

**On Guarding the Welfare of Clinical  
Trial Subjects While Promoting  
Novel Drug Innovation  
A Game Theoretical Approach**

Farida Lada



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WHILE PROMOTING NOVEL DRUG INNOVATION  
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## **ACRONYMS USED IN THIS THESIS**

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CDSCO	Indian Central Drugs Standard Control Organization
COI	Conflict of Interest
CRO	Contract Research Organization
CTSA	Clinical and Translational Science Award (a program of NIH)
DGC	Indian Drug Controller General
EC	Ethics Committee
FDA	United States Food and Drug Administration
FWA	Federalwide Assurance with OHRP
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
ICMR	Indian Council of Medical Research (historically IRFA)
IND	Investigational New Drug exemption issued by FDA
IOM	Institute of Medicine (health arm of the National Academy of Sciences)
IRFA	Indian Research Fund Association (now ICMR)
IRB	Institutional Review Board
MHFW	Indian Ministry of Health and Family Welfare
NCI	United States National Cancer Institute
NIH	United States National Institutes of Health
OHRP	Office for Human Research Protections (within United States Department of Health & Human Services)
PI	Principal Investigator = Clinical Investigator
SOP	Standard Operating Procedure

## INTRODUCTION

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*The value of a drug does not lie solely in the therapeutic functions of new molecules or of modified ones, nor does it depend on novel models of delivery. Drug value is highly charged, economically and politically. It must be negotiated with multiple partners outside the pharmaceutical pricing complex... Treatment access becomes a value in its own right – even if the prioritization of a certain treatment is unclear or the means of access are not specified or are not applied invariably. This valuation can build political support and meet economic goals. Such value discourses do not, however, engage the failure of the market to advance a socially optimal level of drug research and development (Petryna, 2009).*

### 1. Context

Medicines play an important role in the promotion of health and welfare. At an individual level, a medicine either helps prevent certain illnesses, or it serves as a treatment that may reduce suffering of individuals faced with certain illnesses. Prevention or treatment of illnesses at an individual level contributes to a larger population of healthy individuals, who may then become more productive members of society. Thus, societies, or countries, where individuals have greater access to medicines for which there is a local need may benefit economically from a more productive population (Sachs, 2005). Access to medicines is generally gained at a country level, as pharmaceutical companies must seek approval from each country's government to market their drug(s) within the country. The process for receiving this approval starts at pre-clinical stages of drug development and continues until the drug is ready for human use. Clinical trials are a critical part of the drug development process, and they are also the component of the process that expose human subjects on whom the new drugs are tested to the greatest risks. By risk, I refer to any event that may render harm to the clinical trial subject. Thus, the risks to which clinical trial subjects are exposed are not simply the physical risks of being exposed to experimental products; there are also a number of social, financial and psychological burdens which clinical trial subjects may have to bear (Emanuel, Wendler, &

Grady, 2000). Thus, governments often face the challenge of how to adequately protect human subjects of clinical trials.

Fukuyama defines governance as “a government's ability to make and enforce rules, and to deliver services... The government is an organization which can do its functions better or worse” (Fukuyama, 2013). Applying this concept of governance to the oversight of clinical trials, the government must maximize the welfare of its people through functions that balance drug innovation with protection of clinical trial subjects. The challenge for the government is therefore to manage two processes: investing in new drug creation and ensuring safety of subjects in clinical trials such that access to medicines is optimized.

One of the many objectives of governance is to ensure or at least promote ethical conduct. In this regard, the terms *ethics* and *ethical conduct*, as used in this thesis, refer only to the principles identified as necessary for the protection of human subjects of research within the international guidelines for protection of human subjects of clinical trials, within the clinical trial literature and within the regulations for protection of human subjects of various countries. The term *ethical concern*, as used in this thesis, refers to concerns about inadequate protection of human subjects of clinical trials. This thesis focuses on governance policies and strategies for maximizing subject protection (welfare) while allowing clinical trials to take place (promote innovation) as they related to these principles. It is not the intent of this thesis to “investigate answers to moral questions” associated with the conduct of clinical trials as would be done in an ethics or philosophy thesis (Bennett, 2015).

The governance of clinical trials operates at three different levels:

- i. At an international level, many organizations have established standards for the ethical conduct of clinical trials. These include a) the World Medical Association's Declaration of Helsinki, which sets forth “ethical principles for medical research involving human subjects”<sup>1</sup>; b) the International Conference on Harmonisation's (ICH) Good Clinical Practices guidelines, which “describes the

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<sup>1</sup> <http://www.wma.net/en/30publications/10policies/b3/>

responsibilities and expectations of all participants in the conduct of clinical trials”<sup>2</sup>; and the publications from the Council for International Organizations of Medical Sciences (CIOMS), which provide recent dialogues regarding the ethics of research on human subjects<sup>3</sup>.

- ii. At a national level, at least 113 countries have issued some combination of laws, regulations and guidelines governing human subject research<sup>4</sup>.
- iii. At an institutional level, each pharmaceutical company, contract research organization and ethics committee operates under a set of policies, procedures, and/or guidelines.

Despite this multi-level approach to the governance of clinical trials, the present system of clinical trial governance, has its shortcomings, as demonstrated by instances of ethical violations that have occurred throughout the world. Traditional clinical trial markets, such as North America and Western Europe, have been facing ethical dilemmas associated with the conduct of clinical trials for decades. Though the evolution of oversight systems in these markets have helped minimize the occurrences of ethical violations, these continue to occur (Comfort, 2009; Nada & Somberg, 2007; Schüklenk, 2000; Tuskegee University, 2011). Examples of these violations include: i) A United States military sponsored research project in the 1940s, in which prisoners at the Stateville Penitentiary in Illinois “were infected with malaria and treated with experimental drugs that sometimes had vicious side effects. ” The prisoners were used as “reservoirs for the disease and they provided a food supply for the mosquito cultures” (Comfort, 2009); ii) A UK government approved phase 1 clinical trial conducted by TeGenero AG in 2006, which was found to lack scientific integrity, inappropriately qualified physician investigators and failure to arrange for timely medical care of the subjects (Attarwala, 2010); and iii) in India, research involving the administration of human papilloma virus (HPV) vaccine to 2,300 girls from “poor and disadvantaged social groups” in 2009-2010 was conducted without adequate scientific justification and absent appropriate informed consent

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<sup>2</sup> <http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/good-clinical-practice.html>

<sup>3</sup> <http://www.cioms.ch/index.php/publications/available-publications?task=showCategory&catid=53>

<sup>4</sup> <http://www.hhs.gov/ohrp/international/index.html>



(Mattheij, Pollock, & Brhlikova, 2012). This has led some to believe that the “current system of oversight of clinical research... could be improved” (Califf et al., 2003).

The number of actors involved in the clinical trial process and its oversight, combined with their respective, and sometimes conflicting, agendas, makes comprehensive assessment of possible harm to subjects and implementation of mechanisms to minimize such harm difficult. For example, a government may provide regulatory oversight of the clinical trial process to ensure that the drugs that are brought to market are safe and effective; however, it must not do so in a manner that creates barriers for pharmaceutical company innovation. The pharmaceutical industry must innovate in a manner that allows it to make a profit; however, the innovation must not occur in a way that exploits human subjects. Ethics committees must protect clinical trial subjects from serious harm, but in order to do so, they must have complete information about the purpose, procedures, risks, benefits and alternatives. Such information may not always be available in its entirety due to inherent uncertainties involved in the clinical trial process.

To further complicate clinical trial governance, “clinical trials increasingly occur on a global scale as industry and government sponsors in wealthy countries move trials to less wealthy countries”. In recent years, there has been a trend toward globalization of clinical trials, specifically a shift toward emerging markets, such as Asia, Latin America and Eastern Europe (Thiers, Sinskey, & Berndt, 2008). The introduction of clinical trials to these emerging markets is taking place at a much faster pace than the ability of the local governments to develop and implement effective oversight systems. Thus, the risk of ethical violations in these markets is higher than in the traditional markets (Glickman et al., 2009; Petryna, 2005). Difficulties in protecting human subjects of clinical trials in emerging markets are due to a number of factors, including lack of established regulatory oversight system, lack of established and experienced ethics committees, and “disparities in education, economic and social standing and health care systems”, which “jeopardize the rights of research participants (Glickman et al., 2009).

Thus, the central research query of this thesis is to study how all parties engaged in the oversight and implementation of clinical trials (regulatory oversight bodies, the ethics committees, the pharmaceutical companies and

the CROs) can provide adequate protection of clinical trial subjects while allowing for new drug development.

## **2. Aims of this Thesis**

Governance of clinical trials is not limited to regulatory oversight. In addition to regulatory oversight, clinical trial governance requires development and implementation of policies and procedures by pharmaceutical companies, ethics committees, and contract research organizations (CRO). By *regulatory oversight*, I refer to the established rules of a given government's regulatory agencies, and the agencies' enforcement of these rules. For the purpose of this thesis, the policies and procedures of pharmaceutical companies, ethics committees and the CROs will together be referred to as *institutional policies and procedures*. The first issue that must be addressed is how to evaluate whether the regulatory oversight and the institutional policies and procedures each ensure protection of clinical trial subjects while allowing clinical trials to take place. Therefore, the first aim of this thesis is to develop a framework for evaluation of the regulatory oversight and institutional policies and procedures for governance of clinical trials. The framework will then be used to evaluate regulatory oversight in a traditional market, regulatory oversight in an emerging market, and policies and procedures of industry players. A second aim of this thesis is to use the lessons learned from these evaluations to propose possible government policy and strategy as well as institutional strategy outcomes, and to assess their impact on the balance between subject welfare and novel drug development. To accomplish this, I borrow concepts from game theory.

### **2.1. Research Questions**

The overarching question of this thesis is how to maximize the welfare of clinical trial subjects while promoting novel drug innovation.

For the purpose of this thesis, maximizing welfare of clinical trial subjects refers to adequate protection of human subjects of clinical trials. Promoting innovation refers to regulations and policies that do not create any barriers to conducting clinical trials. The focus of this thesis is not to study whether ethical conduct of clinical trials, in and of itself, leads to more welfare and/or more innovation. Rather, it is to study the overall governance of clinical trials to understand how to reach a balance between welfare and innovation.

This thesis also aims to address the following sub-questions:

- a. How to best evaluate the effectiveness of the oversight of the clinical trial process in terms of maximizing subject and society welfare, i.e. what is the most relevant framework?
- b. As the model oversight system, does the United States oversight system provide adequate protection for human subjects while allowing for innovative drug development through the clinical trial process?
- c. As a representative of emerging markets, does the Indian oversight system provide adequate protection of clinical trial subjects while allowing for new drug innovation through the clinical trial process?
  - i. How does India's governance of clinical trials compare to the governance of clinical trials in the United States?
- d. How and to what extent do the industry players protect clinical trial subjects?
  - i. To what extent do international standards provide sufficient guidance for industry players to fulfill their responsibility toward the protection of clinical trial subjects?
  - ii. What challenges do the industry players face in the protection of clinical trial subjects?
  - iii. From the industry players' perspective, what are the possible tradeoffs for maximizing subject protection while promoting innovation, and where is the mutually benefitting balance?

### **3. Methodology**

My thesis deploys a novel combination of two qualitative research approaches: inductive reasoning and game theoretic approach. "Inductive reasoning... is a form of reasoning where the premises seek to supply strong evidence for (but not absolute proof of) the truth of the conclusion... (it) refers to reasoning that takes specific information and makes a broader generalization that is considered probable..." (Preston, 2014). Game theory "is a theory of decision making." Game theory provides a methodology by which one may "...analyze situations of interactive decision making" in "situations involving several decision makers (called players) with different goals, in which the decision of each affects the outcome for all the decision

makers” (Davis, 1983; Maschler, Solan, & Zamir, 2013). Based on these definitions, this thesis starts from the premise that the process of clinical trials requires a number of players to participate in cooperative decision making, which has an impact on the agenda of each player. The main players are the government, the pharmaceutical company (which is often also the sponsor), the ethics committee (also known as the Institutional Review Board or IRB), the contract research organization (CRO), the clinical trial subjects and the civil society.

Using specific information from literature and documentary review, and combining it with concepts pertaining to interactive decision-making that are borrowed from game theory, I develop a conceptual framework to evaluate the governance of clinical trials. The framework is built on basic game theoretic concepts to identify and categorize the nature of uncertainties that these players face during the implementation of clinical trials.

