechanism between these processes, including separate scientific review, privacy officer or board approval, radiation safety board approval, and staffing/pharmacy capacity reviews. Smaller organizations, independent IRBs, and even large healthcare organization IRBs overseeing non-local research may not have these processes or may not use them in reviewing non-local research.

Respondents vary regarding whether their IRB is part of a larger human research protection program (HRPP) or research department. Larger institutions (health care and university) almost universally report that the IRB sits within a larger department or set of departments constituting a HRPP. These related departments and functions provide training for researchers, conflicts of interest management, and domain experts in research regulations.

Among respondents whose institutional research oversight is outsourced to non-local IRBs, respondents vary regarding the extent to which other internal departments or functions provide these services and functions.

Table 7
Internal Factors: Variation in Structural Features – Compliance / Human Research Protection Program

Larger Compliance Function
We have the compliance office at the hospital. And then we have legal, contracting, we have the compliance and the campus. (Large research portfolio government university health system IRB)
We're it. So we are a human research protection program, we have the IRB panels, all of us do the education piece and give talks at both hospitals. And we have the QI/QA. And we tell them – if we're concerned about a PI – go out and give your findings back to us. We are the police and the judge and the jury. (Large research portfolio nonprofit health system IRB)
We do have a compliance officer that attends every IRB meeting as a consultant, so they're not speaking generally, but they can be consulted and sometimes will pipe up if there's something that the committee is going down a route like "Well, okay, from a compliance perspective you need to consider this before you say that. (Mid-sized research portfolio government healthcare organization)
In the VA system, the Animal Protection Committee, IACUC, and the IRB, let's say and the Subcommittee for Research Safety, the Biosafety Committee, all are considered subcommittees to the Research & Development Committee or RDC. (Mid-sized research portfolio government health care organization)
No Larger Compliance Function
No, I mean I've put myself on the list as a compliance officer. Somebody told me that I probably shouldn't do that, so I probably better find somebody else to do that, but there's not. (Mid-sized research portfolio government organization)

2.1.4.2 Monitoring/Auditing

Respondents vary with regard to the extent to which their IRB monitors and audits research occurring locally and/or non-locally (when the IRB is acting as IRB of record). See **Table 8**. Smaller IRBs are more likely to indicate that they believe the external monitors hired by pharmaceutical companies handle the "compliance" required to oversee clinical research at the facility. Interestingly, respondents across organizations report not regularly receiving external monitor reports from the sponsor. IRBs at smaller organizations report not getting monitor reports even when they have asked for them. They rely on the principal investigator and/or research staff to report relevant findings from monitor reports to the IRB. IRBs at larger institutions are more likely to require and review external monitor reports.

Many large institutional IRBs report having a monitoring and auditing function internal to the organization. However, this is not universally the case. Many respondents report that their IRB does not audit principal investigators for cause or not-for-cause.

Table 8

Internal Factors: Variation in Structural Features – Monitoring/Auditing

Significant Monitoring/Auditing
They [Compliance office] audit the IRB, and the IRB office. So we get a list of all the things we did wrong, and which things they have to correct for the record, and things like that too… They do random audits. They're kind of more like a friendly audit, like educational session for the team. That being said, there are corrective actions to be made. In a few cases they have resulted in extra studies being audited and serious consequences for a few bad players. It is actually an arm of the HRPP. It's sort of under the same leadership, but separate, and they report kind of side-ways to avoid conflict of interest, away from the IRB director. (Large research portfolio nonprofit health organization)
Most of the time, that hasn't been necessary to do a site visit. But when a question comes up about history of a protocol violation that we become aware of… then, if continuing review comes up or they submit a new protocol then we'd review this and see that, "Oh, look. In the past they've had this," we would then say, "We have the right to a site visit." And we have someone who has great expertise in doing site visits. (Mid-sized portfolio commercial IRB)
We do random site visits… A couple of times, early on when we first started out as an independent board, I would go anonymously to where the site is… and I'd say I was interested in the study and went through the informed consent process and see how I was treated as a potential subject and then once we got to a certain point where they said, "Well yes, you could be in the study," I'd say, "That's good, I'm here from XXX IRB and we approved this study and I wanted to see how it was being carried out."…. I … had to do it just to make sure that the subjects were being treated the way they should, not just on paper, but in real life (Small research portfolio commercial IRB)
Absolutely. Yes... we do internal audits as well - all different aspects of it, whether that's the consent form, enrollment, and studies. We teach investigators their stats to keep those things in quality assurance, and that we want to find things before it's a problem ... We audit participant payments, we audit pay in-cash - all those sorts of things. We have a high standard that we have in our organization. (Mid-sized portfolio government university healthcare organization – IRB member [scientific])
All VAs have not only a IRB but they have a parallel kind of service, it's the Research Compliance Officer, or Compliance Office... And every VA that has a research program has also a Research Compliance Officer and they're responsible for those compliance sort of issues and … education. At ours it's not so much education but they definitely do the compliance component. And at every VA, these Research Compliance Officers are required to audit, fully audit a study no less than I think it's two or three years. (Mid-size research portfolio government healthcare organization – IRB administrator)
Yes. But it's not the IRB. When we were developing that, we decided that the IRB should be in a non-confrontational position with investigators because we want people to come to us and talk to us and we are providing advice. So …our Research Protection Program has a compliance group and they do multiple cause and not-for-cause audits - and there's 5-6 people in that group…We try not to audit studies that are being monitored by industry or NIH. (Large research portfolio nonprofit healthcare organization – IRB member [scientific])
At [big commercial IRB] we had a robust site visit program…We took that responsibility very strong because that's what we thought we had to do mainly because of our risk, because there were lawsuits. (Former large commercial IRB member / administrator)
No Significant Monitoring/Auditing (Relying on External Monitors)
I have to say that when I first started in the job, I was better at it. I'd look at the inclusion criteria and track doses and I haven't really done a lot of it [lately] because I know, at least the cardiology group, has the

outside monitors are coming in -- and they are finding things. (Small research portfolio nonprofit healthcare organization)
It is a tool we can use but frankly we don't really have the resources to do it. (Small research portfolio nonprofit healthcare organization – IRB member [scientific])
If a study goes to WIRB, for example, the investigator completes a very minimal application for us [home IRB], so we know what he or she is doing. But everything else is handled by WIRB. If there is some significant noncompliance we are informed of it because I think ultimately the investigator belongs to us, so we have some responsibility. But do we do random audits? We, to the best of my knowledge, we do not… I would think that SAEs would be reported back to us. But I do not know what is going on. (Large research portfolio government university healthcare organization – IRB administrator)

2.1.4.3 Conflicts of Interest

Across the board, respondents report being disconnected from a process by which potential conflicts of interests between principal investigators or other staff and research sponsors would be disclosed and managed. See **Table 9**. Many respondents report believing that their institution has some mechanism by which potential conflicts of interest are reported and managed, but they are not sure. The process is often siloed from the work of the IRB. Several respondents indicate that they believe, if a conflict of interest existed, appropriate language would end up in the informed consent form that the research participant would sign, but they cannot personally recall seeing this language in any consent form. This is true even at large healthcare institutions, which have a robust, but separate, conflict of interest process.

At commercial and independent IRBs, respondents report that principal investigators are required to submit a form to the IRB indicating any potential conflicts of interests, but respondents are not sure how these forms are processed or by whom.

Table 9

Internal Factors: Variation in Structural Features – Conflicts of Interest

Tightly Coupled COI Function
They definitely have a mechanism in place for conflicts of interest that comes up on a regular basis…And they cover everybody. Everybody has to go through it and sign off on it—not just investigators—study staff do as well. (Mid-sized research portfolio government healthcare organization – IRB member [non-scientific])
There's a page in the IRB application that ask a number of questions relevant to financial interest: do hold stock, do you have equity… and anyone who answers anything whatsoever on that page, their protocol's reviewed by somebody who, I think, sits jointly in general counsel and in the compliance office…We [institution] ask them … they have advisory roles related to the study or to the sponsor, like on a scientific advisory committee or something like that. Do they have any patents, licensed, or soon to be licensed, or hopefully be licensed, other grants that they're involved with, honoraria, stock options, consulting arrangements…and all that's there for the IRB to see. And the management or disclosure of that is there for the IRB to see as well. The IRB approval won't be final until that's all there. (Large research portfolio nonprofit healthcare organization – IRB administrator)
It's really easy, I'll tell you why. There's an office that handles all conflicts of interest. You [researcher] have to submit a conflict of interest statement, and we used to review them, and now they're reviewed by somebody else, this office, and then they come back to us when there's a conflict. And that always goes

to full committee. And the full committee … we have to approve it. (Large research portfolio nonprofit healthcare organization – IRB member [scientific])
Our chair is still a member of that committee - I just love having 2 IRB members on that committee… We see everything. So the way our system works is they have to file an annual report and then with every single study they submit to the IRB, they have to fill out like an amendment to that report. And those go to the conflict of interest committee and then they alert them if there's an issue - and then of course, we [IRB] would know about it anyway because one of us would be at the [COI] meeting where it was discussed. (Large research portfolio nonprofit healthcare organization – IRB member [scientific])
Loosely Coupled COI Function
There is a COI Committee. I am presumably an ex officio member. I have not yet been to any of those meetings. There has not-- honestly, there has not been any clear connection between the COI Committee and the IRB. If the researcher has a conflict of interest, it's reported to the COI Committee. A management plan is developed. Part of the management plan is necessarily going to include whatever reports need to be made, and the consent form, and whatever things need to be done with graduate students. So that whole thing happens. What the IRB ultimately gets is all that stuff, and doesn't think about it… I have never heard a conflict of interest management plan discussed at a meeting. (Large research portfolio nonprofit government university healthcare organization – IRB administrator)

3. Internal Factors: Capacity/Attitudes and Role Conception

Three factors characterize variation in IRB professionals' attitudes and role conceptions that may impact the committee's capacity to carry out its central mission of protecting human subjects in research. These broad factors are: (1) whether "risk/benefit" is defined narrowly as the risk or benefit of the specific intervention; (2) acceptance of external proxies for research quality; and (3) the IRB's mission and obligation regarding research design and research quality. **Table 10** provides direct quotations to illustrate these factors.

3.1 Risk/Benefit and Scientific Design

Respondents vary in how they describe the concept of "risk vs benefit" in clinical research. Some respondents conceptualize risk/benefit narrowly – to these respondents, risk/benefit analysis focuses on the specific intervention being proposed in the research protocol. These risks may be possible drug interactions, or the way the inclusion and exclusion criteria are defined. These respondents do not consider the overall research design, statistical analysis plan, and other macro-level factors to be part of the risk/benefit analysis in which an IRB should engage.

There is evidence to suggest this variation is systematic. The narrow conception of risk/benefit is more common at smaller healthcare organizations, where IRB respondents sometimes report feeling comfortable assessing the risks and benefits of the specific research intervention, but not comfortable assessing the overall research design. Other small organizations report concern that they do not have sufficient scientific expertise to assess risk/benefit of the specific interventions at issue.

For example, one respondent from a community hospital IRB explained that, while they do not have internal expertise necessary to critically assess statistical analysis plans in protocols, they had a high school student, who is a stats whiz, help the IRB with understanding the statistical analysis plan for research studies as a consultant. Respondents from larger IRBs report more frequent discussion of scientific design, statistical power and modeling.

Respondents report variation in their conception of the IRB's core mission and purpose. Some believe that the IRB's mandate extends only to review of the risk and benefit posed by the particular intervention described in the research protocol (for instance, the risk/benefit to the participant who takes Drug X over the course of the 3 month study). These respondents believe that the IRB's mandate does not extend to matters of scientific validity and research design. Other respondents disagree vigorously with this conception of the IRB's role, arguing that scientific issues cannot be separated from ethics.

3.1 Use of External Proxies for Scientific Quality

Respondents vary regarding whether they consider certain features of research studies to constitute a proxy for the quality of the research project. In particular, respondents from smaller organizations tend to report believing that research studies that have an IND from FDA, a grant from NIH, or other prior peer review have already undergone rigorous scientific review from another source, such that the IRB can rely on these as proxies for the quality of the study.

This is also true for commercially sponsored studies. Some respondents, particularly from smaller organizations, report that they believe industry funded studies have been 'well vetted.' To these respondents, pharmaceutical and device manufacturer sponsors would not invest the time and money in studies that are not well designed. The fact that a pharmaceutical company sponsors the study is therefore evidence of its scientific quality. Larger organizations tend to disagree vehemently with this type of proxy, particularly with regard to NIH studies, which some large IRB respondents report having seen lots of poor quality research obtain NIH funding, particularly investigator-initiated studies.

Table 10
Internal Factors: Variation in Attitudes Toward Key Issues

Risk Benefit
[IRB doesn't discuss] as much about the scientific design and the statistical models. We really don't spend a lot of time on that. But the risks and benefits, for sure. For sure they look at those and make sure that they include everything, and that the alternatives include real alternatives, not just what the sponsor wants to brush over, because we see some of that. ..but no, not the design. I think we don't have that expertise, and that's always been a fear. We had a wonderful local high school kid that was brilliant and we had him as a consultant. We would send the protocols to him. I think he'd done the CLEP or AP or whatever it was: a statistics exam. (Small research portfolio nonprofit healthcare organization – IRB administrator)
[Is our IRB] equipped to grapple with the scientific issues, I would say it's not an issue because these are late stage studies; however, I don't think they would be… I feel like as an institution as a whole, we lack the necessary expertise to help people formulate their studies. (Small research portfolio nonprofit healthcare organization – IRB administrator)
The science is really important to our group. Because our position is, if the science is no good and it's not going to answer the question, why expose somebody to even a blood draw. (Large research portfolio nonprofit healthcare organization – IRB member [scientific])
Our IRB has a lot of scientific expertise, a lot of scientific design expertise, we have a statistician on our committee, and I think we consider that part of our responsibility. We frequently see things that are under-powered clinical trials that are posing a pilot studies - but that's not a pilot study, that's an

underpowered clinical trial. (Large research portfolio nonprofit healthcare organization – IRB member [scientific])
I think risk is important. Benefit is important too and you have to know something about the science to be able to determine whether there are any benefits. (Large research portfolio nonprofit government university healthcare organization – IRB administrator)
External Proxies
When the research has been externally reviewed by the NIH … and by the FDA, then I think that IRB can take a step back on those scientific issues - we cannot have all that expertise. (Large research portfolio nonprofit healthcare organization – IRB member [scientific])
"If a study is, you know, NIH or NCI grant, or cooperative study or something like that, your reviewers would tend to sort of consider that to be a sign of the quality of the scientific design, but that's not the case for industry-sponsored studies…and I would say that…an IND granted by the FDA is a guaranteed shoe-in [for IRB approval]. (Mid-sized research portfolio government healthcare organization – IRB administrator)
Oh, we trash a lot of NIH funded studies. I would say that the industry-funded studies are better put together than a lot of NIH funded [investigator-initiated] studies. (Large research portfolio nonprofit healthcare organization – IRB member [scientific])
I also feel comfortable with that in the sense that these are all pharmaceuticals. I feel like they've been pretty well vetted, I mean they usually have their INDs or they're device studies. And I feel like once they get to this point, the companies want the protocols to succeed so they're not going to create something that doesn't make sense, doesn't have good study design. (Small research portfolio nonprofit healthcare organization – IRB administrator)

4 Findings - External Factors – Multi-Center Studies

After review of the interview data, respondents' comments were organized into 2 broad factors that formed the basis for the taxonomy of external factors that may influence IRB expertise and capacity in *multi-center studies* (see **Table 11**).

Two broad factors characterize variation external features in an IRB's task environment that may impact the committee's ability to carry out its central mission of protecting human subjects in research. These broad factors are (1) Whether SAE/DSMB reports are comprehendible; (2) whether monitor reports are available to the IRB.