The framework is then validated through case studies of the United States (US) and Indian regulatory oversight of clinical trials, and industry player responsibilities and perception. Existing US and Indian regulations are evaluated using the conceptual framework. This is then followed by empirical studies of the two regulatory oversight systems. The US regulatory oversight system is evaluated using publicly available data regarding the various players’ compliance with regulations for the protection of human subjects of clinical trials. Indian regulatory oversight system is evaluated using data obtained through interviews with experts in the field. The industry player’s responsibilities are evaluated by applying the same framework to the international guidelines for conducting ethical clinical trials. Further, the perception of the industry players with respect to their responsibility toward the protection of human subjects is evaluated using data obtained through interviews of industry representatives. All of this together, is then used toward establishing an understanding of the possible policy and strategy outcomes of each decision maker, and its impact on the overall balance of innovation and welfare.

#### **4. Limitations**

I now define the boundaries of my study, which are also the limitations of the present thesis.

With respect to incorporation of game theory, I note that this thesis does not purport to create a new game theoretic model for the conduct of clinical trials. Rather, it borrows concepts from game theory in order to explore policies and strategies that allow for a balance between novel drug innovation and protection of human subjects of clinical trials. The game theoretic notions used are sequential game and informational constraints, and adverse selection and moral hazard within sequential games. These concepts are used to illustrate the premise that the process of clinical trials can be viewed as a game wherein uncertainties and tensions between the players can pose a risk to clinical trial subjects. Such a representation permits a categorization of the sources of risks in clinical trial processes and solutions that can be proposed for the same.

## **5. Contribution and Structure of the Thesis**

This thesis makes two contributions. First, in terms of economics literature on clinical trials, the novelty of the thesis is the incorporation of game theoretic approach to conceptualize the process of clinical trial governance, and to use it to compare various oversight bodies. The thesis also establishes possible policy and strategy outcomes and their impact on the balance between subject welfare and novel drug innovation. Second, for practitioners, the framework for evaluation of governance of clinical trials developed in this thesis will provide a systemic approach to evaluating governance of clinical trials at each of the three levels: international, national, and institutional levels. Additionally, the game theoretic concepts embedded within the framework will contribute to an understanding of how decision makers develop their policies and strategies in light of plausible outcomes for themselves and for the other players. The remainder of this thesis is structured as detailed below.

In chapter 1, I provide a historical overview of the evolution of clinical trials, and the emergence of ethical standards for the conduct of clinical trials using information provided in literature. I then illustrate the clinical trial process based on the US regulations as a model. The process presented in this chapter will be used throughout the thesis as the clinical trial process under study.

In chapter 2, I present literature and documentary review to identify the existing ethical concerns related to the implementation of clinical trials. Three sources of information are used: current literature, regulatory and guidance documents, and reports by non-profit organizations. The

information obtained is then combined to identify themes that will be used toward the development of the conceptual framework for evaluation of clinical trial governance.

Chapter 3 begins by characterizing the clinical trial process using concepts borrowed from game theory. Then, these characterizations are combined with the themes identified in chapter 2 to develop a framework by which to evaluate clinical trial governance at various levels.

In chapter 4, I first describe the US oversight system, and then evaluate it using the framework developed in chapter 3. I then present an empirical study conducted using publicly available data, combined with the framework, to determine the effectiveness of the US regulatory system in promoting subject welfare while allowing for novel drug innovation.

Chapter 5 begins with a presentation of the Indian regulatory oversight system for the governance of clinical trials. Through an empirical study involving interviews with experts in the field, I then identify the strengths and weaknesses of India as a clinical trial market, and any challenges faced by the Indian oversight system in the governance of clinical trials. Next, I use the conceptual framework developed in chapter 3 to evaluate the Indian regulatory oversight system in terms of its ability to balance subject welfare and novel drug innovation. I then conclude the chapter with a comparison of the US and Indian regulatory oversight systems for the governance of clinical trials.

The first goal of chapter 6 is to establish industry's responsibilities toward protection of human subjects of clinical trials. Through literature and documentary review, it is determined that the industry players are primarily evaluated based on the principles outlined in the international guidelines. Thus, these guidelines are evaluated using the conceptual framework developed in chapter 3 to determine the extent to which these establish industry's responsibility toward subject welfare. Finally, I assess industry's perceptions and efforts with respect to its role in maximizing subject welfare through interviews with industry representatives.

Chapters 4, 5, and 6, provide insights into how the uncertainties faced by the players involved in the clinical trial process can be converted into measurable risks. Chapter 7 thus focuses on establishing possible policies and strategies

for containing these risks. The chapter ends with an evaluation of how each of the possible policies and strategies contribute to the balance between subject welfare and innovation.

Chapter 8 closes the thesis with a summary of conclusions, contributions and recommendations.

## **CHAPTER 1: THE CLINICAL TRIAL PROCESS**

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Clinical trials are designed to test the safety and efficacy of new drugs in humans. Introducing new drugs in humans clearly involves risks to the subjects; however, without exposing subjects to such risks, innovation in medicine and access to new drugs would not be possible. As noted in the introduction to this thesis, clinical trial subjects may be faced with possible physical harm, psychological harm, social harm or economic harm. A balance between the possibility of harm and the possibility of benefit to the subjects must be established in order to proceed with a given trial. To ensure an acceptable balance, the design and conduct of clinical trials, with the intention of bringing a product to market, must necessarily consider four elements (Baram, 2001; Califf et al., 2003):

- (i) The scientific design of the clinical trial must be consistent with sound research design, such that the trial will yield valid data in a most effective manner, which requires adequate scientific review by regulatory agency approving conduct of trial;
- (ii) The proposed procedures do not unnecessarily expose subjects to risk; and potential benefits outweigh the potential risks, which requires adequate ethics committee oversight;
- (iii) The clinical trial must be monitored in order to ensure compliance with applicable regulations and ethical guidelines; and
- (iv) Consequences of non-compliance and rewards for ensuring compliance must be considered.

In this chapter, I explore how the process of clinical trials evolved in developed countries, particularly the United States (US). The chapter starts with a brief description of the main events that shaped the process of clinical trials from the 18<sup>th</sup> to the 20<sup>th</sup> centuries, and then explores the clinical trial process in operation in the US at present. The aim of this chapter is to set the stage for this thesis by providing a historical perspective and an in-depth description of the clinical trial process and its governance.

### **1. Evolution of Clinical Trials**

#### **1.1. Early History**

The emergence of ‘clinical trials’ as a process to test the efficiency of drugs emerged serendipitously. Surgeon Ambroise Pare conducted the first



documented “clinical trial of a novel therapy”, when he treated wounded soldiers with an alternative to standard of care treatment due to the low supply of standard treatment. To his surprise, the alternative treatment was more effective than the standard of care (Bhatt, 2010).

Naval surgeon James Lind took the next evolutionary step toward modern day clinical trials in 1747, when he planned a comparative study of the existing treatments for scurvy. Lind divided twelve sailors suffering from scurvy into 6 groups of two, and assigned each group to a different existing treatment. (Bhatt, 2010). “In Lind's opinion, one reason for the prevailing confusion about the diagnosis, prevention and cure of scurvy was that 'no physician conversant with this disease at sea had undertaken to throw light upon the subject'. He set about filling this gap, with a clear commitment to base his work on 'observable facts' rather than the theories of medical decision-making at that time” (Chalmers, 2003). Lind’s comparison became the first documented “prospective controlled trial”.

In 1946, the Medical Research Council (MRC) of the United Kingdom (UK) planned and implemented the first known double-blind controlled clinical trial of the drug patulin. The trial was designed in response to public pressure to determine whether patulin, a product reportedly discovered by a group of the Royal Navy and expected to be better than penicillin in fighting the common cold, was in fact, more effective. The trials committee appointed by the MRC included physicians as well as biostatisticians, making this a “rigorously controlled trial” (Hart, 1999).

## **1.2. Emergence of Ethical Standards**

Most ethical standards for the conduct of clinical trials emerged as a result of abuses of research subjects through unethical experimentation. The first such code of ethics was delineated in the Nuremburg Code<sup>5</sup>, which was published in 1947 primarily as a result of harmful and often deadly experiments conducted by German physicians on concentration camp prisoners during World War II. It is important to note, however, that unethical experimentation on prisoners during World War II was taking place internationally. For example, in the US, the military sponsored a research project in which prisoners at the Stateville Penitentiary in Illinois “were

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<sup>5</sup> [http://www.jewishvirtuallibrary.org/jsource/Holocaust/Nuremberg\\_Code.html](http://www.jewishvirtuallibrary.org/jsource/Holocaust/Nuremberg_Code.html)

infected with malaria and treated with experimental drugs that sometimes had vicious side effects.” The prisoners were used as “reservoirs for the disease and they provided a food supply for the mosquito cultures” (Comfort, 2009). Following such universal practices, the Nuremberg Code provided an overarching ethical code of conduct, which was later followed by more specific guidelines in the World Medical Association’s (WMA) Declaration of Helsinki<sup>6</sup> issued in 1964. The Declaration of Helsinki was prompted by the WMA Ethics Committee’s discussion of a position paper on human experimentation, which the WMA adopted as its “Resolution on Human Experimentation: Principles for Those in Research and Experimentation” in 1954. Further discussion within the WMA resulted in the first version of the Declaration of Helsinki in 1964. Since then, the Declaration has been revised seven times, with all versions incorporating the “essential feature of... balancing the need to generate useful medical and therapeutic knowledge with the need to protect the health and interests of research participants...” (The Oxford Textbook of Clinical Research Ethics, 2008).

Ethical movement in the US followed primarily as a result of the US Public Health Service Syphilis study. Beginning in 1932 and running for 40 years, the Tuskegee Syphilis Study conducted in Alabama by the US Public Health Service enrolled low-income African-American males infected with syphilis in research without their informed consent. When treatment for syphilis became available, these men did not receive the treatment (Seto, 2001; Tuskegee University, 2011). Established in part due to the Tuskegee Syphilis Study, the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research issued The Belmont Report<sup>7</sup> in 1979.

Thus, ethical standards have emerged from a general acknowledgement of wrongdoings, and aim to establish protocols to prevent these from recurring in the future.

### **1.3. Evolution of Regulatory Oversight of Clinical Trials**

Though ethical codes set standards for the conduct of clinical trials, they do not make adequate provisions for the enforcement of the principles they establish. To do so, the US Food and Drug Administration (FDA) passed its

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<sup>6</sup> <http://www.wma.net/en/30publications/10policies/b3/>

<sup>7</sup> <http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html>

Food, Drug and Cosmetic Act in 1938. The Act required that the FDA review pre-clinical and clinical test results for all new drugs prior to permitting their marketing in the US. However, the Act had its shortcomings. “For example, manufacturers could sell a drug if the FDA didn't act within 60 days to prevent its marketing” (United States Food and Drug Administration, 2012). In 1962, the use of thalidomide to treat morning sickness in pregnant women resulted in devastating birth defects in Europe, Canada and some other countries. Partly in an effort to protect the US from a similar disaster, the US passed the Kefauver-Harris Amendments to the Act, which required that the new drug approvals by the FDA “be based not only upon proof of safety, but also on ‘substantial evidence’ of a drug’s efficacy”. The Amendments were soon followed by the 1963 investigational drug regulations, which introduced procedures for FDA’s “control over investigational new drugs” (Junod, 2013).

For decades, Western Europe and the UK used The Helsinki Declaration, and later the International Conference on Harmonization’s Good Clinical Practice (ICH GCP), as standards for the conduct of clinical trials. It was not until 2001 that the European Union issued its Directive, which outlined, for the first time, “the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use” (The European Parliament, 2001). In response to the Directive, the UK issued The Medicines for Human Use Regulations in 2004<sup>8</sup>. The historical evolution of regulatory oversight of clinical trials is outlined in figure 1 below.

Figure 1: History of Clinical Trials & Related Rules

US: Food, Drug & Cosmetic Act			Nuremberg Code		US: Kefauver-Harris Amendments		US: Investigational Drug Regulations	WMA: The Declaration of Helsinki	US: National Research Act	US: The Belmont Report	ICH: Good Clinical Practice	EU Directive	UK: The Medicines for Human Use Regulations
1747	1938	1946	1947	1962	1963	1964	1974	1979	1996	2001	2004		
James Lind: 1st Controlled CT			MRC, UK: 1st Randomized Controlled CT										

\* Author’s creation

\* Data Source: (Bhatt, 2010; Junod, 2013; McCully, 2011)

<sup>8</sup> <http://www.legislation.gov.uk/ukxi/2004/1031/contents/made>

Although efforts to improve oversight, and thereby minimize ethical problems, have been made, ethical problems continue to occur. In 2006, TeGenero AG conducted a phase I clinical trial to test a superagonist antibody TGN1412 in six healthy volunteers in the UK. The clinical trial was approved by the UK Medicines and Health Products Regulatory Agency (MHRA). Each of the six subjects experienced cytokine release syndrome within one hour of receiving the experimental drug, and all developed multiorgan failure before the end of the day. This tragedy resulted in significant debate amongst the media, the public and the scientific community. As a result, the MHRA and an expert scientific group called upon by the BMJ to conduct investigations into the science and ethics of the trial. The investigations revealed a number of concerns, including the scientific validity of the trial, inappropriate qualification of the physician investigators, lack of insurance protection of the sponsor and failure in arranging for timely medical care. As a result of this case, the MHRA issued new rules for first in man clinical trials of high-risk pharmaceutical compounds, requiring that these be evaluated by an Expert Advisory Group of the Commission on Human medicines prior to approval for conduct of the clinical trial (Attarwala, 2010; Nada & Somberg, 2007).

At present, governments of more than a hundred countries have legislation, regulations and/or guidelines with regards to the protection of human subjects in clinical trials (Office of Human Research Protections, 2011). “The U.S. Food and Drug Administration has evolved as one of the world's foremost institutional authorities for conducting and evaluating controlled clinical drug trials” (Junod, 2013). Clearly, the US had a head-start on the development and implementation of its regulations for the oversight of clinical trials. As noted by Abraham, “The US drug regulatory agency, the FDA, is the best resourced in the world, and is renowned for subjecting the pharmaceutical industry to stringent regulatory checks, because it must operate in a relatively transparent environment dependent on considerable legislative oversight by Congress and judicial review in the courts” (2002). As such, for the purpose of this research, the US drug development and approval process will be used as representative of the drug development process in traditional markets, namely the US and Western Europe.

## **2. Clinical Trial as a Process**

### **2.1. Drug Development Process In Advance of a Clinical Trial**

Though the focus of this thesis is the clinical trial process, there are many steps involved in the pre-clinical trial stages of the drug development process. This section provides an overview of the pre-clinical trial processes in an effort to establish baseline understanding of where the clinical trials enter into the drug development process. A new drug development process starts in the laboratory with initial drug development. Once the drug is ready to be tested, the first set of tests is conducted in animal studies, with the intent to determine whether the drug is safe for testing in humans. Animal models are also used for modeling proof of concept or proof of principle studies to establish early evidence of efficacy. At the end of animal testing, the drug developing entity submits an Investigational New Drug application to the government for approval to test the drug in humans. This coincides with the review and approval of the proposed human testing by an Institutional Review Board (IRB), also known as the Ethics Committee (EC) in some countries.

### **2.2. Phases of Clinical Trials**

For the purpose of this thesis, a clinical trial is defined as the use of an investigational drug in an experiment and outside of medical practice, and involving one or more human subjects<sup>9</sup>. Clinical trials are generally conducted in four phases. Phase I clinical trials usually consist of tests on a small group (20-80 volunteers) of human subjects to determine the safety of the drug in terms of most common side effects and metabolism in humans. Phase I is most often conducted on healthy volunteers. Phase I clinical trial is considered successful if the level of toxicity is considered acceptable. Between phase I and phase II, proof of principle studies are sometimes conducted on humans to obtain additional evidence of efficacy before moving to phase II. At this point, a phase II clinical trial may commence, following appropriate IRB/EC approval. Phase I and Phase II trials may also aim to find the optimal dosage. Phase II clinical trials are performed on larger groups (up to about 300 subjects) and are designed to assess the efficacy of

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<sup>9</sup> This definition is loosely based on US FDA's definition of a clinical investigation in 21 CFR 312.3:

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.3>

the drug in humans. Phase II clinical trials often involve comparison of the experimental drug to either a placebo (an inactive substance) or another drug. If phase II concludes with a positive evidence of the drug's effectiveness, the phase III trial may commence. In phase III, the goal is to further evaluate the safety and efficacy of the drug in 300 to 3,000 or more subjects, primarily those individuals with conditions for which the drug is being tested. This is achieved by testing the drug in different populations; testing varying dosages of the drug; and possibly using it in combination with other drugs. Additionally, phase III clinical trials are often conducted in multiple sites. Phase IV clinical trials take place after a drug has been approved for marketing, and aim to obtain additional data "about a drug's safety, efficacy or optimal use" (United States National Institutes of Health, 2012).

Upon successful completion of phase III clinical trials, the pharmaceutical company may submit a New Drug Application (NDA), approval of which would result in permission to bring the drug to market. The NDA review process involves review of animal and human testing data by a team of experts; review of proposed information to be placed on the drug labels; and inspection of the facilities where the drug will be manufactured.

### **2.3. Clinical Trial Processes**

For the purpose of this research, the clinical trial process has been divided into three stages: i) pre-trial process, referring to the procedures that must be implemented prior to starting the main trial procedures on the research subjects; ii) events occurring during the trial; and iii) end of trial effects on subjects and their society.

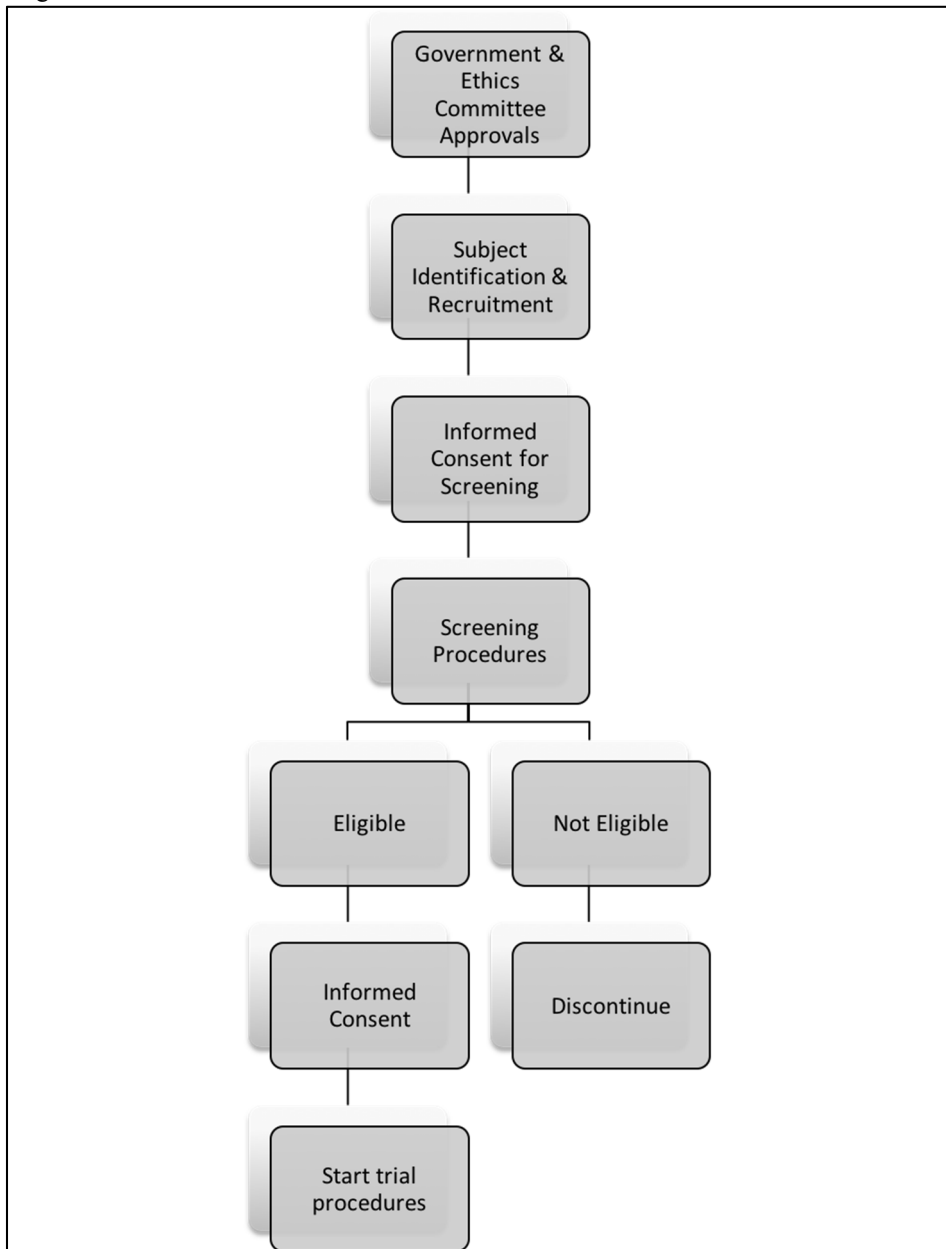
#### **Pre-Trial**

A number of steps, outlined in figure 2 below, must be taken before a human subject is given an investigational drug. Prior to initiating a new clinical trial, the pharmaceutical sponsor and/or the research team must obtain both government and IRB/EC approvals. Once these have been granted, the pharmaceutical company and the Contract Research Organization (CRO) may start implementing their approved protocol. CRO is "a person (or an entity) that assumes, as an independent contractor with the sponsor, one or more of the obligations of a sponsor, e.g., design of a protocol, selection or monitoring of investigations, evaluation of reports, and preparation of

materials to be submitted” for regulatory approval (United States Food and Drug Administration, 1987).

Once both regulatory and ethics approvals have been granted, the research sponsor and team begin the clinical trial process with subject identification and recruitment procedures. This involves following the IRB/EC approved protocol for identifying subjects who may meet the inclusion and exclusion criteria for the trial. Once identified, the potential subjects are recruited using the recruitment procedures approved by the IRB/EC. Depending on the nature of the trial, these procedures may range from widespread advertising using flyers, posters, and media advertisements to targeted recruitment from a given pool of patients using direct contact or physician referral. The clinical trial may or may not require screening procedures to ensure subject eligibility to participate in the trial. Screening activities may include, but are not limited to, medical records review, diagnostic tests, or survey questions. Before such screening procedures may take place, the researchers are expected to obtain informed consent from the subjects for participation in the screening procedures. Subjects who are deemed eligible at the end of the screening process undergo an informed consent process for their participation in the main clinical trial procedures. Once this consent is obtained, the subject may begin participating in the clinical trial.

Figure 2: Illustration of the Pre-Trial Process



\*Author's creation using US FDA process as a model



## Events during a trial

Once a clinical trial is initiated, it must be monitored for adherence to the approved protocol, subject safety, adverse events and unanticipated problems. During the course of the clinical trial, adverse events or unanticipated problems may occur.