4.1 SAE/DSMB Reports

Respondents uniformly report that their local IRB has the capacity to evaluate to evaluate significant adverse events (SAEs) at their local institution, but not in the broader study. IRBs do not have the denominator for the number of participants in the study across sites, so respondents often report "feeling in the dark" about what is going on in the broader study. There is little variation among respondents. Most report that they've stopped receiving SAEs from the whole study, although some report still getting a high volume of non-actionable reports.

Similarly, healthcare organization IRB respondents report that data safety monitoring board (DSMB) reports are "meaningless" because the reports do not provide sufficient or definitive information about what is going on in the larger study.

4.2 External Monitor Reports

As described earlier, some IRB respondents report that they do not regularly receive external monitor reports from research sponsors. Some report having asked for monitor reports and have been told that they cannot have them. Larger organizations are more likely to require and review these reports.

Table 11
External Factors that May Influence Ability: Multi-Center Studies

SAE/DSMB Reports – Searching Review
With every annual review, we do require the data-safety monitoring reports, including their recommendations. And if they don't provide them, we ask them where they are, and don't approve it until we get them. And, also, any study monitoring reports. So, if they have, like, a CRO, or the FDA audits the study or reviews it, we want to see those things as well. And we even ask them for things that don't reach the threshold of needing to be reported to us. We ask them to keep a log. So we have like 2 levels of deviations or protocol violations: significant and minor. The minor ones they report to us at the end of the year. The significant ones they report to us right away, as if they're an adverse event. (Large research portfolio nonprofit healthcare organization – IRB administrator)
[At large commercial IRB,] with individual sites, we got the information, but if this were a multi-site protocol, it was often difficult to understand the number of serious adverse events that were taking place throughout the whole protocol. And so we had to reorganize the reporting system so that the reviewer on continuing reviews would be aware of exactly what was happening not just the site, but with any adverse reaction throughout the system where this new drug was being evaluated. …so that we could look at it and say, "Okay, now I know how many cases there have been even though there were none at the site, you ought to make sure that the consent form now puts that in there in the future for continuing review or puts it in the protocol.".. We would make sure that the sponsor became the responsible party for providing that information to us even though we were only the IRB for that specific site.... I think that's very important because if you're dealing with 12 sites and your site hasn't had any side effects, but they've only had about 5 patients and the other sites have had a 150 patients and they've had serious adverse events, you want to know what those serious events were, how they were reported and what they were, and were they directly related to the study. (Large commercial IRB – former IRB member [scientific])
Yes. Most phase 3 studies have DSMBs. And … every DSMB report has to be submitted to us and I spend a lot of time looking at DSMB reports… I've seen DSMBs stop a trial…I would say that once a week, among the 4 medical reviewers, 3-4 times a month, a DSMB report is that concerning that we ask the investigator for more information. It goes to full board… We're not rubber stamps. Oh we take the DSMB reports really seriously.... Trials are stopped for lots of reasons. (Large research portfolio nonprofit healthcare organization – IRB member [scientific])
Most of our studies have DSMBs. We take a lot of comfort in them… Now, what they send you is just the little summary letter that says well we met. We looked at things. We think it's okay. You know, all that does is it gives you confidence in the fact that they really met. But we… want to look at who is on it. We want to look at their qualifications. And when it's not a formal DSMB we're frequently writing companies and saying "you say your pharmacovigilance committee is going to review this. We need to know who is

on your pharmacovigilance committee." (mid-sized research portfolio nonprofit healthcare organization – IRB member [scientific] / administrator)
SAE/DSMB Reports – Not Useful
We know how to deal with our OWN adverse events, we don't look at ALL the adverse events [across sites]. We used to get them from all the sites, and you couldn't manage that process, so. They don't seem to send them anymore, too much... [Sponsors] send an annual [DSMB] report and…when our study coordinators get them, they send them to us as part of an IRB submission, so we see them. When we're doing continuing review, we'll look to see when was the last time we got one. Not every sponsor sends them every year... I think on the cooperative groups, they'll send a study summary, but not a lot of information. There's no conclusions in any of these things, even the ones that come from the sponsor. (Small research portfolio nonprofit healthcare organization – IRB administrator)
We don't look at DSMBs... Because they're all malarkey...Because they all say the same thing: "We've looked at it. We had our quarterly meeting, we looked at it, and everything's just hunky-dory." …An IRB looking at a DSMB, an IRB looking at an SAE is going to say, "What's the denominator? We've had 5 subjects out of how many, 500? We don't know if this is a one-off or if it's one of a trend." Only the sponsor knows that. (Small research portfolio commercial IRB – member [non-scientific] / administrator)
External Monitor Reports
No. We have asked [sponsors] to do that [send us monitor reports], but I think the outside group lawyer probably said, you don't need to give them that. (Small research portfolio nonprofit healthcare organization – IRB administrator)
I would say that we probably do not get them, although we say we want them. It's one of those, since they're absent we don't notice that they're absent. And so, we could get to the end of a year and think, "Did we get any of those?" I would say they're probably not particularly forthcoming … I think they're [sponsor] obligated to provide it to the investigator. I just don't know that the investigator gives it to me. (Mid-sized research portfolio government healthcare organization – IRB administrator)

6. Findings - Issues Using Non-Local IRBs

After review of the interview data, respondents' comments were organized into 2 broad factors that formed the basis for the taxonomy of issues IRBs face when they interact with non-local IRBs for research review. These include factors related to commercial/independent IRBs, and factors describing issues using non-local IRBs. See **Tables 12-16**.

6.1 Commercial IRBs

Respondents offer a range of opinions and experiences with commercial IRBs.

Table 12
Commercial IRBs - Opinions

I question anything that's done as a for-profit organization, especially when they're working with another for-profit organization like a pharmaceutical company. The business is going to go to the IRB that has the least amount hassle. The basic thing …that I take as being troublesome is the fact that it's so removed from the actual location of the research going on. It's so removed. How can someone somewhere else know anything about the community and how they feel about something. Gosh knows that I couldn't really know... if I was reviewing a study to take place in rural Mississippi. I don't know rural Mississippi!

I've heard of it. I love the music that comes out of there but the music comes from a definite cultural experience. So that's kind of where I'm coming from is that it needs to have a local interaction. (Mid-sized research portfolio government healthcare organization – IRB member [non-scientific])
Some of them, they're now owned by administrators and private equity and things like that. And they're not necessarily - their main mission is not necessarily to protect the rights of their subjects. (Former large commercial IRB member / administrator)

Table 13
Commercial IRBs – Experiences With Them

So first I should disclose that I have enjoyed lunch, and dinner, and an all-expenses-paid trip at the courtesy of for-profit IRBs in the past, so I have a slight bias to think that there's not all that bad. That being said …I think the better reviews are done by the institution where the project is happening. I understand the advantage of a central IRB and I think just because something is done for-profit doesn't mean it's done poorly. That being said, I think if you add the incentive of profit there's something in it: it's a conflict, inherently. (Large research portfolio nonprofit healthcare organization – IRB administrator)
I never had any feeling that we were shoddy in any way or that we weren't doing due diligence with the relationship with the principal investigators. (Former large IRB commercial IRB member [scientific])
WIRB and the others are after this [academic research] business, and they're going to get it. So, unfortunately, I'm going to be giving them more business, because I don't like messing with these stupid, anti-intellectual drug-company-sponsored studies. I want to support the NIH studies, and if I don't have to deal with those drug-company-sponsored studies, I've got the time and energy to be able to make sure these NIH studies get through quickly, get the thorough review they need. (Large research portfolio nonprofit government university healthcare organization – IRB administrator)
They [large commercial IRBs] have been very, very actively courting us… They have offered to do back-office for example, situations where we decide to be the IRB of record for multisite studies, they've agreed to handle back-office pieces. They've come up to me and said, "Look, if you guys join with us, we will give you our software package for managing IRB activities." (Large research portfolio nonprofit government university healthcare organization – IRB administrator)

6.1.1 Variation in Size and History

Commercial IRBs vary in size, both in terms of staff size and the volume and breadth of research being overseen. There are a few very large commercial IRBs, which have most of the market share, and a few 'little guys.'

Many started as family businesses or small businesses. Interestingly, several were started by women. When asked why, several respondents noted that "IRB work" was, for many years, "secretary's work" before the professionalization of the field.

There has been significant market consolidation over the past decade, with the large commercial IRBs acquiring numerous smaller ones. This has created something of a monopoly among the largest commercial IRBs.

There were a few started by academics and others who were deeply motivated by ethics. For instance, Felix Khin-Maung-Ghi, who founded Chesapeake Research Review, was considered a beloved colleague and top-flight ethicist before passing away suddenly in 2014.

Then Chesapeake was purchased by larger IRB. The current owners of large IRBs are typically public companies or private equity firms.

Table 14
Commercial IRBs – Size

Some of the big IRBs are getting very big, alarmingly big … And they're swallowing up a lot of the smaller [IRB] companies. (Large research portfolio nonprofit healthcare organization – IRB administrator)
[Big commercial IRBs are] a different animal. I don't if you've talked to any of these big IRBs, but…like for you: when you called, I answered the phone. If you call one of the big IRBs you get a recording, you know, "Press 1 for this, and this for that." … We've been approached a couple of times to [be purchased] and we've always said, "No," because we don't want to lose our identity. We have a very good reputation. We don't want to lose that. And we just don't want to become a part of this morass. We want to keep our integrity and our independence." (Small research portfolio commercial IRB – member [non-scientific] / administrator)
[Independent IRBs] are being bought by those others.. and so they're just getting bigger and bigger. (Former large commercial IRB member [non-scientific] / administrator)
I think we're going to have mega and mini—there's no middle. Any middle, once it gets to be middle, it's going to be gobbled. Those of us that are so small, non-profitable, they won't bother with. And we'll continue on our merry way just small, but I think it's going to be big and small. (Small research portfolio commercial IRB member [non-scientific] / administrator)

6.1.2 Commercial IRB Behavior

Respondents at commercial and other IRBs report variation in commercial IRB behavior regarding a variety of business activities. These include lobbying activities in Washington DC, attempts to 'woo' academic and other large healthcare organizations with free flights to speaking opportunities.

Some respondents indicate that certain large commercial IRBs, which have acquired clinical research management software companies, have pushed the local organizations to purchase their software products in order to have the commercial IRB take on the work.

Respondents report variation in the extent to which commercial IRBs vet principal investigators and research sites. They all do it to some degree, but seasoned respondents report that it is becoming a 'black box' because of electronic submissions. The reviewing IRB doesn't really "know much" about what is happening at the research site it is meant to be overseeing.

This is tied to another factor, which is the extent to which commercial IRBs audit research sites and principal investigators, either for cause or not for cause. Respondents report mixed behavior. Respondents report not believing there to be a strong compliance feedback loop between commercial review and local research sites.

Table 15
Compliance When using Non-Local IRBs

I think you can still have a local group that just looks at the whole process to make sure it's being done properly, but it doesn't need to be …[a local] IRB , but it can be an oversight. That's a possibility, looking for just an oversight of the local organization, making sure that central IRB or the independent IRB is

doing what they're supposed to be doing. But I think …if we're ever going to convert to a central or independent IRB that that would [need to] be part of the process. (Small research portfolio commercial IRB – member [scientific] / administrator)
I know for us it's possible [to be connected to local compliance] because we have a consultant in Michigan… New Jersey… Colorado… California… Wisconsin, so if I have site visits or something that I need to check on …I will give them the information and say, "Go to Company XYZ and check this out." And then they report back. (Small research portfolio commercial IRB – member [non-scientific] / administrator)
Well, cancer studies are either going to [UNIVERSITY] or they're going to the NCI [central IRB] now, and that was agreed to by the hospital. So, we [local IRB] don't even see those… I don't know who's responsible in the institution to follow up on those—whether that's [UNIVERSITY or this hospital, but this IRB's not. (Mid-sized research portfolio nonprofit healthcare organization – IRB member [non-scientific])
As far as the sponsored studies, I think the FDA is over-reaching when they gave the IRB their responsibility. I think it's very clear … it's the sponsor who [needs to] monitor compliance and that's not what's happening as it should. There's a shortage of CRAs (clinical research associates). They're not trained. They're all looking for stupid little things because [they don't know to look for] all these big things that are happening. (Former large commercial IRB member / administrator)
[large commercial IRBs do not come to the site to audit.] I think that's where kind of having an in-house IRB…has some value because you have all that overlap between your compliance and your IRB and your other administration and your safety, and they all know each other, and they all say "Hey, did you see that thing that so-and-so turned in?" It has value to have that overlap of people and the responsibilities of who you know. (Mid-sized research portfolio government healthcare organization – IRB administrator)

6.1.3 Central IRBs

Table 16
Central IRBs

I think the VA has their own central IRB for multi-site studies where all the studies sites are VA's. I think I've heard of such a beast, I don't know how extensive it actually is. (Mid-sized research portfolio government healthcare organization – IRB member [non-scientific])
Who's going to pay for (us) being the IRB of record for all these other IRBs and all the extra work? (Large research portfolio nonprofit healthcare organization – IRB member [scientific])

6.1.4 Reliance Agreements and Relationships

Many IRBs and research organizations are starting to rely on other IRBs to serve as IRB of record over research happening locally. Similarly, many organizations are starting to serve as IRB of record for non-local research. This is often the case when organizations work together regularly or otherwise have ongoing relationships, such as hospitals and universities in the same region. This is also often the case for health systems or universities that have centralized IRB functions to oversee research at different campuses. Respondents report that these relationships raise challenges. See **Table 17**.

Table 17
Reliance Agreements and Relationships

No Reliance
Here the local VA IRB will only cover stuff done by VA researchers on VA property. [Re: a recent multi-center study], one of the sites is here …and our IRB was like "No, we won't cover your activities at community hospital B because that's not a VA facility—you'll have to get IRB approval from somebody else to do that." (Mid-sized research portfolio government healthcare organization – IRB member [non-scientific])
Reliance
We had to hire another full-time person to handle them.…The IRB review is just one thing that each institution is responsible for, too…especially if the study is being conducted in two institutions. Our IRB facilitates some of the other processes like radiation safety review, making sure that there's appropriate staffing on hand from nursing and social work when a study is planned … to make sure that if somebody becomes upset or expressed suicidal ideations during an interview there's a social worker available—all kinds of things. Whereas an IRB at another institution isn't as integrated with all those departments with another place half-way across the country. So IRB review is just one thing, so it doesn't always streamline things as much—it's not like some magic pill. It's a lot work. Our leadership…has had the foresight to get involved early before it becomes required, so we can figure out what the kinks are and have a system. And I think it's paid off. I think the majority of the agreements we have actually brought us more reviews. More people rely on us than the other way around, which means we spend more money reviewing them. There's extra effort on our part too. We have a full-time employee that we added, and they're a very busy person. (Large research portfolio nonprofit healthcare organization – IRB administrator)
Most [research sites] do not really track the research for which they are the relying IRB. We require an application for all of the research where we are asked to rely on someone else and we ask that every single year they submit an…approval letter and the stamp consent form. Because even though we're not the IRB of record, our Human Research Protection Program is obligated to know what's going on. Most of the other institutions just know when they've agreed to pay review to someone else and they know when the study is closed but they don't know what's happening in between. (Large research portfolio nonprofit healthcare organization – IRB member [scientific])
What happens is somebody asks us to rely on them. I'm always happy to do that because it's no skin off my nose. They take all the heat if something bad happens. I will only cover another institution if the study is minimal risk or if it's somewhat more than minimal risk and it's local or we have some relationship, we know the institution and or have some kind of relationship, but we don't often do that...Partly because the governance has not been appropriately set up and… because there has not been the kind of fiscal support, the kind of institutional support that one needs to put something like this together. (Large research portfolio nonprofit government university healthcare organization – IRB administrator)

6.2 What You Lose with Non-Local Review

Respondents offer insights into what is lost at the local institution when IRB functions are outsourced. See **Table 18**.