Adverse events are

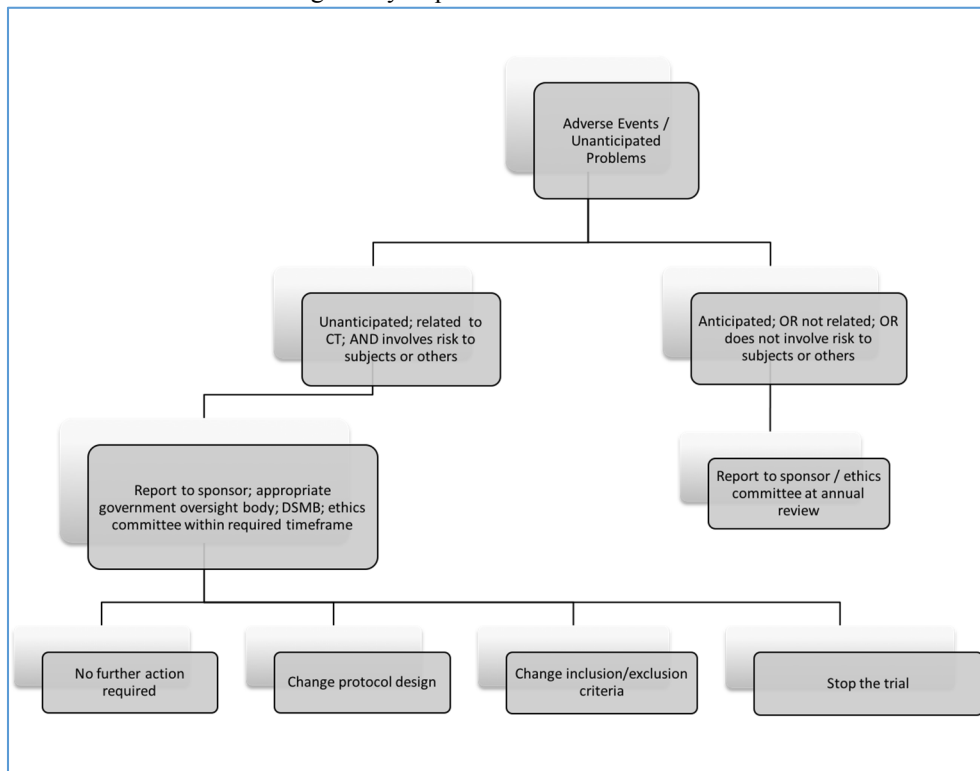
*Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research (United States Department of Health and Human Services, 2007).*

Unanticipated problems are:

*...any incident, experience, or outcome that meets all of the following criteria: (1) unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved [ethics committee approved] research protocol and informed consent document; and (b) the characteristics of the subject population being studied; (2) related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and (3) suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized (United States Department of Health and Human Services, 2007).*

An important aspect of conducting a clinical trial is monitoring adverse events and unanticipated problems, analyzing these and taking appropriate actions, where necessary, to address recurring or serious adverse events and unanticipated problems. Researchers are required to report any adverse events or unanticipated problems that, in the opinion of the researcher, are related or possibly related to the trial, are unanticipated and “suggest that the trial places subjects or others at a greater risk of harm than was previously known or recognized” to relevant regulatory oversight bodies, ethics committees and data safety monitoring boards (DSMB), if any, within a required timeframe. Depending on the type, frequency and/or severity of adverse events and/or unanticipated problems, researchers, oversight bodies, ethics committees and/or sponsor may decide to stop the trial, change the trial design, change the inclusion/exclusion criteria or take no action. A decision model based on the US regulatory requirements is provided in figure 3 below.

Figure 3: Decision model for managing adverse events and unanticipated problems during clinical trials based on US regulatory requirements



\* Author's creation using information from US FDA & OHRP regulations

## End of Trial

At the conclusion of a trial, the data indicates one of the following: i) overall positive effects that outweigh the adverse effects in the experimental group; ii) negative effects in the experimental group; or iii) no effect in the experimental group. The conclusions are used to determine whether i) to continue to the next stage in the clinical trial process; ii) apply for a new drug application; or iii) discontinue the clinical trial process. Another important decision to be made at the end of a clinical trial is whether and how to taper subjects off of the experimental drug, and if not, how to continue providing the experimental drug to the subjects.

The process described in this chapter will thus be used as the clinical trial process under study for the remaining of this thesis.

## **CHAPTER 2: LITERATURE AND DOCUMENTARY REVIEW OF ETHICAL CONCERNS ASSOCIATED WITH CLINICAL TRIALS**

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The primary goal of this literature and documentary review is to identify existing ethical concerns related to the implementation of clinical trials. As previously noted, by ethical concerns, I refer to the concerns associated with inadequate protection of human subjects of clinical trials and the possibility of an unacceptable balance of harm to subjects versus benefit to the subjects. For the purpose of this review, I intentionally conducted a search for clinical trial ethics in general, rather than a narrower more focused search. This was done in an effort to obtain a broad perspective on what issues are being considered as related to clinical trial ethics. It is important to note that ethical concerns and considerations arise throughout the life of a clinical trial, starting with its conceptual inception and clinical trial design, through its implementation and conduct and ending with the reporting of clinical trial results. This thesis is focused on maximizing subject welfare during the conduct of clinical trials, while promoting innovation. Thus, the broad search will then be narrowed to identify the ethical concerns most relevant to this thesis, which are those associated with the implementation of clinical trials and related to the protection of human subjects of clinical trials from any harm. The systematic literature and documentary review presented in this chapter is, therefore, focused on these two specific areas. The relevant results from the literature and documentary review will be categorized into themes to be used in Chapter 3 to develop a conceptual framework for identification of ethical uncertainties in the implementation of clinical trials.

### **1. Literature Review Parameters**

The literature review was conducted using the database Scopus. The search criterion used was “clinical trial ethics” limited to publications from 2000 to present. The search criterion was intentionally kept broad in an effort to capture as many publications related to the ethics of clinical trials as possible. The time frame was limited to begin in the year 2000 in an effort to ensure a relatively current perspective. The search revealed a total of 11,850 results.

First, these results were further narrowed to those with a minimum of 25 citations to identify those with the most impact. This resulted in a total of 1320 results. Next, to ensure that important results from more recent publications were not excluded and to highlight the more current dialogue, I narrowed the search results to 2015-2016 time frame, and incorporated all

<b>Theme</b>	<b>Percentage of total excluded publications</b>	<b>Number of excluded publications</b>
Academic freedom	0.08%	1
Ancillary care	0.08%	1
Animal research	0.34%	4
Authorship	0.51%	6
Clinical practice	6.57%	78
Clinical research*	36.48%	433
Clinical trial*	7.75%	92
Clinical trial – design*	11.54%	137
Clinical trial – economic evaluation	0.08%	1
Clinical trial – history	0.17%	2
Clinical trial – registration	0.84%	10
Clinical trial – reporting*	4.47%	53
Clinical trial – reporting results to subjects*	0.67%	8
Clinical trial – scientific implications of stopping early*	0.67%	8
Clinical trial – treatment of extraneous conditions	0.08%	1
Complementary / alternative medicine	0.34%	4
Data ownership / data sharing	0.08%	1
End of life decision-making and care	1.68%	20
Equipoise*	1.26%	15
Genetic research	3.79%	45
Globalization trends	0.25%	3
Health services research	0.17%	2
Infrastructure	0.84%	10
In vitro fertilization	0.17%	2
Medical education	0.17%	2
Medical ethics	0.17%	2
Medical photography	0.08%	1
Medical travel	0.08%	1
Nanomedicine	0.17%	2

Not related to clinical trial, clinical research or practice	1.35%	16
Orphan drugs	0.08%	1
Palliative care	0.34%	4
Placebo*	4.63%	55
Policy*	4.38%	52
Public health research	0.93%	11
Responsible conduct of research / research misconduct	0.51%	6
Relationships*	0.59%	7
Repositories (data or specimen)	0.84%	10
Retractions	0.17%	2
Risk / benefit analysis*	0.76%	9
Social behavioral research*	3.12%	37
Stem cell research	2.70%	32

results, regardless of the number of citations. This category includes a total of 779 results. Thus, the final total number of publications reviewed was 2,099.

### 1.1. Excluded Publications

The literature search described in section 1 above resulted in the identification of a number of themes. The first step in identifying the articles that are relevant to the development of the framework for the identification of ethical uncertainties associated with the conduct of clinical trials was to identify all articles that can be excluded. 90% of the 1320 results from the first category of results being considered were determined to be irrelevant to the search at hand. These excluded themes are outlined in table 1 below. Justification for exclusion of themes whose exclusion is not self-evident is then provided.

Table 1: Resultant Publications Not Relevant to Current Research – 2000-2016 with 25 or more citations

\* Justification provided for these themes, as their exclusion may not be self-evident

93% of the 779 results from the second category of results being considered were determined to be irrelevant to the search at hand. These excluded

themes are outlined in table 2 below. Justification for exclusion of themes whose exclusion is not self-evident is then provided.

Table 2: Resultant Publications Not Relevant to Current Research – 2015-2016

<b>Theme</b>	<b>Percentage of total excluded publications</b>	<b>Number of excluded publications</b>
Animal research	0.69%	5
Clinical practice	2.77%	20
Clinical research*	39.67%	286
Clinical trial*	11.10%	80
Clinical trial – crowdfunding	0.28%	2
Clinical trial – design*	9.99%	72
Clinical trial – economic evaluation	0.14%	1
Clinical trial – history	0.55%	4
Clinical trial – registration	0.42%	3
Clinical trial – reporting*	3.05%	22
Clinical trial – scientific implications of stopping early*	0.28%	2
Complementary / alternative medicine	1.80%	13
Dual use research of concern	0.14%	1
End of life decision-making and care	0.28%	2
Equipoise*	0.69%	5
Ethical violation report	0.28%	2
Genetic research	1.94%	14
Globalization – exploitation	0.83%	6

Globalization trends	0.14%	1
Infrastructure	0.69%	5
Nanomedicine	0.14%	1
Non-English article	0.14%	1
Not related to clinical trial, clinical research or practice	3.74%	27
Palliative care	0.14%	1
Personalized medicine	0.28%	2
Placebo*	1.53%	11
Policy*	11.37%	82
Public health research	2.36%	17
Responsible conduct of research / research misconduct	0.28%	2
Repositories (data or specimen)	0.14%	1
Risk / benefit analysis*	0.97%	7
Social behavioral research*	1.66%	12
Stem cell research	1.53	11

\* Justification provided for these themes, as their exclusion may not be self-evident



### **1.1.1. Exclusion: Clinical Research**

Literature categorized as *clinical research* comprises of articles resulting from research related to clinical care that does not involve the use of any investigational products, such as investigational drugs, devices or biologics. In this category, I have included publications based on the following: outcomes of specific clinical research, including those of observational studies, surgical research, regenerative medicine research and transplantation research; aspects of ethics of clinical research not relevant to clinical trials; and design of clinical research. Given that these publications did not relate to clinical trial ethics, these were excluded from further evaluation.

### **1.1.2. Exclusion: Clinical Trial**

Literature categorized as *clinical trial* are publications delineating the protocols and outcomes of specific clinical trials. As these are scientific results of particular clinical trials that were conducted, and not discussions regarding the ethical conduct of said trials, these publications were excluded from further analysis.

### **1.1.3. Exclusion: Clinical Trial – Design**

Literature in this category focuses on the scientific design of clinical trials, including publications related to: identification of best methodology; evaluation and comparison of clinical trial design, including randomization strategies; protocol development; strategies for ensuring subject compliance with trial requirements, such as methods for ensuring subjects take the correct dose of an experimental drug at the right times; and effective recruitment strategies. Since the primary focus of these articles is the scientific design of the clinical trial, and not its ethics, these were excluded from further evaluation.

### **1.1.4. Exclusion: Clinical Trial – Reporting**

Literatures categorized as *clinical trial – reporting* includes publications related to the following topics: integrity in reporting research results; requirements of journal editors for publication resulting from clinical trials; bias in reporting clinical trial results, including sponsor input in reporting the clinical trial results; validity of media reports; and transparency of data. Since the focus of this thesis is the ethical uncertainties that exist during the

conduct of the trial, literature related to reporting the results of trials is excluded from further evaluation.

#### **1.1.5. Exclusion: Clinical Trial – Reporting Results to Subjects**

Practitioners often debate the ethics of whether to reveal results of medical tests conducted as part of a clinical trial to the subjects, particularly if the medical test in question itself is experimental. Literature in this category focuses on this debate. At the center of this debate is the question of scientific validity of these results, or clinical care implications and related emotional implications of revealing inaccurate or minimally significant results. Thus, scientific and/or clinical care concerns are at the heart of this debate, and as such these publications are not directly related to the ethical conduct of clinical trials. These publications are therefore excluded from further examination.

#### **1.1.6. Exclusion: Clinical Trial – Scientific Implications of Stopping Early**

Literature in this category discusses the scientific implications of stopping a clinical trial early, whether it be because early stopping rules related to safety of clinical trial subjects are met, or because of overwhelmingly favorable interim results. Though the causes of stopping early may have ethical implications, the literature placed in this category focusses on scientific reasons for not stopping trials early, and not on the ethical considerations. As such, these were excluded from further analysis.

#### **1.1.7. Exclusion: Equipoise**

Equipoise is a state of genuine uncertainty on the part of the clinical investigator regarding the comparative therapeutic merits of each arm in a trial. Should the investigator discover that one treatment is of superior therapeutic merit, he or she is ethically obliged to offer that treatment (Benjamin Freedman, 1987). However, there has been ongoing debate regarding whether equipoise is a realistic expectation. Whereas the concept of equipoise assumes that the clinical trial is an alternate form of therapy, and thus the idea of equipoise itself blurs the line between research and treatment (F. G. Miller & Brody, 2003), it is also difficult to presume that an investigator has no preference for present or experimental treatment throughout the life of the trial. One proposed resolution is to rely on the

views of the medical community with expertise in the field of medicine at hand (B. Freedman, 1987).

Thus, the ethical dilemma of equipoise focuses on the need for an investigator to have no preference amongst the various treatment arms being tested in a clinical trial. Publications placed in this category focus on either the need for clinical equipoise, or on the discussion about idealistic rather than pragmatic views concerning equipoise. From the debate, we can ascertain that the ethical issue pertaining to the conduct of a clinical trial that is truly at hand is that the clinical investigator's bias toward one treatment arm may cause therapeutic misconception on the part of the clinical trial subjects. Thus, equipoise as a theme is being excluded from further evaluation; however, therapeutic misconception will be included.

#### **1.1.8. Exclusion: Placebo**

Literature placed in this category relates to the ethics or effectiveness of using a placebo, whether in the form of a medicine or as sham surgery. Since the decision on whether to use placebo in a given clinical trial is related to the design of a clinical trial with implications on the scientific validity of the trial, and since this decision is made prior to the implementation of a clinical trial, which is the focus of this thesis, literature on the ethics of using a placebo was excluded from this evaluation.

#### **1.1.9. Exclusion: Policy**

Literature placed in this category covered the following themes: i) adequate data collection for policy purposes; ii) establishing the need for governance of clinical trials; iii) conflicting roles of the IRB/EC as a body responsible for both promotion of research and protection of research subjects; iv) IRB infrastructure; v) lack of efficiencies due to requirements for multiple IRB/EC reviews in multicenter trials; vi) variations in IRB/EC reviews; vii) policies related to public health; viii) presentation of actual statements of policy; ix) discussion on regulations as a barrier to clinical trials; and x) regulatory evolution in various countries.

#### **1.1.10. Exclusion: Relationships**

Literature placed in this category discusses the relationships amongst the various players involved in the design and conduct of clinical trials. I will return to these publications in later chapters as I discuss the players involved

in the clinical trial process. However, these are not relevant to the actual identification of ethical uncertainties associated with the conduct of clinical trials, and therefore to the development of the theoretical framework, which is the goal of this literature review.

#### **1.1.11. Exclusion: Risk / Benefit Analysis**

Literature placed in this category concentrates on the risk/benefit analysis of individual clinical trials. This is perhaps one of the key scientific and ethical considerations in *designing* a clinical trial, as each clinical trial should be designed to ensure a favorable risk/benefit ratio. (Council for International Organizations of Medical Sciences (CIOMS), 2002; The European Parliament, 2001; United States Department of Health and Human Services, 1991, amended 2009; World Medical Association, 1964). The focus of this thesis, however, is the implementation of clinical trials, and the ethical uncertainties that arise during the conduct of the trial, assuming that a favorable overall risk/benefit ratio has been established.

#### **1.1.12. Exclusion: Social Behavioral and Humanities Research**

Literature placed in this category was related to social behavioral or humanities research, and not clinical trials. These publications address physician and patient perspectives and attitudes towards research in general, differences in perceptions of different populations and public responsibility to partake in clinical trials. I also include perspectives, editorials and commentaries that do not directly address clinical trial ethics within this category.

### **1.2. Resulting Themes**

I now take the remaining 9% of the articles identified through the search discussed in section 1 above, and categorize them into 9 themes. In this section, I will provide an overview of these themes, as they are discussed in current literature.

#### **1.2.1. Theme 1: Consideration of Available Alternatives**

Only one article that resulted from this search discusses available alternatives. The question raised in the article is whether to consider a treatment available if it is available in a developed country but not in the developing country where the trial may be being conducted. Ultimately, the

author concludes that the most important consideration is that the subject has made a decision based on his/her own preference and desire to contribute to the common good (Veatch, 2002).

### **1.2.2. Theme 2: Coercion**

This search resulted in only one article related to coercion. The article identified coercion as the primary ethical concern associated with phase 1 pediatric oncology clinical trials, given the unrealistic hope for benefit in such trials. The article was aimed at identifying ethical concerns through surveys, and does not provide any possible mechanisms for overcoming this concern (Estlin, Cotterill, Pratt, Pearson, & Bernstein, 2000).

### **1.2.3. Theme 3: Conflicts of Interest**

Three types of conflicts of interest are identified in the literature. The first is the interest of an investigator with a “financial stake in the outcome of the trial”. This type of potential conflict may be present when the investigator serves as a paid consultant to the pharmaceutical company, serves on the advisory board of the pharmaceutical company or has equity interest in the pharmaceutical company (Angell, 2008; Drazen & Koski, 2000; Lemmens, 2004). A second type of conflict of interest exists due to the pharmaceutical company’s profit maximizing agenda, whereby the company may skew the results of the clinical trials, or choose to have more control over the conduct of the trial (Angell, 2008; Rutherford & Johnston, 2000). The final type of conflict identified in literature is associated with the introduction of for-profit contract research organizations (CROs). Given the profit-maximizing agenda of the CROs, their financial interests may be in conflict with the interest of the subjects, or even with strict adherence to the approved protocol (Lemmens, 2004).

Some mechanisms for managing conflicts have been proposed in literature. These include: i) careful review of the contract between the sponsor and the clinical investigator and their advisor; ii) careful examination of the clinical trial protocol by the investigator; iii) careful review by an institutional review board (IRB); iv) inclusion of an “appropriately constituted data-monitoring committee”; v) full disclosure of adverse events (Rutherford & Johnston, 2000); vi) oversight by drug regulatory agencies (Lemmens, 2004); and disclosures of conflicts of interest (Doucet & Sismondo, 2008; Kim, Millard,

Nisbet, Cox, & Caine, 2004; Lo, Wolf, & Berkeley, 2000; Karine Morin et al., 2002; Sollitto et al., 2003).

However, there have been concerns raised about the effectiveness of these mechanisms. There is concern regarding the conflict of interest embedded in the ethics committee or IRB system. The system relies heavily on two types of ethics committee and/or IRBs: committees affiliated with the institution conducting the trial; and for-profit IRBs. There is a clear conflict when committees are affiliated with the clinical trial site, and have an interest in the successful conduct of the trial; as well, there is a clear profit maximizing agenda of the for profit IRBs. Additionally, oversight by regulatory agencies is not an effective way to address conflict of interest issues, since the regulatory agencies are not engaged in the actual conduct of the trial, and themselves rely on the sponsors, CROs and the ethics committees (Lemmens, 2004). Finally, with respect to disclosure of conflicts of interest to the subjects themselves raises concerns of managing the conflict through the decision making of the weakest party involved. Given the amount of information the potential subjects are expected to process during the informed consent process, they may not be able to truly comprehend the implications of such conflicts (Hampson et al., 2006).

Big picture solutions to conflicts of interest proposed in literature include: radical solutions such as the creation of an “Institute for Prescription Drug Trials” “that would fund and oversee the conduct of all clinical trials (Doucet & Sismondo, 2008); and more collaborative solutions “based on an understanding of the interactions between the various regulatory regimes and of their respective strengths and weaknesses” (Lemmens, 2004).

#### **1.2.4. Theme 4: Compensation for Injury**

This search resulted in only one article related to compensation for injury. The article highlights the complexity of this issue. If compensation for injury were being considered, one must also consider the “extent and duration” for which compensation will be provided, and there must be agreement on the party responsible for providing the compensation. The article does not provide recommendations for addressing this issue (Steinbrook, 2006).

### **1.2.5. Theme 5: End of Trial Care**

Providing best-proven treatment to clinical trial subjects at the end of their participation in a clinical trial seems ethically reasonable. However, the challenge resides in the practical implementation of this ethical expectation. First, there must be agreement on whether the experimental treatment has, in fact, proven beneficial. Who decides this? Second, there must be regulatory mechanisms available through which the experimental treatment can be provided to subject(s) for whom it proved beneficial. Third, the duration for which the experimental treatment will be provided must be established, and in doing so the probability and accessibility of the experimental drug eventually being available within the subject(s) market must be considered. Thus, all parties involved in the conduct of the clinical trial must “engage in good faith negotiations” to decide on the best course with respect to end of trial care (Grady, 2013).

### **1.2.6. Theme 6: Informed Consent**

Majority of the literature identified as relevant to this review was related to the topic of informed consent. Literature establishes that consent must be voluntary, i.e. “without being under the controlling influence of another person or condition”. As such, voluntary informed consent must be free from coercion (Nelson et al., 2011). Voluntariness further requires that subjects be given “adequate information on which to make a decision” and “they must also be able to understand that information” (Ferguson, 2002). It has also been recognized that the consent process and/or document have their shortcomings. In particular, subjects are provided with information that is too technical for them to understand (Ferguson, 2002; Stead, Eadie, Gordon, & Angus, 2005), and comprehension of study information varies among participants in both developed and developing countries. Further, comprehension of randomization and placebo controlled designs is poorer than comprehension of other aspects of trials in both settings (Mandava, Pace, Campbell, Emanuel, & Grady, 2012). One difference between the potential subjects in the developed countries versus the developing countries is that those in the developing countries are less likely to refuse or withdraw participation (Mandava et al., 2012).

Literature also established the need for cultural considerations in developing the strategy for informed consent process. The role, if any, of the subject population’s community and extended family must be taken into

consideration, as should the possibility of deference to authority in certain communities (DeCosta et al., 2004; Doumbo, 2005).

Literature also raises concern related to each individual party's perception of informed consent. Some research has demonstrated that an investigator is more likely than the subjects to perceive that various elements of informed consent have been discussed (Cox, Fallowfield, & Jenkins, 2006). Subject motivation for participation in a clinical trial also affects the informed consent process. For example, subjects may be motivated by access to medicines to which they otherwise would not have access, or in phase 1 oncology trials, subjects who have failed all available treatments may be motivated by a hope for cure (Rothmier, Lasley, & Shapiro, 2003; Schutta & Burnett, 2000).

Proposed strategies for improving the informed consent process include: i) more in-depth interactions or discussions with nurses (Cox et al., 2006; Dunn & Jeste, 2001); ii) "educational intervention" provided through tools such as booklets, computer aided presentations and video clips (Agre & Rapkin, 2003; Cox et al., 2006; Dunn & Jeste, 2001; Dunn et al., 2002; Dunn, Lindamer, Palmer, Schneiderman, & Jeste, 2001; Ellis, Butow, & Tattersall, 2002); iii) direct observation of the informed consent process (Cox et al., 2006); iv) focusing on the quality of the communication, both verbal and written, including "clarity of the information provided and disclosure of controversial information" (R. Brown, Butow, Boyle, & Tattersall, 2007; R. Brown, Butow, Butt, Moore, & Tattersall, 2004; R. Brown, Butow, Ellis, Boyle, & Tattersall, 2004; Jefford & Moore, 2008; Stead et al., 2005); v) "empowerment of participants through Community Advisory Boards and other advocacy bodies that can support individual decision-making (Lindegger & Richter, 2000); vi) cultural considerations, including consideration of the individual versus the community and literacy levels (Mystakidou, Panagiotou, Katsaragakis, Tsilika, & Parpa, 2009); and vii) measuring subject understanding through informed consent questionnaires and introducing similar tools to assess subject's capacity to consent (Barrett, 2005; Joffe, Cook, Cleary, Clark, & Weeks, 2001; Karlawish, Casarett, & James, 2002).

### **1.2.7. Theme 7: Monitoring of Clinical Trials**

Literature identifies various players involved in monitoring clinical trial. These include ethics committees, Data and Safety Monitoring Committees



(DMCs), investigators, research staff, research site, sponsors and regulators. It is observed in literature that though the components required for effective monitoring and adverse event management exist in the current adverse event monitoring and reporting systems, there is duplication of effort and lack of harmony in the management of adverse events. Thus, there is a need for an integrated approach across all players (Califf et al., 2003; Eckstein, 2015). It is also noted that there is a need for training and education of researchers with respect to monitoring (Zeng, Liu, Pan, Zeng, & Wang, 2015).