Table 18
What is Lost With Outsourcing

Local / Cultural Context Lost
I think the real issue is their ability to know and understand the local conditions… I think local makes a lot sense in that. You're talking to people who you know as opposed to documents that come from somebody who you don't know, and you don't have that background knowledge to understand. (Mid-sized research portfolio nonprofit healthcare organization – IRB member [non-scientific])
Educational Experience Lost
[Being on the IRB] is a good educational process [for researchers and staff]. You should rotate people under the IRB so that they learn about it, and they learn about what that process is. And, so the central IRB short-circuits that process. (Mid-sized research portfolio nonprofit healthcare organization – IRB member [non-scientific])
Funding Lost
The problem we have in the IRB is we charge fees for renewals. If studies go through a central IRB, we still have to do as much work. So who's going to fund us? There's no funding for us. (Large research portfolio government university healthcare organization – IRB administrator)

VI. Analysis

1. Variation 'On the Shop Floor' – Some Systematic

A hypothesis of the study was that we would expect to see variation 'on the shop floor' when rowing (and steering) is delegated by regulation to local organizations. This bears out, and, in a finding contrary to existing literature, this variation is to some degree systematic. There are tradeoffs to this type of variation on the shop floor. In the case of research oversight, such variation may have consequences in terms of the capacity of the IRB and research site to engage in quality research review.

The observed variation may also have consequences in terms of the organization's capacity to engage in more innovative and flexible governance arrangements. Another hypothesis going in to the study was that IRBs overseeing larger research programs would engage in more innovative and flexible governance techniques, including relying on non-local IRBs for research review and oversight. The data bear this out. IRBs overseeing larger programs tend to engage in quite a few reliance relationships. But small research organizations are using reliance agreements too, particularly in the form of contracting out IRB functions to commercial IRBs, upon which the smaller organizations rely. So organizations across the spectrum of size and internal infrastructure are engaging in these activities. As discussed below, organizations do not have uniform ability to police and manage these relationships.

2. Variation in Structural Factors Leads to Non-Uniform Capacity

2.1 Internal Factors Generally

The data indicate variation in the four internal factors: whether the IRB includes at least one active researcher; whether the organization utilizes a separate scientific review committee or process to vet the scientific aspects of studies; whether the IRB always ensures a relevant

specialist reviews studies; and whether the IRB sits within a larger compliance function. This variation indicates that IRBs are not similarly situated in terms of resources, expertise, and infrastructure. This variation may impact the committee's capacity to carry out its central mission of protecting human subjects in research and engage in quality review. This finding lends itself to hypotheses for later testing in future research.

2.2 Compliance Functions

One particularly troubling area in which variation between organizations is observed is in terms of compliance infrastructure. This variation occurs: 1) at the local infrastructure level in regard to overseeing locally conducted research; and 2) in terms of how organizations process and oversee non-local research when acting as IRB of record.

IRB oversight and approval sometimes fits within a larger, robust set of offices and individuals whose jobs are to ensure the proper functioning of clinical research. Some IRBs at research institutions serve as a coordinating mechanism between several offices or processes at the institution, including conflicts of interest processes, biosafety committees, and compliance offices. This is particularly true among larger, better resourced organizations, and is obviously not at all the case at independent or commercial IRBs, which are freestanding organizations that are not embedded within larger organizational infrastructure.

This embedding and process coupling is also less likely to occur at smaller healthcare organizations, where the IRB may be run administratively by just one person, sometimes as only part of his or her job, and without the support of other functions like compliance trainings, audits, and research integrity. Indeed, many smaller healthcare organizations whose IRB oversees primarily industry-sponsored studies believe that larger issues of compliance are handled or will be 'caught' by external monitors hired by the industry sponsor. However, IRBs do not uniformly receive reports from external monitors or investigators.

This indicates that some organizations have tighter coupling or integration with other aspects of research oversight than other organizations. This variation may impact the committee's capacity to carry out its central mission of protecting human subjects in research and engage in quality review.

Monitoring and auditing, which are key parts of research compliance, also vary. IRBs embedded within large healthcare and academic organizations typically report their organizations having robust audit and compliance units, wherein principal investigators and studies are selected for compliance audits randomly as well as for cause upon IRB request. This auditing function – where studies and investigators may be audited randomly, and for-cause upon IRB request – is atypical at small institutions. Respondents from commercial IRBs of differing sizes report having some mechanisms for site visits in place, although it is unclear how frequently auditing actually occurs in practice.

Related issues arise in the context of reliance relationships. Well-resourced institutions have more infrastructure and resources to handle ceding (or sharing) review with central or commercial IRBs – both in terms of local compliance functions, as well as in terms of the 'other pieces' that go into managing reliance relationships. For instance, one large academic medical center has hired a full-time employee just to handle reliance relationships in research.

This variation has consequences when IRB work is outsourced. When there is not a local compliance and infrastructure for research beyond the IRB itself, when a non-local IRB is used for review, it becomes a black box at the local level. This creates the opportunity for mistakes to

go uncorrected, and for misconduct to be undetected. IRB oversight becomes completely decoupled from the actual work of clinical research, which might occur clear across the country, time zones away. The potential for these gaps appears particularly profound at smaller, community-based institutions (for instance, community hospitals, physician practices and freestanding research sites). When dealing with central or commercial IRBs, the data indicate, at least sometimes, the existence of a compliance gap due to a lack of local compliance backstop, in the absence of local IRB oversight. Is anyone doing any audits? Investigator trainings? Conflicts of interest management and communication to participants? Often, the answer is no. The promise of management-based regulation was that regulated entities were in the best position to most effectively and efficiently do the rowing. When the regulated entities further contract out, this ability to row become even more attenuated.

3. Variation in Attitudes, Behaviors Leads to Non-Uniform Capacity

Variation is also observed in IRB professionals' attitudes toward key issues in research oversight. Some attitudes and behaviors evidence more or less expertise and comfort with scientific design. This variation provides evidence that IRBs are not similarly situated when it comes to expertise and capacity, which may impact their ability to carry out its central mission of protecting human subjects in research and engage in quality review.

Some IRB professionals describe the risk/benefit calculation of clinical research in a narrow manner, with regard to whether a particular intervention poses significant risk to a participant, without regard to the overall scientific design of the project, which design may be quite flawed. This is a less sophisticated way to conceive of risk/benefit than other professionals, who speak in terms of the overall scientific quality of the project rather than exclusively the particular intervention (e.g., a blood draw). This indicates differences in sophistication and capacity.

In addition, many IRB professionals use external proxies for quality, including the fact that FDA may have granted an IND for the study, or that NIH funded the study, or simply the fact that a pharmaceutical company has sponsored the study. This finding is interesting for a couple of reasons. First, the fact that some individuals believe FDA's granting an IND is an indication of the scientific quality and value of the study indicates that there appears to be something of an unclear division of labor between FDA and IRBs. This is true regarding INDs, but also around devices. Often, "they [FDA] think we're [IRBs] doing it [scientific review], and we think they're doing it."

Second, the pharmaceutical proxy points to a cognitive bias and a structure of decision making that may unjustifiably benefit sponsors of research studies. This harkens to Susan Sturm's work around 'second generation discrimination.' It suggests the possibility of a type of 'second generation' of unethical research that slips through because of cognitive biases, structures of decision-making, and patterns of interactions that have replaced the 'first generation' research abuses that involved deliberate or obvious research abuse.

4. Variation in External Factors in Multi-Center Research

The data here indicate that IRBs vary in regard to the relevant and actionable information they receive from research sponsors, principally the pharmaceutical industry. It is supposed to be the sponsor's obligation to determine significant adverse events and report those to the

research sites, but this information does not get back to IRBs uniformly. Some IRB professionals report that data safety monitoring board reports are helpful to them in assessing whether ongoing studies are dangerous to participants, while others suggest these reports are not valuable.

This pattern of behavior has come out in numerous instances of litigation against the pharmaceutical industry, which has buried harmful studies, not provided sufficient information to participants, physicians, and others. Among others, this has involved litigation related to Seroqel and VIOXX.

There is a bit of a disconnect. Many respondents feel on the one hand that industry-sponsored studies are generally not particularly risky, because they are often "me too" studies or because the company wouldn't bother with the study if the drug didn't seem to be working. But on the other hand, many respondents report not receiving all actionable and relevant information from the sponsors that they would need or want, and that the information about ongoing studies they do receive is generally in the form of brief "all clear, proceed" missives without substance.

5. Flexible Regulation Without Baseline (Expertise/Infrastructure) + Weak Enforcement = Lack of Uniformly Capable Organizations.

The move from command and control to flexible regulation was motivated in part by the assertion (often by firms) that they had more information and were better equipped to find their own solutions to regulatory challenges. This type of system produces heterogeneity, which may be positive or negative, or both.

But while well-resourced organizations may be able to come up with good, innovative solutions, this may not be the case for less resourced organizations. Flexible regulation without a clearly required baseline – in terms of broader compliance and infrastructural requirements – coupled with a weak enforcement system (a weak "stick"), is not producing uniformly capable organizations (IRBs). This type of significant heterogeneity is of concern in the context of an important public health and safety function like the review and oversight of new drugs and device testing.

This heterogeneity in capacity can be observed through the findings presented herein: variation in internal structural features; variation in attitudes/behaviors toward key issues in research review; and variation in external factors in the task environment, all of which may impact the ability of IRBs to carry out their central protection and quality review tasks.

6. Non-Local Review is Challenging; Research Organizations and External IRBs are Not All Situated to Succeed

This heterogeneity in capacity, expertise and ability is most starkly problematic when research review is outsourced to non-local IRBs. This is definitely the way the world is going, and many organizations are struggling to adapt.

6.1 Commercial IRBs

Many commercial IRBs started as small family-owned or expert-run businesses. Over time, the largest commercial IRBs have subsumed most of the mid-sized independent IRBs and many small ones too. The large commercial firms engage in tactics not dissimilar to the pharmaceutical industry or other companies – they compete for business, wining and dining IRB

administrators at research sites. Many IRB professionals are wary of large commercial IRBs, which they see as having financial conflicts of interest between their business relationships with their pharma clients, and their purported role as protecting human subjects. Respondents who have served at large commercial IRBs report no malfeasance, but do indicate that the business has changed, the original founders who were bioethics professionals have left or passed away, and that current operations are very much focused on profit.

Nonetheless, IRB professionals report hiring commercial IRBs, particularly large commercial IRBs, more frequently than in the past.

Respondents do report certain commercial IRB activities that warrant future analysis. First, the market consolidation among commercial IRBs raises the question of whether the few largest commercial IRBs have obtained a monopoly over the market in violation of antitrust laws, or at least such that future acquisitions should be analyzed by states attorneys general or others. Second, commercial IRBs that push or require research site clients to use the commercial IRB's proprietary software as a condition of review may raise 'tied products' questions under antitrust law. And third, commercial IRBs' activities to woo business from physicians and IRB administrators (such as flying them first class to conferences and providing expensive meals) are reminiscent of pharmaceutical industry behavior towards physicians, which has been prohibited over time as inappropriate kickbacks. A similar analysis should be done with regard to the appropriateness of commercial IRB business development activities.

6.2 Reliance is Hard, Expensive To Do Well

The effort to reduce redundant reviews of multi-center studies by multiple IRBs has led to an explosion of IRBs relying on one another. Respondents report that reliance relationships are hard, particularly for IRBs that are relied upon by other institutions. As one respondent at a large research hospital explained, "[Reliance] doesn't always streamline things…it's not like some magic pill. It's a lot of work."

Reliance is challenging for a few reasons. First, IRB professionals at research organizations report that is that it is hard to feel comfortable with research happening elsewhere, and it is hard to feel comfortable taking on responsibility for research elsewhere. An organization really needs a lot of infrastructure and resources to do that well. And research organizations are not always in a position to provide the resources necessary to allow the IRB to staff up and be able to do this remote oversight properly. Small organizations, which typically do not have well-resourced IRBs, generally do not serve as reliance IRBs for this reason.

6.3 Certain Things are Lost with Non-Local Review

Respondents typically report a preference for having some level of local research review. In the course of ceding review to non-local IRBs, certain things are lost for the institution at which research is occurring, and for the research process itself. This includes the loss of local and cultural context where the research will be taking place. In addition, outsourcing can involve losing the educational experience of serving on the IRB for clinical researchers. Similarly on the administrative side, when IRB administration is outsourced, this creates a vacuum at the organization, which may no longer have any staff with relevant research expertise. And finally, when some IRB oversight is outsourced, the local IRB often still has to function – just minus the fees charged to sponsors for research now overseen elsewhere. This means that funding for

research oversight and administration declines, making the IRB and its related offices more resource strapped.

7. Best Practices and Ideas for Doing Better

There are clear sectoral movements towards the consolidation of multi-site research review, which will increasingly be carried out by non-local IRBs. The findings of variation in capacity and infrastructure among reviewing organizations presented in this study suggest certain policy interventions. In particular, it may be appropriate to pursue regulations that would require more from organizations at which research is being performed, beyond simply requiring that some IRB somewhere approve the study. For instance, it may make sense to require that research sites establish policies and procedures regarding mandatory for-cause and random auditing, researcher and staff training, at least for FDA-regulated products. This would help ensure that, if an organization outsources IRB functions, there is still someone at the local level "manning the ship", and some reasonable baseline requirements for internal institutional capacity.[14] Even at bigger organizations with robust structure, there may be need for more coordination when non-local IRBs are used.

Respondents are handling these issues on the ground in a variety of ways. Their responses point toward a set of best practices, as well as ideas for how systems can improve. Below is a chart of challenges faced by IRBs and our analysis of best practices and innovative ideas proposed by respondents.

Challenge	Best Practice / Innovation / Suggestion
Board Expertise	Include at least one active clinical researcher on board
Compliance Coupling at Research Organization	Require random audits of PIs and studies
	Interlocking board membership between COI committee, IRB, and compliance committee
External Reports from Sponsors	Require DSMB reports and all external monitor reports be provided to IRB as part of site contract with sponsor (during the study and for a period of time afterwards)
	Do not allow IRB approval of annual/continuing review unless DSMB reports provided and reviewed
	Ensure IRB asks for proof of DSMB independence from pharmaceutical sponsor
Compliance When Local Site Uses Non-Local IRB Review	Retain some local formal mechanism for research oversight, including auditing and training

[14] Note that, at institutions performing federally funded research, certain institutional requirements exist for, e.g., researcher training, but these are conditions of federal funding, not general requirements for all organizations performing biomedical research.

	Require that reliance IRB provides relying institution with copies of COI and IRB approval materials and reports

VII. Conclusion and Next Steps

The paper offers empirical and theoretical contributions. The paper evaluates IRBs descriptively, providing a first-ever analysis of IRB empirics (such as how many there are, where they are located). It also provides qualitative information about how IRBs vary in terms of internal organizational factors, external features of the task environment, and other environmental factors.

Second, the paper offers analytical insights about the nature of variation among IRBs. Scholars admit there is a dearth of empirical research about the functioning of light touch regulatory regimes. This paper reports on extensive qualitative research with professionals in the IRB space. It reports on a few findings that have significant implications for understanding the functioning of this particular instance of light touch regulation.

The paper has two central findings. The first is the observation of significant variation "on the shop floor" in terms of how these delegated regulators function. This includes variation in internal features and external factors that may influence IRB expertise and capacity. This variation is a consequence of management-based regulation as a form, because the management-based approach is designed to afford regulated entities the ability to craft individual solutions. This variation may be a 'feature' of this regulatory system (when the variation is responsive to local conditions), or a 'bug' (where the variation is detrimental in terms of health and safety).

Of further interest, at least some of this observed variation is systematic, based principally on the size or ownership status of the organization housing the IRB. This in turn has implications in terms of the likely quality of the research ethics services that IRBs provide. This has implications in terms of the types of organizations we might like to encourage, and others we might like to discourage, through public policy (and, as consumers and patients, by voting with our wallets in terms of where we seek care). The finding of systematic variation challenges existing literature asserting that variation in IRB behavior is not systematic.

The second central finding is that, in particular, significant variation is observed among IRB-housing organizations with regard to larger compliance capacities. This too appears at least somewhat systematic. Whether the IRB is part of a larger research compliance function, or is tied back to compliance functions at the local level (for non-local IRB reviews) is critically important. This is particularly true in the case of reliance relationships, where local research sites rely on an external IRB to review and oversee research. This is increasingly common and will essentially be mandated by new federal regulations for multi-center research studies.

A larger implication is that flexible regulation without a clear set of baseline standards as a floor, and a weak enforcement system (a weak "stick", in the forms of regulatory enforcement and litigation), is not producing uniformly capable organizations (IRBs). This type of significant heterogeneity is of concern in the context of an important public health and safety function like clinical research oversight. The finding lends itself to policy interventions to create a stronger baseline set of requirements (including compliance) at the IRB level and the research organization level.

Another implication and finding is that research is increasingly been 'overseen' by IRBs that are not at the site where research is taking place. The paper argues that the movement towards using external IRBs to review research, which may actually be performed thousands of miles away at sites the IRB has never seen, raises challenges in implementation, including potential gaps in oversight, and misalignment of financial and business incentives.

Finally, the paper highlights challenges that research sites face when increasingly relying on non-local IRB, offers a set of best practices, and suggests future areas of inquiry, particularly related to certain troubling aspects of large commercial IRB business development activities.

CHAPTER 4: THE MARKET FOR ETHICS: ATTITUDE TOWARD COMMERCIALIZATION OF RESEARCH ETHICS REVIEW IN THE UNITED STATES AND CANADA

I. Introduction

Following the revelations at the Nuremberg Trials of atrocities conducted against human subjects by Nazi physicians and researchers during World War II, a set of basic principles emerged related to the rights and autonomy of persons involved in biomedical research, including clinical trials. However, the same historical events, and subsequent agreement upon basic principles, have resulted in different institutional structures and arrangements for research oversight across nations. Comparing how different countries have approached research oversight is important in order to understand the strengths and weaknesses of different policy approaches and to better inform future policy development choices.

The institutional design of biomedical research governance in the United States is similar in certain fundamental respects with the design chosen by peer jurisdictions throughout the world, including Canada. Indeed, at first blush, there may not seem to be very much distinctive about the American model. In both the US and Canada, research oversight systems have emerged in which committees of somewhat diverse individuals jointly decide to allow (or disallow) research involving human subjects to proceed, based upon generally shared ethical principles aimed at protecting the safety and autonomy of human research participants. These committees are called institutional review boards (IRBs) in the US, and research ethics boards (REBs) in Canada (herein referred to collectively as "research ethics committees").

However, the particular formal institutional designs of such committees, and the broader task environments in which they operate, differ substantially between the US and Canada. These differences create conditions under which policy trajectories may diverge, particularly over time, as nations adapt to new challenges and changing circumstances.

Differences in formal committee design between the countries include the extent to which committees are public bodies or privately-based. In addition, considerable differences exist between key elements of the larger task environments in which committees function, including the availability of national health care and the extent to which the legal and regulatory environment is adversarial.

Canada and the US have experienced similar exogenous pressures to streamline and speed up review and oversight of clinical trials, particularly multi-center studies. These pressures have come from a few sources: first, research sponsors, primarily the pharmaceutical industry, which seeks jurisdictions that provide quick regulatory processes in which to run trials (Fisher 2009; Preto 2014). Second, patients who, at various points and in relation to particular diseases and conditions, have pushed vocally for quicker pathways to drug access (Annas 1991). And third, the government has pushed for streamlining in order to attract researchers and sponsors to the country.

The two countries have also experienced similar changes in the task environment. While most clinical research was, for decades after World War II, conducted within university and large health system contexts, this work has increasingly shifted toward non-institutional, community settings – particularly physician practices and freestanding clinical trials centers (Fisher 2009; Preto 2014).

Both the exogenous pressures and the changes in the task environment have led to the establishment of an auxiliary industry supporting the clinical trials enterprise. This industry includes contract research organizations (CROs) that serve as middlemen between industry sponsors of clinical research and research sites, which are increasingly in community settings. The industry also includes for-profit research ethics committees.

However, the two countries have pursued somewhat different approaches to address these shifts, in part due to different levels of accommodation to the pharmaceutical industry and its ancillary industries. Perhaps not unexpectedly, the US has embraced a market-based solution to the challenge of needing to streamline review, through the increasing use of commercial IRBs to oversee multi-center research at both institutional and community-based sites. By contrast, Canada has been more reluctant to turn toward the market for ethics review. This is demonstrated by the fact that Canadian research institutions are not permitted to use commercial IRBs, and instead have turned toward the formation of non-profit consortia and regional government REBs to oversee multi-center institutionally-based research. Commercial REBs have gained a foothold for community-based clinical research, although here too other policy options have been explored and implemented, including province-wide REBs for community-based clinical trials.

Research ethics committees play an essential role in protecting public health and safety, as they serve as ethical gatekeepers for clinical trials. It is estimated that 2-3 million Americans participate in clinical trials each year[15], and thousands of Canadians[16]. Yet despite their importance, these organizations are empirically understudied. The clinical research environment has undergone dramatic changes in the past 30 years. While IRBs in the US were once housed nearly exclusively at universities and teaching hospitals, they have proliferated in form and venue as the pharmaceutical industry has become the central funder of research and has pushed it from the academy into the community. The scant literature on IRBs has focused almost exclusively on academic IRBs. There is also limited literature about research ethics committees in Canada, although several of the world's leading scholars on applied research ethics are Canadian, and have been among the most vocal critics of commercial IRBs.

The present project was motivated by a curiosity about whether attitudes toward, and experiences with, commercial IRBs and other means to streamline research review would differ between the US and Canada. I suspected this might be the case, at least in part because of differences in the broader institutional environments in which these research ethics professionals operate.

I was interested in what the comparison between attitudes and knowledge about this ancillary clinical research industry might portend for the future in Canada, which has followed a more cooperative, less commercial approach to institutional research review and health services sector activities in general, compared to the United States.

To address these questions, I designed a qualitative study intended to provide an in-depth perspective about the ways in which research organizations in the US and Canada are responding to similar exogenous pressures to quicken and streamline ethics review of clinical research,

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[15] Note that while IRBs also oversee social science research, generally at universities, this paper does not include social science research within the purview of its analysis. This paper is **exclusively** focused on IRBs overseeing biomedical research, principally clinical trials of drugs and devices.

[16] Canadian cancer groups have estimated that 10,000 Canadians are enrolled in cancer trials, but broader numbers are not known. See Shuchman 2008.

including perceptions of, and experiences with, market-based and non-market-based approaches to ethics review.

The paper analyzes the results of an empirical study to 1) characterize the empirical extent to which Canadian and US research organizations are using different mechanisms for research review, including the services of commercial ethics review boards, 2) characterize the attitudes and knowledge of professionals regarding the menu of options, particularly commercial ethics review, and 3) explore and generate hypotheses about the extent to which differences in regulatory approach between these peer nations can be explained by differences in the broader task environments in the countries, both in terms of formal policy and in terms of the menu of solutions considered. The first two objectives were to establish an empirical base; the third was to generate hypotheses about what the current evidence can teach us about broader themes in comparative regulatory politics in the context of a neoliberal global climate, and project suggestions for likely future regulatory paths in this area between the nations.

The paper offers empirical and theoretical contributions. First, the paper provides a description of REB empirics (such as how many there are, where they are located). It also provides qualitative information about the extent to which research oversight professionals in the US and Canada are responding to and experiencing pressure to streamline research review, including using the services of commercial ethics firms, and their attitudes and beliefs regarding the use of such commercial firms versus other noncommercial ethics review streamlining mechanisms. This paper offers the first analysis, empirical or theoretical, exploring differences between penetration of commercial for-profit research ethics between the American and Canadian research ethics systems. Second, the paper offers a new case study using the frameworks of comparative regulatory policy studies.

The central findings are:

1) With regard to clinical trials in *institutional settings* such as hospitals and universities, Canada and the US are using different approaches. While research organizations in the US have responded to pressures to streamline and quicken clinical research review and oversight by turning to the market, in accordance with broader neoliberal institutional logics at work in the US, including longstanding institutional logics within health care delivery, Canadian research organizations have not. This derives from a separate set of institutional logics and historical circumstances, which have over time privileged non-commercial and government-based regulatory solutions, particularly in health care.

2) While that is all well and good with regard to *institutional* settings, most clinical trials now occur *outside of institutional settings*. And commercialization of ethics review is happening in these settings in both countries. However, this commercialization of research review is much less visible to Canadians in the ethics review community than to similarly situated Americans. This was a surprising result. In the US, everyone in the research community knows about commercial IRBs, including professionals at academic and government institutions. Not so in Canada. Some Canadian respondents at institutional settings were unaware of the existence of commercial ethics review firms, while others were unaware that private review is widespread and growing. This invisibility may be driven in part by the fact that institutional review of Canadian research has not succumbed to commercialization, while it has in the US.

3) Also regarding non-institutional settings, all of this research review is going to commercial IRBs in the US. In Canada, some of it is going to commercial REBs as well, with this mechanism layered on to existing review infrastructure. But there are also innovative, government-based approaches being explored. For example, the province of Alberta has

established an REB under its medical licensing agency to oversee clinical trials occurring in non-institutional settings. In this way, Canada has more policy options on its menu than does the US when it comes to overseeing clinical trials occurring in the community.

4) The fact that Canada has a larger menu of government and non-profit based policy options than does the US is at least in part because of the broader context of institutional research and health care in Canada, which is a strong single payer system. This means that health care in Canada is – at least for now - more insulated from market penetration in general. This suggests that broader institutional logics and contextual factors in the two countries have shaped the availability of options on the policy menu.

5) The analysis, however, suggests that this insulation may not last forever, and suggests hypotheses for future exploration. In the future, as market consolidation in research and countries continue to compete to remain an attractive venue for research, a few developments may occur. One is whether Canadian academic and government facilities agree to use commercial IRBs, as have their peer organizations in the US. Another would be whether the government-based approaches to community-based clinical trials review such as the Alberta experiment fail. Either development could be a "dam breaking" moment that would signal that the noncommercial approach Canada has taken for review clinical research is an ineffective solution. Future research would then need to explore the causes and drivers for such developments, including the extent to which such developments may adhere to broader trends of a neoliberal push for market solutions.

The paper proceeds as follows. Section II provides a brief background about the regulation of biomedical research and research ethics committees in the US and Canada. This includes a discussion of the policy trajectories related to biomedical research, as well as shifts in the institutional environment over time. Section III provides a literature review of key texts in institutionalism, institutional change and institutional logics. Section IV provides the methodology for the original research study. Section V provides key results, and Section VI provides an analysis of the findings. Section VII concludes with limitations of the present study and suggestions for future research.

II. Background: Human Subjects Research

In order to understand the issues discussed in this paper, it is first necessary to provide a brief history of human subjects research, its regulatory regime's development, how IRBs/REBs fit into the system, and how the enterprise has changed over time.

A. Human Subjects Research - US

a. History of IRBs as Key Regulatory Mechanism

The ethics of involving human subjects in medical research has a long and storied past. What constitutes 'ethical' or 'unethical' research is context-specific, and changes over time. Prior to the mid-20th century, physicians made decisions of research ethics without input from outsiders (Halpern 2008; Rothman 1991; Starr 1982). This settlement reflected the public's trust in doctors, and the political and social power of medicine (Starr 1982; Rothman 1991). Medical research and medical practice were part and parcel of the same set of professional activities, subject to professional self-regulation.

Commercial interests were not prominent in biomedical research until the late 20th century. Early American pharmaceutical interests were not particularly active in clinical research – they were principally manufacturing firms, as most drugs were invented in Europe. As Robert Kagan has noted, government regulation tends to emerge when other legal means (such as litigation) and the market do not result in socially acceptable levels of protection, and the government is willing and able to enact it (Kagan 2000). Up until about the 1950s, clinical research was unregulated largely because the public did not perceive that other legal means and the market were inadequate to protect people.

A variety of factors caused a shift in this perception, including early efforts by government funders to shield themselves from liability, lawsuits related to governmentally funded medical research, the civil and patients' rights movements, and the rise in suspicion of authority and physicians (Starr 1982; Rothman 1991). These circumstances created the conditions under which prior types of research programs like those at Willowbrook and Tuskegee came to be seen as scandalous. Public values shifted, as did the risk assessment of government funders. Key stakeholders including the public and government funders came to believe that other legal means and the market were no longer producing adequate levels of protection (or legal cover) (see, e.g., Rothman 1991).

The system of government regulation that emerged was a slight ratchet up, from pure self-regulation to a delegated, management-based governance technique. Its centerpiece was the IRB. Use of the IRB was mandated by federal law in 1974, although it had been required for federally-funded projects since the 1960s and had been in practice at NIH since the 1950s. The IRB as a mode of governance was premised on the self-regulation of physician-researchers and the peer review mechanism that has long been a feature of professional regulation. Most decision-making was left up to local actors in peer review, principally in academic settings. The government's role was to steer at a distance; IRBs themselves would do the 'rowing.'

At the same time, the regulation of pharmaceutical products emerged along a different trajectory. It emerged following a product regulation logic, rather than via a professional self-regulation logic. Regulations requiring IRB oversight of products intended to be submitted to FDA for marketing approval were not finalized until 1981. Once those regulations were established, the same activity (research oversight) and the same set of organizations (IRBs) came to be overseen by two distinct agencies. FDA oversees IRBs as a part of the regulation of medical products; HHS's Office for Human Research Protections (OHRP) oversees IRBs as part of the agency's duties as a research funder. Both agencies are responsible for enforcement, which involves routine FDA audits and inspections, and OHRP investigations in response to complaints (FDA Guidance 2006; Weil 2010).

b. Research Shifts from Academy to Community

Much has changed in the institutional environment in the intervening decades, particularly the rise of the pharmaceutical industry as central funder of clinical research, rather than the government or the academy. Nonetheless, the regulatory structures applicable to human subjects research oversight have remained stable. The major shifts can be traced to various policies established during the Reagan administration that broadly conform to a neoliberal perspective on the role of government.

Chief among these were the Bayh-Dole Act and the Hatch-Waxman Act, which repositioned patent law in a way that led to a meteoric rise in the activity and profits of the

pharmaceutical industry (Angell 2005). The pharmaceutical industry replaced the federal government as medical research's funder in chief. While academic physician-researchers had once been instrumental in designing clinical studies, including industry-backed studies, this too changed as industry developed its internal research capacities (Davidoff 2001; Falit 2006). As the main funder of clinical research, and with its own internal preclinical research capacities, industry grew to need the academy less. Over time, it found it could run trials more quickly and more cheaply in alternative venues and with alternative partners, particularly those in community-based, rather than institutionally-based, settings[17].

This led to the rise of a clinical research industry full of ancillary companies that help industry test its products. In the past two decades, the US pharmaceutical industry has completely reorganized the clinical testing of its products, moving from academic medical settings into the community (Fisher, 2009). Indeed, the vast majority of industry sponsored clinical research now occurs in community settings, such as physicians' offices and freestanding research clinics (Fisher 2009, Petryna 2011, Preto 2014). The physicians engaged as investigators in this research are not scientists; they are contractors implementing industry-written protocols (Fisher 2009). As of 2005, commercial sponsors provided 70% of funding for clinical drug trials in the US (Falit 2006, citing Mello 2005). That number has gone up, and more recent estimates are that 80% of clinical research is industry funded (Fisher 2009).

c. Response to Pressures - Rise of Commercial IRBs

IRBs have also evolved. They are also no longer located just in academic or governmental settings. As described in Section IV, there are now approximately 1,250 unique IRB organizations registered to oversee clinical research in the US.[18] Some of these are at universities and academically-affiliated medical centers; but others are located in a variety of other institutional and organizational settings. These include community and health system IRBs (including nonprofit, for-profit, and government health providers), non-profit independent IRBs, and IRBs operated by local, state, and federal government divisions and agencies. There are also commercial IRBs, which are for-profit businesses that review clinical research for a fee.