### **1.2.8. Theme 8: Payment for Participation**

The primary concern associated with payment for participation is the possibility of undue influence on potential subject's decision to participate in the clinical trial. However, there are counter arguments, specifically that cognizant individuals may still be able to make informed decisions for themselves, and that money may not solely be as influential as the possibility of access to medicine (Grady, 2001, 2005). There has been some empirical research on the possibility of payment for participation to pose undue influence, which shows that though high amount of payment may motivate individuals to participate in a trial, there is no evidence of "commonly used payment levels" presenting undue influence (Halpern, Karlawish, Casarett, Berlin, & Asch, 2004). Suggested mechanisms for minimizing the possibility of undue influence identified in literature include an effective IRB review and adequate informed consent (Grady, 2005; Tishler & Bartholomae, 2002).

### **1.2.9. Theme 9: Therapeutic Misconception**

Therapeutic misconception occurs when there is a lack of comprehension regarding the true purpose of a clinical trial, i.e. when an individual does not understand that the reason for a subject's participation in a clinical trial is to contribute to knowledge and not to personally benefit or treat them (Henderson et al., 2007). Empirical research shows that therapeutic misconception is "widespread", with "less than a college degree" and "income less than \$60,000" being significant contributing factors (Pentz et al., 2012). Patients with less education or worse cognitive functioning manifest higher levels of therapeutic misconception (Dunn & Jeste, 2001).

Proposed strategies for minimizing therapeutic misconception are similar to those of improving informed consent: i) clearly distinguishing between research and clinical care during the informed consent process; ii) computer

aided presentations; iii) educational initiatives; iv) clear communication; v) testing subject's comprehension (Dresser, 2002; Dunn et al., 2001; Glannon, 2006; Horng & Grady, 2003; Franklin G Miller & Joffe, 2006, 2008).

## **2. Documentary Review: Regulations and Guidelines**

Review of regulations and guidelines related to the protection of human subjects of clinical trials and the ethical conduct of clinical trials was conducted through the review of a diverse set of regulations and guidelines. These include:

- a. United States Department of Health and Human Services Office for Human Research Protections regulations at 45 CFR 46<sup>10</sup>
- b. United States Food and Drug Administration regulations at 21 CFR 50<sup>11</sup> & 56<sup>12</sup>
- c. The World Medical Association's Declaration of Helsinki (World Medical Association, 1964)
- d. Directive 2001/20/EC of The European Parliament and of The Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (The European Parliament, 2001)
- e. Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences (CIOMS), 2002)
- f. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice Guidelines (GCP) (ICH Expert Working Group, 1996)
- g. Indian Council of Medical Research Ethical Guidelines for Biomedical Research on Human Participants (Indian Council of Medical Research, 2006)

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<sup>10</sup> <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html>

<sup>11</sup> <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=50>

<sup>12</sup> <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=56>

Table 3 below shows which of the ethical issues identified in literature review are addressed in each of the regulations and guidelines (a-g) identified above.

Table 3: Literature based inclusion criteria in regulations & guidelines (a-g)

	<b>a</b>	<b>b</b>	<b>c</b>	<b>d</b>	<b>e</b>	<b>f</b>	<b>g</b>
Alternatives	√*	√*			√*	√*	√*
Coercion	√	√			√	√	√
Conflicts of interest	√**	√**	√		√		√
Compensation for injury	√*	√*	√	√	√	√*	√
End of trial care			√		√*		√
Informed consent	√	√	√	√	√	√	√
Monitoring	√	√	√	√		√	√
Payment for participation	√*	√*	√		√*	√*	√
Therapeutic misconception							
Undue influence	√	√			√	√	√
Other (in addition to those in literature)	√+	√+	√++	√#	√++	√++	√++

\* only in terms of disclosure in informed consent

\*\* only the conflict of interest of IRB members

+ equitable subject selection; informing subjects of cost of participation; informing subjects of any treatment for injury; privacy of subjects; confidentiality of data

++ privacy of subjects; confidentiality of data; ensure treatment for injury

# privacy of subjects; confidentiality of data

Other than therapeutic misconception, each of the themes identified through literature search also appear in the regulatory and guidance documents reviewed. In addition to these, the regulatory and guidance documents raise several areas of protection of human subjects that were not identified in literature. These include: i) equitable subject selection; ii) cost of participation; iii) treatment for injury; iv) privacy of subjects; and v) confidentiality of subject data. Since strategies for subject selection are a trial design issue, and not directly involved in the implementation of a clinical trial, equitable subject selection will be excluded from the final included themes used in the development of a framework in chapter 3. Cost of subject participation is only addressed within these documents in terms of informing the subjects of any costs they may bear. However, whether subjects should bear any cost of participation in a clinical trial is not addressed. Treatment for injury is expected to be provided in several of the unenforceable guidance documents. The only regulatory requirement is that of informing subjects of whether treatment for injury will be provided. Several of the documents indicate that there ought to be measures in place to protect subject privacy and confidentiality of subject data.

### **3. Documentary Review: Reports**

Two sources of reports related to the ethics of conducting clinical trials were reviewed:

- The Access to Medicines Index 2014 sub-section on clinical trial conduct and data transparency<sup>13</sup>
- Clinical trial publications by the Centre for Research on Multinational Corporations (SOMO)<sup>14</sup>

#### **3.1. The Access to Medicines Index**

The Access to Medicines Index “ranks pharmaceutical companies’ efforts to improve access to medicine in developing countries.” It does this by using “a weighted analytical framework to consistently capture and compare data from the top 20 research-based pharmaceutical companies across a set of countries, diseases, and product types.” One of the areas measured by the

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<sup>13</sup> <http://www.accesstomedicineindex.org/ranking>

<sup>14</sup> <http://www.somo.nl/>

index is research and development, and within this area, the index analyzes clinical trial conduct and transparency. With respect to the ethical conduct of clinical trials, the Index measures compliance with the Declaration of Helsinki and ICH GCP. Additionally, it considers monitoring of clinical trials by the pharmaceutical companies. Overall, the 2014 Index found that: i) there is increased effort by the industry with respect to monitoring to ensure compliance with ICH GCP and incorporating concepts from the Declaration of Helsinki into their codes of conduct; and ii) though pharmaceutical companies express a commitment to providing end of trial care when it proves to be beneficial, there is no evidence that the companies actually provided such care (Access to Medicine Foundation, 2012b). The index does not identify any new themes to be added to this literature and documentary review.

### **3.2. Reports by the Centre for Research on Multinational Companies (SOMO)**

SOMO “investigates multinational corporations and the consequences of their activities for people and the environment around the world.” For the purpose of this review, I went to their database of publications<sup>15</sup> and ran a search for “clinical trials”. The search resulted in a total of 7 reports. One of the reports is not included in this review, as its purpose is to provide “a detailed understanding of the research system in Kenya” (Patel, 2006). In terms of the ethical conduct of clinical trials, the reports raise concerns regarding: inadequate informed consent; coercion and/or undue influence in recruiting vulnerable populations; “insufficient arrangements for post-trial treatment access”; inadequate monitoring and insufficient response to concerns raised as part of trial monitoring; conflicts of interests; compensation for injury (Agostini Balbinot et al.; I Schipper & Colona, 2014; Irene Schipper & Weyzig, 2008; Srinivasan, 2009; Weyzig & Schipper, 2008).

Though the reports identify the ethical issues of concern, they do not provide any recommendations for addressing these individual issues. Recommendations for ensuring that complete information is reviewed during the drug approval process, transparency by both regulators and sponsors, and for improving enforcement of regulations through consequences such as

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<sup>15</sup> <http://www.somo.nl/publications-en>

penalties and sanctions are provided (Irene Schipper, 2009; Irene Schipper & Weyzig, 2008).

#### **4. Conclusion**

To summarize, the ethical concerns associated with the implementation of clinical trials, as identified through the above literature review are:

- i. Consideration of available alternatives
- ii. Undue influence including coercion
- iii. Conflicts of interests
- iv. Compensation for injury
- v. End of trial care
- vi. Informed consent
- vii. Monitoring of clinical trials
- viii. Payment for participation
- ix. Therapeutic misconception

Some or all of these ethical concerns are also addressed in each of the regulations and guidelines reviewed. The regulatory and guidance documents also add the following to this list:

- x. Treatment for injury
- xi. Cost of participation
- xii. Privacy of subjects
- xiii. Confidentiality of data

The documentary review of reports did not add any new considerations. Thus, this final list of ethical concerns will be considered in the development of a framework in chapter 3.

### **CHAPTER 3: DEVELOPMENT OF A FRAMEWORK**

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Game theory is the study of “conflict and cooperation between intelligent rational decision-makers” (Myerson, 2013) and is employed by scholars “to model interdependent decision making” (Lucas, 2013). It mathematically models “how people interact and make decisions... under the assumption that each person’s behavior impacts the well-being of all other participants in the game” (McAdams, 2004). From chapter 1, it is clear that the process of conducting clinical trials consists of sequential and simultaneous interactions amongst a variety of economic actors, such that the outcome of each interaction depends on the actions of each of those involved. This is typically the context of a dynamic game. Dynamic game models are used to examine “relationships with some or all” of the following characteristics: “complex long-term agreements may be mutually beneficial; legal enforcement of contracts is difficult or impossible; asymmetries of information place limits on the use of other enforcement techniques” (Crawford, 1985). Based on the above, though the rationale for modeling clinical trials as a dynamic game seems self-evident, it has not been treated as a game in the clinical trials literature.

In general, the current literature is silent on the consideration for an overarching economic impact of the clinical trial process, especially in terms of demonstrating how the clinical trial process and its key stakeholders may each benefit from its outcomes under different policy systems. Further, there is little examination of the viable options for the welfare maximizing governance of the clinical trial process, its consequences, or possible tradeoffs between the different players. A cursory examination of Google Scholar using the search criteria of “economic impact of clinical trials”, “economics of clinical trials”, or “economics of clinical trial industry” only reveal articles related to economic analysis of specific clinical trials or specific condition-based economic impact. A search of EconLit, the American Economic Association’s bibliography of economic literature, using the search criteria “clinical trial” and “economics,” also reveals articles limited to the economic analysis of certain aspects of clinical trials. However, there are no results providing an overarching view of the economic or social impact of clinical trials.

More specifically, majority of the results from a Google Scholar search of “clinical trial” and “game theory” returns results of literature related to

clinical practice or research, and not associated with clinical trials. With respect to clinical trials, there are a few articles on scientific design of clinical trials, and diagnostic and treatment forecasting (Basanta, Gatenby, & Anderson, 2012; Chang, 2014; Gammon, 2012). One article uses a game theoretic approach to address drug launch strategies (Bhaduri & Ray, 2006). Some articles address subject participation, trust and cooperation (Dixon-Woods & Tarrant, 2009; Djulbegovic & Hozo, 2012). However, the analysis presented in these articles is not based on the clinical trial process as a whole or on encounters with players other than the physician investigator and the subject.

This chapter will focus on characterizing the clinical trial process using concepts borrowed from game theory. These features will then be combined to develop a framework by which to evaluate clinical trial oversight at the various levels of its governance.

## **1. The Clinical Trial Process from a Game Theoretic Perspective and Definitions of Concepts Borrowed from Game Theory**

As shown in chapter 1, a clinical trial is a complex process because i) it is a continuously evolving process that involves uncertainty; ii) it involves many different actor groups with diverse interests; iii) the actors play games within the game of a clinical trial; and iv) the outcome of the game cannot be entirely controlled, by any of the players, including the government.