The regulations requiring IRB approval of FDA-regulated products and federally-funded research have remained stable despite these shifts. IRBs remain the ethical gatekeepers for medical products testing. They are still subject to light-touch regulation, based on a legacy of the self-policing powers of the medical profession.

Most academic literature on research oversight focuses on IRBs housed in academic environments, although this is an ever-shrinking segment of IRBs overall. Other types of IRBs include independent IRBs and commercial IRBs (Mirowski & Van Horn 2005). Comparing local (generally academic) IRBs to independent/commercial IRBs, they note that independent IRBs review protocols faster, are subject to less regulation (just FDA regulations, as opposed to also NIH and OHRP regulations) (Mirowski & Van Horn 2005). Although the use of commercial IRBs has accelerated, FDA has long acknowledged the existence and regulatory acceptability of commercial IRB review (Nightingale 1983).

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[17] See Appendix A for schematics demonstrating changes in primary relationships between sponsors, researchers, and IRBs.

[18] The literature often states that there are more than 3,000 IRBs in the US, although my research shows that there are actually about 1,700 IRB panels, and about 1,250 unique organizations, that are registered as active in good standing on OHRP/NIH's database to oversee FDA-regulated research. The database includes thousands of IRBs in deactivated status, and hundreds not registered to oversee clinical research.

American and Canadian legal scholars and bioethicists looking specifically at *biomedical* IRBs have expressed deep anxiety over the rise commercial IRBs. Scholars in this tradition are apprehensive that the profit motive may drive these IRBs to exhibit inappropriate laxity, approving risky protocols that may be ethically and scientifically improper (Lemmens & Freedman 2000; Emanuel, Lemmens & Elliot 2006; Elliot 2010). Some question whether IRBs should be able to operate as for-profit companies at all (Emanuel 2006; Shamoo & Woeckner 2006; Lemmens and Friedman 2000; Lemmens and Thompson 2001). Little empirical work informs this conversation.

In 2009, the Government Accountability Office (GAO) ran a sting of commercial IRBs, in which an egregiously scientifically and ethically inappropriate protocol was sent to three commercial IRBs for approval.[19] While two turned it down quickly, Coast IRB approved it. Later, it was discovered that Coast had only disapproved a single protocol of the several hundred it had approved in 5 years, and had revenue of close to $10 million a year (Elliott 2010, 159). Despite the blip of bad press, commercial IRBs are a growing industry. More than 40 for-profit IRBs in the US collected more than $60 million in 2002; Western IRB alone holds 50% of the market share (Fisher 2009, 11). Chesapeake IRB was named by Deloitte as one of the fastest growing 'tech' companies in the US, and in 2007, a major stake in Western IRB was sold to private equity firm Boston Ventures (which also owns majority interests in NASCAR and Six Flags) (Elliott 2010, 166).

The literature typically situates discussion of commercial IRBs in the context of community-based clinical trials. Less attention has been paid to the extent to which institutional research sites in the US, such as universities, hospitals and health systems, have outsourced their own research oversight to commercial IRBs – either in total or piecemeal.

B. Human Subjects Research – Canada

a. History of REBs and Regulatory System

As in the US, Canada's system of research oversight also begins with Nuremberg trials revelations after WWII and the resulting Nuremberg Code and Declaration of Helsinki. These documents, which center on the concepts of informed consent, voluntary participation, and ethical review of research, are the foundations of Canada's approach to clinical research oversight as they are in the US and elsewhere in the world.

Canada was slower to adopt a formal regulatory system of clinical research oversight than was the US, although its Medical Research Council released its report, *Ethics in Human Experimentation*, in 1978, a year before the Belmont Report was released in the US (Vanderwel 2012).

As the largest foreign recipient of NIH funding during the 1980s (and likely before as well), Canadian research institutions were required to provide NIH with assurance that US standards were being met for NIH-funded research in Canada, including ethics review. Presumably, this indicates that universities and research hospitals in Canada had established REBs during the 1970s and 1980s, and the institutional research landscape looked similar to the

[19] The protocol described pouring potentially toxic liquid into open cavities during surgery. Post-scandal, Coast went out of business. This operation produced a 2009 report and statement to Congress entitled "Human Subjects Research: Undercover Tests Show the IRB System is Vulnerable to Unethical Manipulation," and the transcript from the 2009 Senate Hearing, "Institutional Review Boards that Oversee Experimental Human Testing For Profit."

US. During the 1980s, as the pharmaceutical industry globalized and exploded with activity, Canada experienced pressure to harmonize it's standards, and even had informal discussions about bringing all of Canada's medical research under the FDA's Office for Protection from Research Risks jurisdiction (McDonald 2009).

In 1987, the Medical Research Council published *Guidelines on Research Involving Human Subjects* (McDonald 2009). Additionally, the National Council on Bioethics in Human Research (NCBHR), sponsored by the Royal College of Physicians and Surgeons and the Medical Research Council, also produced policy statements regarding REBs and informed consent (McDonald 2009).

In order to streamline the policies, and response to a general awareness that the uncoordinated policies were creating a cumbersome patchwork for researchers, the three federal granting agencies (Canadian Institutes for Health Research, Social Sciences and Humanities Research Council, and National Science and Engineering Research Council) developed the Tri-Council Policy Statement on the Ethical Conduct of Research Involving Humans (TCPS) in 1998 and a second edition, TCPS2, in 2010. TCPS2 is similar to the Common Rule in the US in that it applies to clinical trials funded in whole or in part by Canada's three federal funders or at institutions taking such funding.

The other mechanism for research oversight is via Health Canada, the federal regulator of drugs and devices. Health Canada's authority to regulate clinical trials and approve new drugs in Canada is established in the Food and Drugs Act and further described in its Division 5 Regulations (Drugs for Clinical Trials Involving Human Subjects) (Preto 2014, 15; Food and Drugs Act, R.S.C. 1985, c. F-27; Division 5 Regulations C.R.C., c. 870). The Regulations and GCP Guidelines apply to all clinical trials in Canada, regardless of their funding or location (Preto 2014). Division 5 regulations pertain to clinical trials involving human subjects, and among other things, require that the agency grant prior authorization for all research involving investigational drugs, and that sponsors to provide the agency with information regarding all clinical trial sites and their overseeing REBs (Vanderwel 2012).

It is relevant to note that law and policy in Canada is significantly constrained by constitutional division of power between federal government and the provinces. Health Canada's clinical trials regulations address sponsor responsibilities. But they do not address responsibilities of other key partners in the clinical research enterprise, including REBs, CROs, and researchers. These gaps are filled by guidelines and non-legislative policy instruments including ICH-GCP Guidelines and TCPS2. This is in contrast to the US FDA regulations, which address IRB, CRO, and researcher responsibilities directly. The Canadian approach is probably at least in part a reflection of a desire to avoid potential constitutional conflicts with the provinces, which have primary jurisdiction over health care, medical licensure and related issues (Preto 2014, 162).

b. Research Shifts From Academy to Community

As in the US, academic health centers and research institutions in Canada have also lost much of their share of clinical trial activity to the private sector, but continue to rely on industry sponsored research for their survival and to fund other and important basic research initiatives (Preto 2014, 1). 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 (Preto 2014, 2). About 80% of all

clinical trials in Canada are funded by industry (Lexchin 2012); and, mirroring the dramatic shift away from the academy toward the private community-based physician practices in the US as sites for research, 70% of all clinical trials in Canada are now being done in the community and only 30% done in academically affiliated sites (Ogilvie 2012; Preto 2014, 2).

Clinical research is an important economic area in Canada. The activities of Canada's Research Based Pharmaceutical Companies alone contribute over $3 billion to the Canadian economy every year (Preto 2014, 17). But Canada's share of clinical trials is dropping, and competition for industry dollars is growing as industry sponsors continue to search for host countries with dense, often treatment naïve populations, lower costs, and in many cases lighter regulatory requirements (van Huijstee and Schipper 2011; Preto 2014, 19).

c. Public/Private Distinction

While the distinction is typically made in the US context between 'academic' or 'institutional' sites on the one hand and 'community-based' research sites on the other, in the context of Canada's publicly funded health care system, it is more accurate to describe research sites as falling either inside or outside the public system. Public sites in Canada include universities, large academic hospitals, smaller community hospitals, and other medical units within the various health authorities (Preto 2014, 33-34). Private sites are physician practices and freestanding for-profit clinical trial centers. See **Figure 1** for a chart with the terminology of research sites in Canada and the US.

Figure 1. Research Sites – Terminology in Canada and the US.

Research Site	Canada	United States
Hospital	Public	Institutional
University	Public	Institutional
Physician Practice	Private	Community-based
For-Profit Research Center	Private	Community-based

d. Response to Pressures – Public (Institutional) Site Streamlining

Canada is responding to these pressures and changes in circumstances differently than the US in a few key ways. First, Canada is working toward streamlining its ethics review in the public (institutional) setting *not* with a turn to commercial REBs, but rather with a variety of national and provincial initiatives and networks. These include efforts to harmonize ethics review, improve infrastructure and streamline regulatory requirements (Preto 2014, 20).

These efforts include the BC Ethics Harmonization Initiative (BCEHI), which is funded and facilitated by the Michael Smith Foundation for Health Research (MSFHR). The initiative involves British Columbia'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). It has been in operation 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 are among the hurdles this initiative needs to overcome (Glass 2006; Hebert & Saginur 2009; McDonald 2000; McDonald et al. 2011). An important milestone

was achieved in May 2013 when an agreement was reached granting the 14 REBs under the jurisdiction of the various BCEHI collaborators authority to work together to develop processes by which to streamline ethics review between participating institutions (Preto 2014, 22)

Another example of efforts to streamline institutional review is Clinical Trials Ontario, which aims "to make Ontario a preferred location for global clinical trials, while maintaining the highest ethical standards." A main goal of the initiative, which launched in 2012, is to reduce time and cost of conducting trials in Ontario by harmonizing the ethics review and other administrative processes (Preto 2014, 22). Additionally, another key initiative is the Ontario Cancer Research Ethics Board, which functions as a single REB in that province to facilitate scientific and ethical review of multi-center oncology trials. (Preto 2014, 23).

e. Response to Pressures – Private (Community-Based) Sites

It is important to note that, while most efforts currently underway target the streamlining and harmonization of activities and structures for research taking place within academic or public institutions, most (65- 75%) clinical trials in Canada now occur in private (community-based) settings. (Vanderwel 2012, 58; Preto 2014, 23).

As explained earlier, in the context of Canada's publicly funded health care system, research sites can be classified as public (universities, large academic hospitals, smaller community hospitals, and other medical units within the various health authorities), or private (physician practices and freestanding for-profit clinical trial centers).

As Christina Preto notes, an important difference between how public and private sites operate is in relation to what REBs perform research ethics review and oversight. Whereas clinical trials taking place at investigative sites that are part of the public system **must** be approved by that site's institutionally-based REB, private investigative sites may use private REBs. 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 (Preto 2014, 35).

To put it more clearly, in the U.S., *institutions* (universities and hospitals) may delegate ethics review of clinical research to private REBs. In Canada, research collaborations between industry and academy must be reviewed by the institutional REB (Preto 2014, 42-43). Private REBs cannot be used if the research site is a recipient of any government research funding (Hemminski 2015). In other words, whereas in the US there has been a movement for universities and hospitals to increasingly rely on commercial IRBs, the same is not true in Canada.

There has been a surge in community-based clinical trials, including in Canada (Caulfield et al 2004, 365). Physicians in the community have to use independent REBs. Canadian legal and bioethics scholars have expressed concern about commercial REBs in the academic literature. One creative approach that has been articulated as a policy option for the review of research at private sites is through provincial licensing agencies (provincial colleges of physicians and surgeons), which can exercise their regulatory authority to oversee industry-sponsored, community based clinical trials.

This has been done in Alberta, where in 1998 the Alberta College established the Research Ethics Review Committee (RERC) to oversee the research activities of licensed physicians in the province. Before an Alberta physician may engage in research, she must obtain approval from the RERC or a university REB in Alberta. In practice, this means that most

community-based (largely industry sponsored) research is reviewed by Alberta's RERC. This function has now been subsumed within Alberta Health Services, at the Clinical Trials Committee of the Health Research Ethics Board of Alberta (Alberta Health Services Website 2018).

f. Larger Context - Canadian Health Policy

Beyond the research ethics context, it is important to briefly describe Canadian health policy, as research is embedded in the broader health system. Canada has publicly funded health care. The division between provincial and federal jurisdiction is an important factor in the development of Canadian health policy over time.

Health care as a right of social citizenship has been "the central tenet of Canadian Medicare since its inception." (Bhatia 2010, 40). Social rights are grounded in normative, moral doctrines rather than legal doctrines. These norms were central to Canada's postwar citizenship regime, in which a pan-Canadian identity was forged, tied to the protection of shared social rights. These norms are enshrined in the five criteria of the Canada Health Act: universality, accessibility, comprehensiveness, portability, and public administration (Bhatia 2010, 41).

Canada has experienced pressures of globalization and the effects of global neoliberal ideas and policies, as have all industrialized countries. Health care discourse has shifted over time from one of health care as a *moral* right of citizenship, to health care being a *legal* right of citizens (Bhatia 2010, 42). However, the regime has remained stable over time, the "institutions and policy apparatus of Medicare…virtually unchanged from their original configurations in the 1960s" (Bhatia 2010, 43). There has been some incursion of privatization in health services, or "passive privatization", in particular for services not covered by Medicare. As private social provision expands, "it reshapes public expectations, institutions, and the organization of private interests." There has also been some policy drift, defined and described in Section III below, wherein the Canadian government has failed to expand Medicare to include the large and growing number of services that fall outside its ambit (Bhatia 2010, 46).

In the 1990s, proponents of comprehensive, market-driven health care reform did not put forward a "culturally and ideologically resonant discourse necessary to legitimize privatization and weaken support for the public health care system created during the postwar era", and it failed (Bhatia and Coleman 2003, 732-733; Beland 2010, 625). The Canadian Medicare system remains a well-liked institution, with opinion polls indicating that Canadians' support for the program has remained essentially constant since its inception, and it is not currently the subject of mainstream retrenchment efforts (Morgan and Daw 2012).

III. Literature Review – Institutionalism, Institutional Change and Institutional Logics

The frameworks of institutionalism and institutional logics are useful in order to understand the trajectory of health policy in Canada and the US over time.

Broadly, institutionalism as a body of scholarship takes on the central project of articulating the role of institutions in political and social life. While there are several threads of institutionalism, the framework of historical institutionalism in particular characterizes institutions as settlements in political struggles between key stakeholders at key moments in time (Thelen 1999). Rather than explaining the emergence and existence of institutions primarily as mechanisms that coordinate and sustain equilibrium (as does rational choice institutionalism), or

as shared cognitive scripts (as does sociological institutionalism), historical institutionalism emphasizes the emergence and development of institutions as political settlements contingent upon particular constellations of people, movements and temporal events.

The framework defines 'institution' broadly, encompassing formal institutions and organizations, as well as public policies, all of which originate and exist within larger political and social contexts. Thus, institutions emerge from and are sustained by a matrix of institutional arrangements, which include political and social elements at the micro decision-making level as well as well in broader macro-level context (Thelen 1999).

Historical institutionalism in a particular strand of institutionalism that conceptualizes institutions as the political legacies of concrete historical struggles between competing actors and circumstances. The framework is particularly sensitive to issues of politics and timing (Pierson 2000). At its core, historical institutionalism construes institutions as the result of struggles between actors within a larger political and temporal context. The timing and sequence of events is key, and early events and choices often have powerful and potentially unpredictable long-term consequences (Pierson 2000; Capoccia and Kelemen 2007). Once established, institutions tend to become self-reinforcing over time, in part because the costs of making radical changes to existing institutional infrastructures increase over time (Pierson 2000; North 1990). This can lead to lock-in, where it may be difficult to affect change – even if the institutional status quo is no longer (or was never) efficient or rational.

Change is possible, however. It may be more likely under conditions of exogenous shock or punctuated equilibrium (Capoccia and Kelemen 2007). But it can also arise subtly through gradual shifts over time (Mahoney and Thelen 2010). These shifts can include layering, conversion, and drift. Layering occurs where new elements are grafted onto an existing institutional framework, which can alter the overall trajectory over time (Thelen 2004). A classic example of layering is the addition of private savings accounts into a pay-as-you-go pension system (Thelen 2003). Conversion occurs when new goals are actors are brought in to an institutional space, which alters the core objectives of the program (Beland 2007).

The general failure to update policy in the face of significant shifts in the institutional environment has been described by political scientist Hugh Heclo, and later by Jacob Hacker and others as policy "drift" (Heclo 1974; Pierson 2000; Beland 2007; Hacker 2004). Drift occurs when policies are not updated to reflect changing or changed social or institutional circumstances. By failing to update policies to match changed social risks or changes in the institutional environment, the policy itself transforms endogenously. Importantly, policy drift does not necessarily mean that a certain public policy has become ineffective in achieving its goals over time. Instead, drift is a policy process by which the policy itself changes, often endogenously. Stated another way, drift is not a measure of the output or effectiveness of a public policy; rather, it is itself a policy process. While Hacker and other political scientists tend to use this concept in relation to larger scale social welfare programs (which often have large regulatory components), the concept can be applied to smaller scale regulatory programs and policies too.

Institutional logics shape the behavior of institutions. They are "socially constructed, historical patterns of material practices, assumptions, values, beliefs, and rules by which individuals produce and reproduce their material subsistence, organize time and space, and provide meaning to their social reality." These logics provide a link between "individual agency and cognition and socially constructed institutional practices and rule structures." (Thornton and Ocasio 2008). The broader meta-theory is that individual and organizational behavior must be

located within a social and institutional context. These logics both regularize behavior and provide opportunities for agency and change (Thornton and Ocasio 2008).

More specifically regarding Canada, Daniel Beland's work often explores comparisons between US and Canadian policy, including in health care, drawing from institutionalism and institutional logics frameworks. Drawing from historical institutionalism, he has explored how political institutions, state capacities, and previously enacted policies impact policy trajectories, particularly over time. He has augmented these theories with the idea of social learning as a political process (Beland 2006). In comparing the policy trajectories of pension reform in the US and Canada, for example, he has argued that social learning and federal decision-making processes in Canada favored the use of government institutions as solution to pension reform, whereas in the US, social learning and policy is often located outside of government, which led to the legitimization of Social Security privatization, although it ultimately was not enacted.

Policy makers look for cognitive shortcuts similar to the concept of 'satisficing' from organizational theory (Simon 1972). These shortcuts often involve the "logic of availability," essentially the idea that policymakers place particular value on information that is immediate and available, including existing policy forms and formats (Beland 2006, 562). This, combined with cross-national variations in state capacity and policy institutions, helps explain how countries arrive at particular regulatory or policy styles.

Beland notes that, while Canada is a federal polity, "power at the federal level is far more concentrated than in the United States." (Beland 2006, 562). For instance, in the context of pension reform, in the US there was "widespread opposition to state involvement," related to the "historically modest role of the federal government in the U.S. economy." (Beland 2006, 572) In describing differences between pension reform options between the US and Canada, he notes that because "the Canadian state had long played a more direct role in economic regulation, business leaders and neoliberal experts were less prone than their US counterparts to view state investment as a dangerous departure from existing economic institutions" (Beland 2006, 578).

IV. Methods

A. Study Design and Sample

a. Total IRB/REB Universe

I first undertook to characterize the entire population of IRBs in the United States and Canada that are registered with FDA/OHRP to oversee biomedical research. IRBs/REBs are not required to be accredited or approved by any governmental or non-governmental agency or organization in order to oversee biomedical research. Instead, IRBs/REBs are simply required to submit a short form to the appropriate federal agency with basic information about the IRB/REB. FDA/OHRP then list the name and location of each such registered IRB/REB online at a publicly available website.

While US regulations including IRB/REB registration do not necessarily apply at Canadian medical research facilities, many such facilities are recipients or sub-recipients of US federally-funded research projects, under which compliance with US regulations will be a condition of the grant or funding. In addition, when manufacturers submit clinical trial data to FDA, they may be required to certify that data was collected from facilities in compliance with US regulations; thus pharmaceutical, device, and other research sponsors may require Canadian

sites comply with US regulations as a matter of contractual obligation or similar extralegal process. There may be some Canadian research ethics boards who do not participate in US sponsored research or participate in clinical research that may support FDA marketing applications. But this is likely to be quite low, since both institutional (public) and community (private) sites will likely oversee industry sponsored clinical trials needing to meet FDA standards. Therefore, while imperfect, I think that using the FDA/OHRP database as a mechanism to ascertain the identity of REBs is reasonable.

b. Qualitative Study

I then undertook a qualitative study, based on open-ended interviews conducted with current and former IRB/REB members, administrators, and counsel, each from US- or Canadian based, OHRP/FDA-registered IRBs. Interviews occurred during site visits and remotely from November 2015 – May 2018. The qualitative approach was chosen for several reasons. First, with few exceptions, few studies have compared the experiences of REB/IRB members between the US and Canada. Qualitative research is particularly well suited for exploratory studies for which previous literature is limited (Crabtree and Miller 1999; Bradley et al. 2001). Such studies are useful for generating hypotheses that can later be tested with quantitative data (Crabtree and Miller 1999; Glaser and Strauss 1967). In addition, I anticipated that some factors, such as experience with commercial IRBs and potential risks related to commercial review, were complex and challenging to measure. Further, interviews at this stage can also lead one to identify new concepts and factors that were not considered at the outset. Qualitative research provides a method to describe the diverse facets and dimensions of such factors (Bradley et al 2001; Miles et al 1994).

As is standard in qualitative research (Bradley et al 2001), I chose sites and interviewees using purposeful sampling to ensure that I included a diverse set of IRBs/REBs and IRB/REB professionals. Study IRBs were selected to reflect a range of geographical locations, size, ownership type; study interviewees were selected to reflect a range of roles within the IRB and related organization. Additional IRBs and interviewees were recruited through snowball sampling, including through the author's professional networks and professional associations. Additional interviews were conducted until no new concepts were identified, in other words, until the point of theoretical saturation. This occurred after 26 interviews (19 in US; 7 in Canada). The characteristics of the study IRBs and interviewees are displayed in **Tables 2** and **3**.

Eligible interviewees were current or former IRB/REB members, administrators, or counsel, from eligible IRBs/REBs, defined as those IRBs/REBs with active registration to conduct FDA-regulated human subjects research on the FDA/OHRP database as of the interview date.

B. Data Collection

a. Total IRB/REB Universe

A search for all US-based IRBs registered in active standing on the OHRP/FDA database to review biomedical research on April 26, 2017 yielded 1712 IRB panels. This search excluded IRBs registered to review *social science research only*, and included only those IRBs registered to review FDA research only (27), or FDA/OHRP research (1685).

Of the 1712 total active IRB panels, there were 1274 unique IRB entities. The remainder are multiple IRB panels at the same organizations. For instance, VA Greater Los Angeles Health Care System has 3 IRB panels separately registered on the OHRP/FDA database, but is counted as 1 unique IRB entity. The methodology to determine if multiple IRB panels were part of a single unique entity was to assess if the IRB entry had the same name and was in the same city as another IRB entry. If the name or city were different, the two entries were considered to constitute two unique IRB entities. If the name and city were the same, the two were considered as one unique IRB entity. See **Table 1**.

A search for all Canadian-based REBs registered in active standing on the OHRP/FDA database to review biomedical research on October 13, 2018 yielded 76 REB panels. This search excluded REBs registered to review *social science research only*, and included only those REBs registered to review FDA research only (0), or FDA/OHRP research (76).

Of the 76 total active REB panels, there were 61 unique REB entities. The remainder are multiple REB panels at the same organizations. See **Table 2**.

b. Qualitative Study

In-depth, open-ended interviews were conducted in person and via teleconference with study interviewees. In the US, 19 interviews were conducted with interviewees at 19 IRBs, for a total number of 19 key respondents interviewed with experience at 21 separate IRBs. These included 12 IRB members and 13 IRB administrators (note, some respondents had both an administrative role and membership on their IRB).

In Canada, 7 interviews were conducted with interviewees at 6 REBs. These included 5 REB members, and 2 REB administrators. See **Table 3** and **Table 4**.

With the exception of one interview, the author conducted each interview with a single participant. In one case, two participants were interviewed at the same time from the same REB. Interviews took place in person (15) or on the phone (11). Interviews were each one to three hours in length. All interviews were audio-recorded and transcribed by independent researchers and professional transcriptionists.

Interviews were conducted using an interview guide instrument (provided at **Appendix C).** For each question, interviewees were encouraged to provide specific examples and details from their experiences. All qualitative interview procedures, interview guides, and recruitment plan were approved by the UC Berkeley institutional review board.

C. Data Analysis

Transcribed interviews were analyzed using coding techniques common to qualitative data (Bradley et al 2001). Coding of the data was accomplished through a series of steps. An initial code list was generated based upon the interview instrument, and was then refined during review and analysis of the transcribed interviews. The process of iterating the code structure involved adding and redefining codes as new insights emerged, as well as identifying relationships within code categories.

Using this final version of the code structure, the author coded the transcripts and Using this final version of the code structure, the author and a research assistant independently coded the transcripts and recorded the data using Excel to capture recurrent themes, links between themes, and quotations of interest.

Techniques were used to maximize the systematicness and verifiability of data analysis. These included consistent use of the interview guide instrument, audio recording, independent transcription, and consistent use of the coding structure in data analysis by two individuals for intercoder reliability.

V. Results

A. Descriptive Statistics

a. IRB Ecology

Table 1
Descriptive statistics of US-based IRBs registered in active standing to review biomedical research as of April 26, 2017

State	# of Unique IRB Entities	Percent of Total
Alabama	24	1.88
Alaska	1	0.08
Arizona	23	1.81
Arkansas	10	0.78
California	115	9.03
Colorado	22	1.73
Connecticut	25	1.96
Delaware	7	0.55
Florida	57	4.47
Georgia	37	2.90
Hawaii	8	0.63
Idaho	7	0.55
Illinois	50	3.92
Indiana	27	2.12
Iowa	14	1.10
Kansas	10	0.78
Kentucky	16	1.26
Louisiana	17	1.33
Maine	8	0.63
Maryland	46	3.61
Massachusetts	57	4.47
Michigan	37	2.90
Minnesota	17	1.33
Mississippi	12	0.94
Missouri	30	2.35
Montana	6	0.47
Nebraska	8	0.63
Nevada	7	0.55
New Hampshire	13	1.02
New Jersey	37	2.90

New Mexico	6	0.47
New York	91	7.14
North Carolina	32	2.51
North Dakota	6	0.47
Ohio	50	3.92
Oklahoma	14	1.10
Oregon	19	1.49
Pennsylvania	75	5.89
Rhode Island	12	0.94
South Carolina	16	1.26
South Dakota	3	0.24
Tennessee	25	1.96
Texas	68	5.34
Utah	6	0.47
Vermont	2	0.16
Virginia	37	2.90
Washington	22	1.73
Washington DC	11	0.86
West Virginia	6	0.47
Wisconsin	25	1.96
Total	**1,274**	**100.00**

b. REB Ecology

Table 2
Descriptive statistics of Canadian-based REBs registered in active standing to review biomedical research as of October 13, 2018

Province	Number of Unique IRB Entities
Alberta	2
British Columbia	9
Manitoba	2
New Brunswick	3
Nova Scotia	2
Ontario	28
Quebec	13
Saskatchewan	2
Total	**61**

c. IRBs and IRB Professionals in the Study

Table 3
Descriptive statistics of IRBs in the study (n=25)

	US	Canada	
Ownership Type			
For-profit	3		1
Non-profit	9		0
Government	7		5
Org Type			
Healthcare	15		2
Commercial IRB	3		1
Public Agency	1		3
Size of Research Program (Active)*			
1-100 protocols	4		1
100-500 protocols	8		3
>500 protocols	5		2
Location			
California	4	Ontario	1
Massachusetts	4	British Columbia	4
Washington	2	Nova Scotia	1
Arizona	1		
Connecticut	1		
Ohio	1		
New Mexico	1		
Oregon	1		
North Carolina	1		
Pennsylvania	1		
Texas	1		
Minnesota	1		

* Two commercial IRBs declined to provide this data.

Table 4
Descriptive statistics of IRB professionals interviewed in the study (n=26)

	US	Canada
Role*		
Administrator	13	2
Member (Scientific)	8	1
Member (Lay)	4	4
Gender		
Male	10	2
Female	9	5
Tenure in HSR		
<10 years	4	2
>10 years	15	5

***** Some respondents have more than one current role.

B. Findings about Commercial IRB Market Penetration and Other Research Streamlining Approaches

After review of the interview data, respondents' comments were analyzed. Uniformly, US-based respondents report awareness of commercial IRBs, and many report direct experience at research institutions that have used the services of commercial IRBs. Several respondents had themselves served on commercial IRBs in the past or present.

Table 5
US: Experiences and Exposure to Commercial IRBs

So first I should disclose that I have enjoyed lunch, and dinner, and an all-expenses-paid trip to Seattle at the courtesy of for-profit IRBs in the past, so I have a slight bias to think that there's not all that bad. That being said…I think the better reviews are done by the institution where the project is happening. (Large research portfolio nonprofit healthcare organization – IRB administrator)
[Organizations using commercial IRBs] It looks like that's going to become more the norm. (Mid-sized research portfolio nonprofit healthcare organization – IRB member [non-scientific])

By contrast, Canadian-based respondents are far less likely to report awareness of the existence of commercial IRBs/REBs, and many exhibited shock that such firms exist. Uniformly, Canadian-based respondents reported that commercial IRBs are simply not used by research organizations like universities and hospitals. Some savvy professionals report knowing that commercial REBs are used in the context of research conducted by physicians without affiliation to any hospital or university.

Table 6
Canada: Experiences and Exposure to Commercial IRBs

what I read recently was that at a lot of institutions in the US, the institution is now farming out its reviews [to commercial IRBs], which here they don't do, they will not do. You're not allowed to do that....It has to be done in house. (Large research portfolio public entity – REB administrator / member [non-scientific])
There's an area in my region…not directly connected with the health centers that do some research locally, so within clinical offices, within family-physician-type situations... But, the reality is all those family physician clinicians have an affiliation with the health authority somewhere. They're affiliated—they have clinical privileges at—a health authority hospital, an ER, an actual freestanding hospital. That ties them to that REB and so I think there have been points in time when some of their REB activities have been handled through independent REBs, but there has been effort to bring them under the umbrella of the health authority REBs. (Small research portfolio healthcare REB – administrator)
[Re: commercial reviews] We don't have that here, do we?... We don't have very many [commercial REB reviews] that I'm aware of. (Large research portfolio public entity – REB administrator / member [non-scientific])
In Canada, I don't understand how it [commercial review] fits into the landscape. Are there commercial REBs? What role do they fill? I'm not really sure. (Mid-sized research portfolio healthcare REB – administrator)

Canadian respondents agree with their US counterparts that there is a general pressure to streamline review. See **Table 7**.

Table 7
Pressures to Streamline Review

It's the usually the health authorities in those provinces that are trying to centralize reviews to make it more robust and also more attractive to sponsors coming in and wanting to conduct research there. (Large research portfolio public entity – REB administrator / member [non-scientific])
There is a huge push at every level of government and every level of research institutions to attract industry-clinical class. We are losing - just like everybody else, we are losing our share… that means our budget is shrinking... There are conferences that are… on how to become more attractive to industry... My personal feeling is that we are working so hard to attract industry …we're streamlining and reducing obstacles to research ethics board approvals among other things and regulatory approval, without ensuring sufficient protection are in place. (Large research portfolio healthcare organization – REB administrator / member [non-scientific])
I think it's [harmonization] a work in progress. I think there's a little bit of friction coming here and there. But I think that's a normal process for independent organizations, which are… devolving some of their independence. In turn, what do they get - they get some efficiency, and they get some efficiency from the researchers as well. And I think in the end that will become the driver because there's more and more stress on the system. (Large research portfolio public entity – REB member [non-scientific])

American respondents report that their institutions are increasingly using the services of commercial IRBs for review of all or some of the research at the site. By contrast, Canadian respondents report that their institutions have turned toward the development of government-

based and non-profit consortia for reliance relationships. Many are unaware of the shadow industry servicing the Canadian private research sector. See **Table 8**.