The continuously evolving nature of the clinical trial process, which involves uncertainties along the way, can be understood as follows. Looking at figure 2, we can see that the government's conditions with respect to its approval for the clinical trial will affect the ethics committee's determinations and stipulations. The ethics committee's decisions and stipulations will then impact the CROs strategy for subject recruitment and for obtaining informed consent. The information presented during the informed consent process and the manner in which it is presented will affect the subject's decision to participate. Even though some individuals may agree to participate, they may not be able to participate if they are found ineligible after initial screening. Though not shown in the simplified model presented in figure 2, high levels of ineligibility may bring the CRO and the ethics committee, in consultation with the government and the pharmaceutical company, back to the drawing board of modifying the protocol. Figure 3 then demonstrates that, even after a trial has begun, the process may continue to evolve in face of uncertainties



associated with the possibility of adverse events and unanticipated problems occurring. The diverse interests of the actors involved in this process will be further detailed in section 2 below. From figure 2, however, we can see the diversity of interests, even at the early pre-trial stage. The government is interested in both allowing the trial to begin, which is in the interest of the local economy, and in protecting the subjects. The ethics committee is interested in protecting the subjects. The pharmaceutical company and the CRO are both interested in beginning the trial. By games within the games of clinical trials, I refer to “players... playing by different rules” (Jackson, 2011). The rules by which each of the players is participating or playing in the overall clinical trial game are based on the goals that each of the players are trying to achieve. Finally, none of the players can truly control the outcome of the game or clinical trial, since the outcome at each step, as demonstrated in figures 1 and 2, depend on the decisions at each level by different players.

An uncertainty is “a context wherein the likelihood of future events are indefinite or incalculable” (Knight, 1921). Uncertainty arises whenever one or more of the players are uncertain about (i.e. do not know the likelihood of) one or more of the following:

- i) Environmental parameter(s) that impact payoffs;
- ii) Past actions of players;
- iii) Some characteristic of the other player(s) (e.g. reasoning, beliefs, resources etc. (Osborne & Rubinstein, 1994))

Uncertainty thus refers to the absence of certainty and by its very nature denotes a risk from the unknown. Risk is then rendered measurable by proposing a set of possible outcomes in place of the unknown and a set of corresponding probabilities with which each possibility is likely to occur.

Furthermore, from chapter 1, one can see that clinical trials can be viewed as a process, making it amenable to being perceived as a sequential game. A sequential game is a game in which players play in an ordered sequence. Finally, from chapter 1, it can be seen that there can be various types of informational challenges in the clinical trial processes, as each of the players relies on information presented by the other player(s) in order to make one’s own decision. For example, the government and the ethics committee rely on information presented by the CRO and the pharmaceutical company to

determine whether the clinical trial can be approved for initiation; the subject relies on information presented by the CRO to decide whether to participate in the trial; the pharmaceutical company and the ethics committee rely on information about adverse events presented to them by the CRO through the subjects; and so forth. Various types of sequential games with informational challenges have been introduced in literature:

- i) A sequential game is one with perfect information “if only one player moves at a time and if each player knows every action of the players that moved before him at every point” (Gibbons, 1992). Any sequential game that does not have perfect information poses the challenge of imperfect information to its players.
- ii) A sequential game with asymmetric information is one wherein one or more players have private information. “By private information we mean knowledge about parameters of the game that is possessed by some players and not possessed by other players. Private information does not have to be certain, but can also take the form of probabilistic beliefs. When one or more players have private information in a sequential game – it is one with asymmetric information” (Bierman & Fernandez, 1998).
- iii) A sequential game with incomplete information: “In this game, the strategic possibilities, the information and knowledge base and/or payoff functions of one player or more players is private information. This is represented in sequential games as a move by nature which chooses the type of the player among possible types, such that only the player concerned knows his/her true type” (Rasmusen & Blackwell, 1994).

To this repertoire of informational challenges, let us introduce two new definitions concerning the nature of uncertainty:

- i) A sequential game with a systemic uncertainty: for one or more of the players, there is uncertainty about the governance parameters that cannot be changed through the actions of any one of the players alone and which nevertheless impact the outcomes of one or more of the players.

A sequential game with systemic uncertainty is being introduced because, in theory, in a sequential game, the rules of the game are limited to the order of play and the payoff structure of the game. However, in real life situations like clinical trials, the outcomes may be decided by the systemic norms which are unclear. For instance, there may be an absence of rules or the existence of multiple rules for conflict resolution. As noted in the introduction to this thesis, the clinical trial process is governed at three levels: international guidelines, with which there is an expectation of compliance, but no enforcement power; national regulations; and institutional policies and procedures of the pharmaceutical company, the CRO and the ethics committee. Thus, in a clinical trial, systemic uncertainty is present due to the governance by multiple layers. Table 4 demonstrates the diverse approaches to the same issues by the various national and international governing bodies. In addition to these, there may be variance in institutional policies and procedures. Thus, there may be an absence or multiplicity of rules, which creates problems of choice. I refer to these as systemic uncertainties.

An example of systemic uncertainty in the clinical trial process is an absence of rules associated with the issues of cost of treatment and compensation for injury. “In the United States, despite decades of discussion and recommendations by national commissions, sponsors and institutions are not required to provide either free medical care or compensation, although some do” (Steinbrook, 2006). This absence of rules thus creates an uncertainty for subjects in terms of what will occur should they become injured due to their participation in the clinical trial. The uncertainty of cost of treatment can be further intensified if the pharmaceutical company, the CRO and the ethics committee allow the cost of treatment to be passed to the subject’s third party payer. In this instance, prior to the subject’s enrollment, the subject is uncertain whether an injury will occur, and if so, whether the third party payer will cover the cost.

An example of multiplicity of rules in the clinical trial process is with respect to the monitoring of the trials, and the resultant management of adverse events and unanticipated problems. As noted in table 4 above, all except 1 of the regulatory and guidance documents reviewed address establish rules for monitoring of clinical trials. However, as observed by scholars and noted in section 1.2.7 of chapter 2, there is a need for coordination amongst these rules. Lack of harmony within the various rules can result in uncertainty

associated with the party responsible for each step of the management process, including monitoring, reporting, analysis and resultant action.

- ii) Endogenous uncertainty: One or more of the players faces uncertainty about the past or future moves of any of the players and/or their characteristics (e.g. resources, beliefs, objectives, etc.) arising from imperfect or incomplete information.

Endogenous uncertainty gives rise to two classic types of strategic challenges studied in economics:

- a. Moral Hazard: “Player A faces a moral hazard problem from player B if player A is uncertain about a past move or a future (unpreventable) move of player B that lowers player A’s payoffs. In other words, player B can make a choice that cannot be observed or controlled by player A, but which can lower player A’s payoffs. This is also referred to as the problem of ‘hidden actions’” (Kreps, 1990).

For the purpose of this thesis, this then refers to the “increase in hazard” or “increase in harm” or negative outcome for one or more of the players due to the hidden actions of a player that cannot be observed and/or verified. Moral hazard refers to hidden actions of a player that are initiated after an information agreement or formal contract has been initiated between two parties. In terms of clinical trials, this may then occur either after a sponsor and CRO have entered into a clinical trial agreement, or a CRO and a subject have entered into an agreement through the informed consent document.

- b. Adverse selection: “Player A faces an adverse selection problem from player B if player B has information unknown to player A that can nevertheless impact the game outcomes of player A’s strategies. This is also referred to as the problem of ‘hidden information’” (Kreps, 1990).

For the purpose of this thesis then, this refers to communication of information that cannot be verified and which leads another player to make an “adverse selection” that s/he would not have made had there not been an informational asymmetry. Adverse selection refers to wrong choices that can be made before an informal agreement or a formal contract is entered into by two parties due to the non-verifiable information issued by another player.

Thus, this would occur prior to a clinical trial agreement or prior to an informed consent agreement.

In addition to these two classic types of strategic challenges, I consider a third type of strategic challenge, namely corruption, which may also arise in clinical trials.

- c. Corruption: “a private exchange between two parties... which: (1) has an influence on the allocation of resources either immediately or in the future, and (2) involves the use or abuse of public or collective responsibility for private ends” (Macrae, 1982).

For the purpose of this thesis, this refers to implicit or explicit agreements between two or more players prior to the game to play a certain strategy that increases their payoffs and is unknown to the other players.

Endogenous uncertainty is being introduced because the uncertainties in a clinical trial may lead to a combination of moral hazard, adverse selection and corruption problems. For analytical purposes, there is no need to distinguish between these. Thus, in this thesis, the sources of adverse selection, moral hazard and corruption are being termed sources of endogenous uncertainty.

The three endogenous uncertainties, adverse selection, moral hazard and corruption, can occur under the context known as ‘principal-agent’ models. “In the principal-agent model, the payoff to the principal depends on an action taken by the agent.” However, prior to the implementation of a contract, the principal does not know what types of actions the agent will take. Nonetheless, the principal must make an incentive offer to the agent before a contract can be executed. The agent decides whether to enter into the contract based on this incentive offer, and once a contract is executed, the agent decides on the actions that maximize his/her payoff. Thus, within the context of the principal-agent model, the principal must commit to an incentive prior to being aware of the actions that will be taken by the agent, and that in turn have a direct impact on the principal’s payoff (Gintis, 2000).

Conflicts of interest arise when a principal contracts with an agent to perform specific duties that are in the best interest of the principal but may be costly to or not in the best interest of the agent. The principal-agent problem

develops when a principal does not create an environment in which an agent has incentives to align its interests with those of the principal. It is necessary for a principal to create an incentive mechanism that motivates the agent to align its actions with the principal's objectives, even after the contract has been executed. This is imperative because the principal faces information asymmetry, and is not fully informed of the agent's intention and ability to effectively complete the contract.

## **2. Establishing the Need for a Framework**

As observed by the results of literature review in chapter 2, current literature identifies individual ethical concerns regarding the protection of human subjects of clinical trials and discusses how to improve individual processes such as the informed consent process and the monitoring process. Two important aspects related to the governance of clinical trials, however, are missing from literature. First, literature does not provide a comprehensive framework for identifying the elements of and evaluating governance of clinical trials. Second, current literature focuses on the responsibilities of individual players, without sufficient consideration of the impact of the decisions or strategies of one player on the subsequent decisions or strategies of the other players. An integrated approach is necessary in order to truly understand the interdependencies amongst the many players involved in the clinical trial process, and to identify how best to develop integrated strategies toward social good. To this end, a framework for understanding and evaluating the governance of clinical trials, which includes considerations of the interdependencies of the various decision makers, is needed.

## **3. The Players**

As mentioned in the introduction of this thesis, clinical trials are a critical step in the drug development process. Many players are involved in the drug development process in its entirety. However, as this thesis focuses on clinical trials, the players identified in this section are those limited to the clinical trial process only. Thus, the players involved in the early drug development stages of product development, animal testing and pre-clinical testing, as well as the players involved in post-trial marketing and commercialization are not included. The players involved in the clinical trial process are: the government, the pharmaceutical company, the sponsor, the contract research organization (including the research site, physician

investigators and the research team), the ethics committee (EC) or an institutional review board (IRB), the civil society and human subjects.

## Government

The government is responsible for “reducing risks to the community and to the individual citizens”. In case of public health, this responsibility extends to ensuring public access to necessary drugs; ensuring that the drugs that are being made available to the public are safe and effective; and accomplishing this via a safe and effective process that avoids unnecessary delays while giving sufficient consideration to the good of the patients (Sass, 1989).

The arguments of the preceding chapters clearly indicate that oversight of clinical trials is necessary in order to protect the interests of individuals and public health, while allowing for innovation by the pharmaceutical industry. By *oversight*, I refer to regulatory and policy-based supervision. Regulatory oversight is dependent upon legislation that “gives expression to public policy and provides support and governance to those who are charged with authority and responsibility to implement the policy” (Epstein et al., 2009). Thus, regulations governing clinical trials aim to set standards for and provide resources toward effective oversight of clinical trials.

In the clinical trial process, the government plays a multi-faceted role. First, the government, through its regulatory agencies, evaluates whether pre-clinical testing, up to the completion of animal studies, provides sufficient evidence that the drug may be safely tested in humans, and whether there is any early indication of efficacy. Next, during the course of the clinical trials, the regulatory agencies provide oversight of the conduct of clinical trials through the implementation of the laws and regulations governing the protection of human subjects. Finally, the regulatory agencies evaluate data obtained through pre-clinical studies and throughout clinical trials to make a decision on whether to approve the drug for marketing. If approved, the agency also approves the labeling appropriate for each drug.

In terms of the principal-agent model described at the end of section 1 above, within the relationship between the government and the pharmaceutical company, the government is the principal and the pharmaceutical agency is the agent. The government sets the incentives for the pharmaceutical company to bring clinical trials to its market through regulations that promote

innovation and do not serve as a barrier to the conduct of clinical trials. Based on the regulations, the pharmaceutical company decides whether to choose the country as a clinical trial site, and if so, submits an application to obtain government approval to conduct clinical trial within the country. The government's approval is thus the contract that the government as the principal and the pharmaceutical company as the agent enter. Upon receipt of the approval, the pharmaceutical company implements the clinical trial based on its ability to maximize its gains.