Table 8
Canadian Solutions for Streamlining Review

Nunavut [has established central REB], and Alberta's working on it. Quebec has something similar… Newfoundland, they have it because it's so tiny. A particular type of health research has to go to there... British Columbia… there were 5 REBs who were trying to sort of deal with them as a whole rather than these individual bodies… The provinces, they're changing all the time, so it's hard to keep up with what's happening. But yeah, there's a lot of movement towards that. (Large research portfolio public entity – REB administrator / member [non-scientific])
We're really trying to follow an example set in Ontario by OCREB in terms of facilitating…and really trying to break down the walls and avoid duplication. (Large research portfolio healthcare organization – REB administrator / member [non-scientific])
[BC Harmonization] is not direct reciprocity…A board will be designated as board of record. There will be guest reviewers from the other sites sitting on that to bring their local view. And so they'll have the opportunity to raise their concerns and all that. Once an approval has made or obtained, then at that point, yes it's recognized by the other boards but it's not without input from the other sites. (Large research portfolio healthcare organization – REB administrator / member [non-scientific])
Newfoundland put in a centralized review process partly because of the geography: a huge land mass, some very distant institutions, extreme lack of resources. So it really worked well, provides a resource approach that meets that geography really well. Out west, there is some centralized review… We're looking at it too -- Maritimes have some issues, again, with lack of resources, wide landmass, few people. How do you provide solutions? (Mid-sized research portfolio nonprofit healthcare organization – REB administrator]

VI. Analysis

1. Similar Pressures, Different Solutions

Despite facing similar pressures, Canadian and US respondents report experiencing different solutions for the review of institutionally-based clinical trials. Further, Canadian respondents also describe non-market-based solution for review of trials at private sites in the case of at least Alberta. In the US, respondents report widespread use of commercial IRBs in institutional and non-institutional settings. This indicates a general turn toward the 'market for ethics' – the use of commercial IRBs is common and increasingly ubiquitous. In Canada, by contrast, respondents describe the development of, and participation in, an array of non-profit and government-based REBs and research oversight consortia.

These solutions are in line with the different institutional logics at work within US and Canadian regulatory policy. The former derives from distrust in government solutions, a neoliberal flair for market-based solutions, and a lack of a coherent national policy and infrastructure for health care coverage and delivery. The latter derives from a cultural legacy of trust in government solutions, generally more centralized regulatory policy, and a coherent and comprehensive national policy and infrastructure for health services.

The solutions are also in line with the institutionalist concepts of understanding policy development over time, including drift and layering. The US systems of private (non-governmental) social welfare protection became an important feature of the institutional and political environment for biomedical research over time. The use and expansion of commercial IRBs was consonant with other dominant actors and features of the political and institutional environment. Later shifts in the broader institutional environment, including the decline of academic medicine as primary site for research and the rise of non-academic sites (driven primarily by the rise of the pharmaceutical industry as prime sponsor of clinical research), and particularly without a dramatic 'focusing event' (e.g. large crisis) (Kingdon 1984), have led to lock in and drift in this space (Goldstein 2017), all of which has contributed to increasing power and dominance of market-based actors. Timing and sequencing are important - because private systems of oversight and protection came first, it remains dominant, with no significant public system in competition.

The trajectory has been different in Canada. The presence of national health system created conditions for more centralized, and certainly more governmentally-based, research oversight processes than in the US. The presence of a coherent national public health agenda and coherent national research institutions created conditions under which, over time, research oversight, even multi-center, would be handled under different set of mechanisms. When the need for multi-center review arose in Canada, it would have been surprising to see a turn toward the market in the context of institutionally-based research. The growth of community-based, physician-office industry-sponsored research is an exception to this – but as Beland and Hacker would predict, because the public system of REB review came first, the private system of commercial REBs plays only a supplementary role, layered onto the original institutions, and is not in direct competition with the public system.

2. Different Visibility in Commercial Ethics Review

Canadian research ethics professionals are not universally aware of the existence of private research review in Canada, overseen by commercial REBs. Further, some respondents who are familiar with private REBs report the inaccurate belief that such reviews are infrequent or that the volume of such reviews is relatively low. By contrast, their professional counterparts in the US report universal familiarity with commercial IRBs, and with the widespread movement of clinical trials from the academy to private sites over the past decades.

The relative invisibility of private clinical trials in Canada was reinforced by my experience attending both the premier US and Canadian research ethics conferences in 2015 and 2016. The US conference featured multiple speakers from commercial IRBs, which sponsored tables and events. The Canadian conference did not feature any speakers from commercial IRBs, and one local Canadian independent IRB was the only tabler from this industry.

There is a strange disconnect, since 70% of research happens in private (community) settings in Canada, as in the US. In the places we might expect, such as professional conferences and in conversation with ethics professionals, the existence and scale of this research enterprise is largely unacknowledged or unknown. This is in contrast to the US, where the industry is very well known to research professionals and has a big presence within the community.

One possible explanation is that most research ethics individuals in Canada do not encounter the existence of commercial IRBs in their professional activities, because the public institutions where they work do not allow local research to be overseen by commercial IRBs.

These individuals also do not seem to encounter the industry in professional circles and conferences, so their exposure to their activities is limited.

There is an additional possible explanation: perhaps this low visibility is intentional on the part of the industry. Perhaps the commercial IRB industry sees an advantage in keeping a low profile in Canada. And, or, perhaps that industry's patron, the pharmaceutical industry, has contributed to the strategy of keeping a low industry profile because it sees some leverage or advantage in this strategy. While my research does not offer direct evidence of this potential explanation, perhaps future research can explore the possibility. More generally, future research will need to track this divergence to see if Canadian awareness "catches up" with the US or if the industry maintains low visibility over time.

3. Conclusion and Implications

At first blush, the Canadian and US research oversight systems may appear quite similar. Committees decide whether to allow (or disallow) research involving human subjects to proceed, based upon generally shared ethical principles aimed at protecting the safety and autonomy of human research participants. Further, both countries have experienced similar shifts in the broader task environment in which clinical trials occur: pressures to streamline review of multi-center studies and a shift away from academic and toward physician practices and freestanding clinical trials centers as the principal sites for clinical trials.

The present project was motivated by a curiosity about whether attitudes toward, and experiences with, commercial IRBs and other means to streamline research review would differ between the US and Canada. The qualitative study reported herein was intended to provide an in-depth perspective about the ways in which research organizations in the US and Canada are responding to similar exogenous pressures to quicken and streamline ethics review of clinical research, including perceptions of, and experiences with, market-based and non-market-based approaches to ethics review.

First, with regard to clinical trials in *institutional settings* such as hospitals and universities, the study finds qualitative evidence supporting the fact that Canada and the US are using different approaches to streamline review. While research organizations in the US have turned to commercial IRBs to oversee this work, Canadian research organizations have not.

Second, most clinical trials now occur *outside of institutional settings*, and it is known that commercialization of ethics review is happening in these settings in both countries to some degree. However, this study finds that commercialization of research review is much less visible to Canadians in the ethics review community than to similarly situated Americans. This is surprising. In the US, everyone in the research community knows about commercial IRBs, including professionals at academic and government institutions. But in Canada, not all respondents were aware of the existence of commercial ethics review firms, and some were unaware that private review is widespread and growing.

Further, while all community-based research review is going to commercial IRBs in the US, the author learned in interviews that Canada is exploring innovative, government-based approaches in addition to private REB review. The province of Alberta has established an REB under its medical licensing agency to oversee clinical trials occurring in non-institutional settings.

Overall, the study finds that Canadian respondents report experience with a larger menu of government and non-profit based policy options than does the US. This may be at least in part

because Canada's strong single payer health care system has been – at least for now - more insulated from market penetration in general. This suggests that broader institutional logics and contextual factors in the two countries have shaped the availability of options on the policy menu, with newer options layered on to existing institutional arrangements.

However, this insulation may not last forever, and this study suggests avenues for future exploration. In the future, as market consolidation in research continues and countries remain in competition as venues for research, a few developments may occur. First, Canadian academic and government facilities may begin to agree to use commercial IRBs, as have their peer organizations in the US. Second, the government-based approaches to community-based clinical trials review such as the Alberta experiment may fail, and/or the government consortia such as the BC Ethics Harmonization Initiative and OCREB in Ontario may fail. Either development could be a "dam breaking" moment that would signal the end of the noncommercial approach Canada has taken for review clinical research and the start of commercialization as has occurred in the US. Future research would then need to explore the causes and drivers for such developments, including the extent to which such developments may adhere to broader trends of a neoliberal push for market solutions in the face of loud industry preferences, including the pharmaceutical industry.

CHAPTER 5: CONCLUSIONS

Reporting on the results of an original qualitative research study, the chapters in this dissertation explore various aspects of the current IRB ecology, given how significantly the institutional and economic environments in which clinical research occurs have changed since its regulatory regime was established decades ago.

The second chapter explores IRB professionals' experiences with, and responses to, the legal and regulatory environment in which these professionals and their organizations operate. The chapter offers empirical and theoretical contributions. First, the chapter evaluates IRBs descriptively, providing a first-ever analysis of IRB empirics (such as how many there are, where they are located). It also provides qualitative information about how IRB members and senior staff experience regulatory and legal encounters, perceive and respond to such risks, and use legal counsel in the performance of their research oversight activities. The second chapter also offers analytical insights about how professionals from different types of IRBs experience legal and regulatory encounters, how they understand and respond to risks, including legal and regulatory risks, and how this influences behavior. A central finding is that IRB professionals across various types of organizations do not experience significant legal or regulatory encounters of an adversarial kind, and do not perceive legal or regulatory risks as particularly high. This has implications for theories of organizational sociology, and sociolegal studies.

The second chapter also offers analytical insights about how different IRBs translate 'law on the books' into 'law in action.' A central finding is that, while the laws on the books are vague (by design in this case – it is a feature of management-based regulation, of which IRB oversight is an example), IRBs differ in the frequency with which they call upon legal counsel to assist in translating the vague requirements into practice. Data from this study suggest this variation may be systematic: organizations overseeing large research portfolios tend to use counsel frequently and speak positively about their role, while smaller organizations and independent IRBs tend to use counsel very infrequently and do not tend to report that counsel has much value.

The third chapter explores variation between types of IRBs, identifying governance gaps and best practices. The chapter offers empirical and theoretical contributions. First, the chapter evaluates IRBs and provides qualitative information about how IRBs vary in terms of internal organizational factors, external features of the task environment, and other environmental factors. Second, the chapter offers analytical insights about the nature of variation among IRBs. Scholars admit there is a dearth of empirical research about the functioning of light touch regulatory regimes. This chapter reports on extensive qualitative research with professionals in the IRB space. It reports on a few findings that have significant implications for understanding the functioning of this particular instance of light touch regulation, as well as insights into conditions under which this form of regulation (increasing in frequency), in which regulated entities do much of the steering (instead of government agencies) may fail to achieve its public health and safety purposes in other domains.

The third chapter has two central findings. The first is a finding of significant variation "on the shop floor" in terms of how these delegated regulators function. This includes variation in internal features and external factors that may influence IRB expertise and capacity. This variation is a consequence of management-based regulation as a form, because the management-based approach is designed to afford regulated entities the ability to craft individual solutions.

This variation may be a 'feature' of this regulatory system (when the variation is responsive to local conditions), or a 'bug' (where the variation is detrimental in terms of health and safety).

The variation reported herein is troubling because they indicate that shifts in the broader institutional landscape (including the shift toward centralized and non-local research review) has produced organizations that do not all have similar levels of capacity and sophistication.

Interestingly, the findings suggest that at least some of this variation is systematic, based on the size or ownership status of the organization housing the IRB. This in turn has implications in terms of the likely quality of the research ethics services that IRBs provide. This has implications in terms of the types of organizations we might like to encourage, and others we might like to discourage, through public policy (and, as consumers and patients, by voting with our wallets in terms of where we seek care). The finding of systematic variation challenges existing literature asserting that variation in IRB behavior is not systematic.

The second central finding is that, in particular, there is significant variation among IRB-housing organizations with regard to larger compliance capacities. This too appears at least somewhat systematic. Whether the IRB is part of a larger research compliance function, or is tied back to compliance functions at the local level (for non-local IRB reviews) is critically important. This is particularly true in the case of reliance relationships, where local research sites rely on an external IRB to review and oversee research. This is increasingly common and will essentially be mandated by new federal regulations for multi-center research studies.

A larger implication is that flexible regulation without a clear set of baseline standards as a floor, and a weak enforcement system (a weak "stick", in the forms of regulatory enforcement and litigation), is not producing uniformly capable organizations (IRBs). This type of significant heterogeneity is of concern in the context of an important public health and safety function. There is evidence of gaps in oversight, which raises the risk of insufficient research oversight and the potential for harms to research participants. The finding lends itself to policy interventions to create a stronger baseline at the IRB level and the research organization level.

Another implication and finding is that research is increasingly been 'overseen' by IRBs that are not at the site where research is taking place, and that the movement towards using external IRBs to review research, which may actually be performed thousands of miles away at sites the IRB has never seen, also creates potential gaps in oversight, and misalignment of financial and business incentives. This too suggests that it may be time to update the management-based regulations that govern research oversight to provide more a baseline set of requirements, given the new world of non-local research review.

In short, the third chapter provides evidence of variation, some but not all of which is to be expected in a management-based regulatory regime; evidence of gaps in oversight and capacity 'on the shop floor'; and a few emergent best practices and suggestions for policy updates.

The fourth chapter explores the attitudes of IRB professionals toward the commercialization of research ethics review in the United States and Canada. The chapter was motivated by a curiosity about whether attitudes toward, and experiences with, commercial IRBs and other means to streamline research review would differ between the US and Canada. I suspected this might be the case, at least in part because of differences in the broader institutional environments in which these research ethics professionals operate. The chapter offers empirical and theoretical contributions. The chapter provides a description of REB empirics (such as how many there are, where they are located and provides qualitative information about the extent to which research oversight professionals in the US and Canada are responding to and experiencing

pressure to streamline research review, including using the services of commercial ethics firms, and their attitudes and beliefs regarding the use of such commercial firms versus other noncommercial ethics review streamlining mechanisms.

The central findings of the third chapter are as follows: 1) With regard to clinical trials in *institutional settings* such as hospitals and universities, Canada and the US are using different approaches. While research organizations in the US have responded to pressures to streamline and quicken clinical research review and oversight by turning to the market, in accordance with broader neoliberal institutional logics at work in the US, including longstanding institutional logics within health care delivery, Canadian research organizations have not. This derives from a separate set of institutional logics and historical circumstances, which have over time privileged non-commercial and government-based regulatory solutions, particularly in health care.

2) While that is all well and good with regard to *institutional* settings, most clinical trials now occur *outside of institutional settings*. And commercialization of ethics review is happening in these settings in both countries. However, this commercialization of research review is much less visible to Canadians in the ethics review community than to similarly situated Americans. This was a surprising result. In the US, everyone in the research community knows about commercial IRBs, including professionals at academic and government institutions. Not so in Canada. Some Canadian respondents at institutional settings were unaware of the existence of commercial ethics review firms, while others were unaware that private review is widespread and growing. This invisibility may be driven in part by the fact that institutional review of Canadian research has not succumbed to commercialization, while it has in the US.

3) Also regarding non-institutional settings, all of this research review is going to commercial IRBs in the US. In Canada, some of it is going to commercial REBs as well, with this mechanism layered on to existing review infrastructure. But there are also innovative, government-based approaches being explored. For example, the province of Alberta has established an REB under its medical licensing agency to oversee clinical trials occurring in non-institutional settings. In this way, Canada has more policy options on its menu than does the US when it comes to overseeing clinical trials occurring in the community.

4) The fact that Canada has a larger menu of government and non-profit based policy options than does the US is at least in part because of the broader context of institutional research and health care in Canada, which is a strong single payer system. This means that health care in Canada is – at least for now - more insulated from market penetration in general. This suggests that broader institutional logics and contextual factors in the two countries have shaped the availability of options on the policy menu.

5) The analysis, however, suggests that this insulation may not last forever, and suggests hypotheses for future exploration. In the future, as market consolidation in research and countries continue to compete to remain an attractive venue for research, a few developments may occur. One is whether Canadian academic and government facilities agree to use commercial IRBs, as have their peer organizations in the US. Another would be whether the government-based approaches to community-based clinical trials review such as the Alberta experiment fail. Either development could be a "dam breaking" moment that would signal that the noncommercial approach Canada has taken for review clinical research is an ineffective solution. Future research would then need to explore the causes and drivers for such developments, including the extent to which such developments may adhere to broader trends of a neoliberal push for market solutions.

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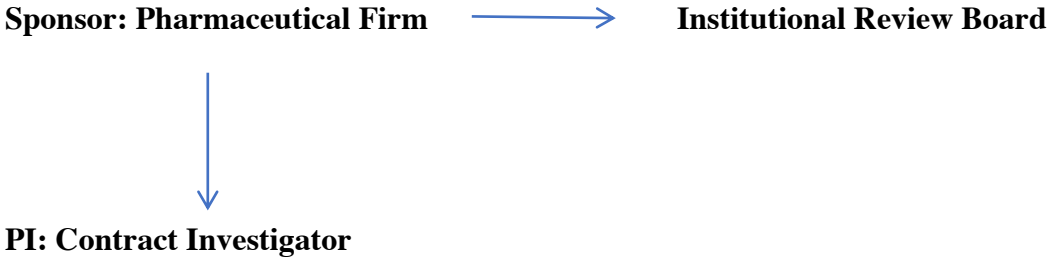
APPENDICES

Appendix A

A. Schematic of Primary Relationships between Sponsor / Investigator / IRB: 1955-1980

B. Schematic of Primary Relationships between Sponsor / Investigator / IRB: 1980 - Present



Appendix B

Interview Instrument Guide (US)

A. Background Questions

1. Interviewee. Tell me a little bit about your background and experience with IRBs, including the one you're currently sitting on (e.g., length of tenure, title/positions)
    a. **Are you an IRB chair, administrator, member**?
    b. How did you come to be in your current position?
    c. Are you an active researcher? What kind of research?
    d. Have you served on (or been admin of) the IRB at more than one organization?
    e. Did you have a mentor?

2. Organizational characteristics. Tell me a little bit about your organization.
    a. Non-profit, for profit, univ, part of a health system, etc?
    b. How large is the research program at your org?
    c. What types of research? What phases?
    d. How many active research protocols a year // how much is federally funded, commercially-funded, other (e.g. foundation)?
    e. How many IRB panels? Is there a "Human Research Protection Program" that's larger than just the IRB?
    f. How important is research to the overall organization?

B. Administrative // Your IRB

3. Who's on the IRB? How are people chosen? **Community member?**
    a. [for commercial IRBs] – do you pay community members?

4. Are there active researchers on the IRB? How many?

5. Is there a separate scientific review committee? If so, who staffs it? If so, what do you see as the difference between the roles of the IRB and SRC?

6. What administrative support is available to your IRB?

7. Do you and the members feel they can keep up with the workload?
    a. Are members paid?
    b. Do you think members are engaged? Some more than others?

8. Training requirements?

9. How do you think the IRB is seen within the organization?

10. What is the relationship b/t IRB and org leadership? What kinds of conflicts, if any? **Does IRB report to the board** or leadership?

11. Is there a compliance office? How well does IRB intersect/interact with that office? Risk Management?

12. **Do you think the IRB and its activities is siloed from the rest of the organization or is it well integrated into the rest of the organization's activities?**

C. Legal and Regulatory Risk Perception:

13. What do you think of the role of legal counsel w/r/t IRB activities? Is there a lawyer on the IRB, or one available to you?
    a. Does the IRB have a lawyer from within the org come to meetings, either voting member or ex-officio? In theory do you see an issue w/ org attorney on an IRB?

14. Do you think this IRB is worried about a lawsuit? Has it been sued in the past few years or has there been a threat of litigation?

15. **Complaints**? From subjects? Researchers? Research coordinators? Sponsors?

16. It's interesting b/c there's so much litigation/complaints in med/clinical practice and little in clinical research. **Do you have any ideas about why that is true**?

17. Do you think this IRB is worried about a regulatory enforcement action? Has it been subject to FDA or OHRP audit or inspection in the past few years?

18. Do you think the federal regulators are easy to work with? Have you interacted with them or do you have a sense of their friendliness level?

19. Do you // does your IRB consider federal GUIDANCE to be mandatory or voluntary?

D. IRB Meetings // Deliberations

20. When you think about deliberations, can you talk about how much time is usually spent talking about risks and benefits, or scientific issues, and how much is spent on the consent form / process?
    a. Do you agree with the lament that too much time is spent on the consent form and not enough on risk/benefit?

21. **Does your IRB usually feel equipped to evaluate the scientific issues / merit**?

22. Does your IRB oversee 'risky' research such as placebo-controlled trials when a treatment exists, or in psych? Do these give the IRB concern?

23. Does your IRB approach reviewing industry-funded research differently from other types of research?

    a. Is your IRB aware of 'low social value' studies, like postmarketing studies (non-FDA required) and non-inferiority trials? Is it worried about these?

    b. Is your IRB aware of studies where the protocol alters diagnostic criteria for disorders (ie, 'game' the inclusion/exclusion criteria), poor comparators, etc? How does it approach these issues? "underpowered" studies masquerading as a pilot.

    c. Are you aware of the CTA process? Are you / the IRB involved? Indemnification? (especially for comm. IRBs)

24. What do you think the role of the FDA is, with regard to ethics? Research design?

25. If you know a study has already been approved at big brand-name institutions, do you review it differently or does it give you some comfort? Do you rely on FDA and/or sponsor to vet the science?

26. Does your IRB review specimen studies? Including collection of specimens in clinical trials? Is this a concern for the IRB?

E. Compliance // SAEs // COI

27. How does IRB come to know of SAEs? DSMBs? Particularly in multi-site studies, there can be a lot of AE reports flying around.
    a. Does the board have the expertise to evaluate SAEs? What do you do?
    b. Do a lot of studies you see have DSMBs? Do you think it should be required for all multi-site trials? [medical monitor, internal 'safety group']

28. **Does the IRB/HRPP audit PIs or sites? For-cause/random?**

29. Is there a COI committee? What kind of relationship between IRB and COIC?

30. How does the IRB come to know an investigator has a COI?

31. [**If you use or are a] commercial/central IRBs – how do they come to know of a PI COI? Regulatory reporting?**

F. Flexible Governance // Commercial IRBs

32. Are you aware of these types of initiatives? "Flex Coalition;" IRB Reliance Agreements or Memos of Understanding with other institutions? "Unchecking the box"?

33. In the past year, has your IRB relied on another IRB or been relied on?

34. In past year, has your IRB used a central IRB? A commercial IRB?

35. Do you have any thoughts about commercial IRBs? Regarding the quality of review?

36. Do you have thoughts about central IRBs? (the idea of single- IRB of record)

37. In using commercial/central IRBs, I'm curious about how reliance relationships work w/r/t compliance function at your org. E.g., if there is a problem in the trial, how does that get relayed to the external IRB and how do they respond?

38. Does your org have a FTE or other employee who focuses on reliance/external IRB relationships?

39. Do you have a sense of how many commercial IRBs there are, or what that market is like?

40. Are you aware of commercial IRB outreach to orgs like yours? Speaking gigs, events?

41. Does your IRB have an appeal mechanism? Different types of panels for different types of studies?

42. Does your IRB have a formalized or informal mechanism to promote institutional memory of how certain issues have been dealt with/decided already? E.g., mechanisms to use prior cases in current cases, avoid discrepancies, over time?

    a. For institutions w/ multiple panels: mechanisms to coordinate across panels?

G. <u>IRB Operations and the Future</u>

43. Who do you think is the IRB's primary client? Researchers, subjects, the institution, regulators, sponsor?

44. The IRB's job is to: protect institution; ensure the study is scientifically appropriate; protect subjects.

45. The Notice of Proposed Rulemaking contemplates several changes to IRB operations, including expanded use of central IRBs, and different ways to approach research involving data and specimens. Any thoughts about these proposals? Would these help your program/IRB?

46. If you've been involved w/ IRBs at more than one org, what do you think are the biggest differences // similarities between them?

47. What do you think is the greatest pressure facing IRBs today?

Appendix C

Interview Instrument Guide (Canada)

Background Questions

1. Interviewee. Tell me a little bit about your background and experience with REBs, including the one you're currently sitting on/administrator of/counsel for (e.g., length of tenure, title/positions)
    a. Are you a chair, administrator, member, counsel?
    b. How did you come to be in your current position?
    c. Are you an active researcher? What kind of research?
    d. Have you served on (or been admin of) the REB at more than one organization?
    e. Did you have a mentor coming into this profession?

2. Organizational characteristics. Tell me a little bit about your organization.
    a. Non-profit, for profit, univ, part of a health system, etc? Gov-funded?
    b. How large is the research program at your org?
    c. What types of research? What phases?
    d. How many research protocols a year // how much is gov-funded (US/Canada), commercially-funded, other (e.g. foundation)? Phases of research??
    e. How many REB panels?
    f. Is there a "Human Research Protection Program" that's larger than just the REB at your institution?
    g. How important is research to the overall organization?

Canadian System

3. Regulatory System. What is the general feeling among research ethics folks in Canada about the system?

4. Coordination / Centralization. Is there a movement to centralize clinical trial review? Is this well-received, or does it depend?

5. Connection to US system / requirements. How important is the US IRB regulations, guidance documents, regulatory reform efforts, and so forth? AAHRPP accreditation, IRB forum, etc?

6. Industry. What is the general relationship between industry and academic/health systems regarding clinical trials in Canada?

Administrative // Your REB

7. Who's on the REB? How are people chosen? **Community member?**
    a. [for commercial REBs] – do you pay community members?

8. Are there active researchers on the REB? How many?

9. Is there a separate scientific review committee? If so, who staffs it? If so, what do you see as the difference between the roles of the REB and SRC?

10. What administrative support is available to your REB?

11. Do you and the members feel they can keep up with the workload?
    a. Are members paid?
    b. Do you think members are engaged? Some more than others?

12. Training requirements?

13. How do you think the REB is seen within the organization?

14. What is the relationship b/t REB and org leadership? What kinds of conflicts, if any? **Does REB report to the board** or leadership?

15. Is there a compliance office? How well does REB intersect/interact with that office? Risk Management?

16. **Is the REB and its activities siloed from the rest of the organization or is it well integrated into the rest of the organization's activities?**

17. Does the IRB think about the quality of its services? Does it audit itself or undergo other evaluation?

Legal and Regulatory Risk Perception:

18. What do you think of the role of legal counsel in how this or other REBs conduct business? Is there a lawyer on the REB, or one available to you?
    a. Does the REB have a lawyer from within the org come to meetings, either voting member or ex-officio? In theory do you see an issue w/ org attorney on an REB?

19. Do you think this REB is worried about a lawsuit? Has it been sued in the past few years or has there been a threat of litigation?

20. Complaints? From subjects? Researchers? Research coordinators? Sponsors?

21. Do you think this REB is worried about a regulatory enforcement action? Has it been subject to FDA or OHRP or Health Canada audit or inspection in the past few years?

22. Do you think the (US/Canadian) regulators are easy to work with? Have you interacted with them or do you have a sense of their friendliness level?

23. Do you // does your REB consider governmental GUIDANCE (FDA, OHRP, Health Canada) to be mandatory or voluntary?

24. How do you think about risk in the context of clinical trials? Whatever "risk" means to you – legal risk, physical risk to the subject, reputational risk to the org

25. Do you think this REB is too cautious, not cautious enough, about right? About certain types of research or in general?

26. Do you think that this REB has a high tolerance for risk (if so, what kind of risk)? Is that risk tolerance driven by people on the committee, or institutional leadership, or something else?

27. What do you think might happen if the REB was named in a lawsuit or was subject to regulatory enforcement action? What's the worst thing that could happen, what's the best outcome, and what do you think is most likely?

28. Do you have a sense of how this REB operates with regard to risk tolerance compared to other REBs?

REB Meetings // Deliberations

29. When you think about deliberations, can you talk about how much time is usually spent talking about risks and benefits, or scientific issues, and how much is spent on the consent form / process?

30. Do you agree with the lament that too much time is spent on the consent form and not enough on risk/benefit?

31. **Does your REB usually feel equipped to evaluate the scientific issues / merit**?

32. Does your REB approach reviewing industry-funded research differently from other types of research?

    a. Is your REB aware of 'low social value' studies, like postmarketing studies and non-inferiority trials? Is it worried about these?

    b. How does your REB approach studies like placebo controlled trials when a treatment exists, or in psych?

    c. Is your REB aware of studies where the protocol alters diagnostic criteria for disorders (ie, 'game' the inclusion/exclusion criteria), poor comparators, etc? How does it approach these issues? "underpowered" masquerading as a pilot.

    d. Are you aware of the clinical trial agreement process? Are you / the REB involved? Indemnification? (especially for comm. REBs)

33. What do you think the role of the FDA/Health Canada is, with regard to ethics? Research design?

34. If you know a study has already been approved at big brand-name institutions, do you review it differently or does it give you some comfort? Do you rely on FDA and/or sponsor to vet the science?

35. Does your review specimen studies? Including collection of specimens in clinical trials? Is this a concern for the REB?

Problems

36. How does REB come to know of SAEs? DSMBs? Particularly in multi-site studies, there can be a lot of AE reports flying around.
    c. Does the board have the expertise to evaluate SAEs? What do you do?
    d. Do a lot of studies you see have DSMBs? Do you think it should be required for all multi-site trials? [medical monitor, internal 'safety group']

37. Does the REB/HRPP audit PIs or sites? For-cause/random

Conflicts of Interest

38. Is there a COI committee? What kind of relationship between REB and COIC?

    a. [Does your org have a COI policy? Just for US (PHS) federally-funded rsh or more broadly? Institutional COI too?]

39. How does the REB come to know an investigator has a COI?

40. Is the REB part of the COI process? Communication w/ COI Committee? Corporate compliance?

41. [**If you use or are a] commercial/central REBs – how do they come to know of a PI COI? Regulatory reporting?**

Flexible Governance // Best Practices

42. Are you aware of these types of initiatives? "Flex Coalition;" REB Reliance Agreements or Memos of Understanding with other institutions? "Unchecking the box"?

43. In the past year, has your REB relied on another REB or been relied on?

44. In past year, has your REB used a central REB? A commercial REB?

45. Do you have any thoughts about commercial REBs? Regarding the quality of review?

46. Do you have thoughts about central REBs?

47. Does your REB have an appeal mechanism? Different types of panels for different types of studies?

48. Does your REB have a formalized or informal mechanism to promote institutional memory of how certain issues have been dealt with/decided already? E.g., mechanisms to use prior cases in current cases, avoid discrepancies, over time?

    a. For institutions w/ multiple panels: mechanisms to coordinate across panels?

REB Operations and the Future

49. The Notice of Proposed Rulemaking contemplates several changes to IRB operations, including expanded use of central IRBs, and different ways to approach research involving data and specimens. Any thoughts about these proposals? Would these help your program/REB?

50. If you've been involved w/ REBs at more than one org, what do you think are the biggest differences // similarities between them?

51. What do you think is the greatest pressure facing REBs today?