### Pharmaceutical Company

The pharmaceutical company, often but not always the sponsor of the clinical trial, leads the innovation process of new drug development. Pharmaceutical companies invest heavily in the research and development associated with each new drug, the most costly aspect of which are the clinical trials on humans. In addition to performing the research and development activities leading up to the new drug application process, the pharmaceutical company may also be required by the government to conduct additional safety and effectiveness studies after the approval of a drug for marketing. During the course of conducting clinical trials, the pharmaceutical company is also responsible for the protection of human subjects of clinical trials, for safety monitoring procedures, and for providing its assessment regarding any safety concerns.

As noted above, in the relationship between the government and the pharmaceutical company, the government is the principal and the pharmaceutical company is the agent.

### Sponsor

“Sponsor means a person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization.”<sup>16</sup> Since a large number of the clinical trials are sponsored by the pharmaceutical company whose product is being investigated, unless

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<sup>16</sup> US FDA regulations, 21 CFR 312.3:  
<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.3>



otherwise specified, the term “sponsor” throughout this thesis refers to the pharmaceutical company as the sponsor.

### Contract Research Organization (CRO)

CRO refers to “a person (or an entity) that assumes, as an independent contractor with the sponsor, one or more of the obligations of a sponsor, e.g., design of a protocol, selection or monitoring of investigations, evaluation of reports, and preparation of materials to be submitted” for regulatory approval (United States Food and Drug Administration, 1987). For the purpose of this research, the term CRO is being used to include: i) an organization contracted by the pharmaceutical company to implement one or more aspects of the drug development process, such as initial drug development, pre-clinical research, clinical trial management, data collection, data management, pharmacovigilance, and commercialization; ii) sites where the clinical trials are being conducted, such as a hospital, a clinic or a research site; and iii) the investigators and the research team involved in the conduct of clinical trials. In addition to performing the services defined in their contract with the sponsor, the CROs are also responsible for the protection of human subjects of clinical trials.

In terms of the principal-agent model, the CRO is the agent of the sponsor. Thus, in this relationship, the pharmaceutical company’s role changes into that of a principal. The pharmaceutical company presents financial incentives to the CRO, who then decides whether to enter into a clinical trial contract with the company. The CRO, as the agent, then implements the trial in a manner that maximizes its gains.

### Ethics Committee / Institutional Review Board

Governments generally delegate the responsibility of ethical oversight of clinical trials to an ethics committee (EC) or an institutional review board (IRB). These are reviewing bodies comprised of scientific and non-scientific reviewers as well as reviewers who represent the community from which subjects will be recruited. Depending on local regulations and requirements, the EC/IRB may be a central independent body, a governmental body or a body affiliated with a research institution.

ECs or IRBs are expected to serve three distinct roles, though in practice not all ECs or IRBs effectively execute each of these. The first responsibility of the EC/IRB is to review proposed clinical trials to ensure protection of human subjects of clinical trials. A second responsibility of the EC/IRB is to ensure adequate education and awareness regarding the protection of human subjects within the research community and the society at large. A third responsibility is one of monitoring the trial after giving its initial approval to ensure ongoing ethical conduct and compliance with the EC/IRB approved protocol (Benatar, 2002).

Typically, the EC/IRB review is requested by and issued to the CRO. Thus, in terms of the principal-agent model, the Ethics Committee is the principal and the CRO is the agent. The EC/IRB, by establishing policies and procedures that do not become a barrier to the conduct of clinical trials, provides incentives to the CRO to conduct the trial within the local community. The EC/IRB's approval serves as a contract, and the CRO decides on its implementation of this contract in accordance with its goal of maximizing its gains.

### Research Subjects

Research subjects are individuals who are recruited to participate in clinical trials based on the inclusion and exclusion criteria identified in the clinical trial protocol. Subjects are asked to participate in one or more aspects of the clinical trial during an informed consent process. Once they have given consent to participate in a trial, the subjects are asked to adhere to the protocol defined procedures, and monitored by the research team. The research subjects have the right to withdraw from the clinical trial at any time. It is in the best interest of the subject to communicate his/her decision to withdraw from the clinical trial so that the research team can advise as to any necessary steps the subject should take to taper off of the investigational drug.

In terms of the principal-agent model, the research subjects are the agents of the CRO. The CRO provides potential subjects with incentives, such as access to treatment, monetary benefits or participation in social good, in an effort to recruit subjects to participate in the clinical trial. The potential subject then decides whether to participate. The informed consent document then serves as a contract between the CRO and the subject, and the subject

may or may not comply with the protocol described within the consent document depending on his/her perception of what s/he gains from participation.

### Civil Society

The World Bank defines civil society as “the wide array of non-governmental and not-for-profit organizations that have a presence in public life, expressing the interests and values of their members or others, based on ethical, cultural, political, scientific, religious or philanthropic considerations. Civil society organizations therefore refer to a wide array of organizations: community groups, NGOs, labour unions, indigenous groups, charitable organizations, faith-based organizations, professional associations, and foundations” (World Economic Forum, 2013).

With respect to clinical trials, the civil society may play a number of roles:

- It may serve as a citizen watchdog by holding government and industry accountable and demanding their transparency.
- It may serve as subject advocates by making subjects more aware of their rights as research subjects, and ensuring that subjects understand what it means to participate in the clinical trial, including why clinical trials are conducted.
- Represent the community from which subjects are being recruited to ensure that the vulnerable populations are not being exploited, and to identify and/or negotiate ways in which the community may benefit from the clinical trials.
- Set standards for recruitment and consent processes for a given community and for subject’s rights within a society.

The civil society is not a decision maker in the clinical trial process. However, it has played an important role in the recognition of ethical violations in clinical trials and the resulting corrective actions by the decision makers (Sharav, 2009). For the purpose of this thesis, the civil society is considered a tangential player.

## **4. Ethical Stance of the Players**

For the purpose of this thesis, ethical stance of a player means that no player with an informational advantage in an asymmetric information situation is

exploiting it against another, whether it be before, during or after the clinical trial. From a game theoretic perspective, this means: i) no player induces ‘adverse selection’ by another player through communication of information, typically provided before an agreement, that cannot be validated; ii) no player poses a ‘moral hazard’ for another player, through hidden actions once an agreement has been implemented; and iii) no sets of players coordinate, either implicitly or explicitly, prior to the clinical trial to choose a particular strategy before, during or after the clinical trial to increase their respective payoff, i.e. there is no corruption.

In this section, I provide examples of how the problems of moral hazard, adverse selection and corruption can emerge in the different stages of a clinical trial. The examples are based on themes drawn from literature review presented in chapter 2.

#### **4.1. Conflict of Interest (theme 3)**

##### **Example 1: Corruption – Agreement between reviewer and sponsor prior to the initiation of a clinical trial**

A government or ethics committee reviewer might agree to give a sponsor a favorable determination in exchange for financial compensation for self or other specific individuals; equity for self or other specific individuals; or intellectual property rights.

##### **Example 2: Corruption – Agreement between reviewer and sponsor prior to the initiation of a clinical trial**

A government or ethics committee reviewer might agree to give a sponsor a favorable determination because of the reviewer’s or their immediate family member’s potential role as a research team member; as a treating clinician of potential subjects; and/or as a potential patient and recipient of the investigational treatment.

#### **4.2. Coercion (theme 2), Informed Consent (theme 6) and Therapeutic Misconception (theme 9)**

##### **Example 3: Adverse Selection – Misinformation, over-information or under-information provided to clinical trial subjects prior to their participation in the trial**

During the subject identification, recruitment and consent procedures, the pharmaceutical company, the CRO and/or the ethics committees may not ensure that potential subjects are provided with adequate information; that they are not being coerced into participation in research; and that potential subjects are not presented with undue influence during the recruitment and consent processes.

The ethical principle of respect for persons requires that “individuals should be treated as autonomous agents. To respect autonomy is to give weight to autonomous persons' considered opinions and choices”. In order to accomplish this, an informed consent process requires that subject be given adequate information so as to make informed decisions regarding their participation in research (Ryan et al., 1979). Asymmetry of information may also result from an inadequate informed consent process. In order for an informed consent process to be effective, it must take into consideration the potential subjects' language, literacy level, cultural context and their capacity to consent (Bhutta, 2004). Absent these considerations, the adverse selection of subjects may occur due to an ill-informed subject.

Example 4: Adverse Selection – Misinformation, over-information or under-information provided to clinical trial subjects for acceptance of treatments of unknown efficacy prior to their participation in a trial

Treating clinicians are often also involved in the subject identification, recruitment and consent processes for clinical trials of treatments of unproven efficacy “that can be integrated easily into a course of a treatment” (Karine Morin et al., 2002). During the subject identification, recruitment and consent procedures, the clinical investigator or the CRO may not clearly distinguish between clinical treatment and investigational treatment. Additionally, the sponsor and the ethics committee may not ensure that there are procedures in place to ensure that subjects are not agreeing to participate in the research due to a therapeutic misconception.

Therapeutic misconception occurs as a result of either the clinician's bias manifesting itself when s/he is presenting information about the clinical trial to the potential subject; or the potential subject's perception that the clinician is presenting the clinical trial to the subject because it is in the subject's best interest. In the former scenario, there is adverse selection of the subject as a result of asymmetrical information between the clinician and the potential

subject. In the latter, the asymmetry of information resulting in adverse selection of the subject is caused by the potential subject's disregard of the possible risks of the trial based on deference to authority.

### **4.3. Monitoring of Clinical Trials (theme 7)**

#### **Example 5: Moral Hazard – Under-reporting or mis-reporting of adverse events or unanticipated problems by CROs during the clinical trial**

During the course of a clinical trial, there is the possibility of adverse events or unanticipated problems occurring. The CRO would have the most information regarding such event(s). However, the CRO might choose not to keep the pharmaceutical company, the ethics committee and the government adequately informed of the extent of such events.

The CRO, the pharmaceutical company, the ethics committee and the government each establish their respective policies and procedures that must be followed with regard to reporting adverse events and unanticipated problems, evaluating such events, and taking appropriate action in response to the events. However, the pharmaceutical company, the ethics committee and the government ultimately depend on the CRO to ensure adequate reporting.

### **4.4. An Illustration of Adverse Selection, Moral Hazard and Corruption Within the Clinical Trial Process**

Having established that the problems of adverse selection, moral hazard and corruption may exist in the clinical trial process, I now present an illustration of the presence of these problems in the process as a whole in figure 4.

At A4, the government or the ethics committee is the principal and the CRO is the agent: either the government or the ethics committee makes a favorable determination due to incomplete or mis-information provided by the CRO.

#### **Example of moral hazard demonstrated in figure 4:**

At M1, the sponsor is the principal and the CRO is the agent: CRO exploits subjects and/or takes advantage of its distance from the sponsor to take actions that would afford it profitable outcomes.

Figure 4: Illustration of the problems of adverse events, moral hazard and corruption with the clinical trial process

\* Author's creation

At A1, the government is the principal and the sponsor is the agent: sponsor selects research site (and therefore subjects) based on ease of access, and not based on the national healthcare priorities.

At A3, the CRO is the principal and the subject is the agent: CRO persuades subjects to enroll in the clinical trial through incomplete or mis-information.

#### Examples of corruption demonstrated in figure 4:

At C1, there is an agreement between the reviewer and the sponsor or the CRO, whereby the reviewer agrees to make a biased favorable determination for approving the proposed clinical trial in exchange for financial gain.

At C2, there is an agreement between the reviewer and the sponsor or the CRO, whereby the reviewer agrees to make a biased favorable determination for approving the proposed clinical trial based on non-financial personal gains.

### **5. Framework for the evaluation of governance of clinical trials**

As noted above, there is a clear need for a framework for evaluation of governance of clinical trials that incorporates how ethical concerns identified through literature and documentary review presented in chapter 2 are addressed, and takes into consideration the impact of one player's policy or strategy on the decisions or actions of another player. Also as noted above, the complexity associated with the interdependencies of the various players is embedded in the uncertainties related to each player's decision or action. Thus, the framework must allow for evaluation of how and to what extent the policies and strategies of each player addresses the uncertainties faced by the various players involved.

Based on the literature review presented in chapter 2, I identified nine themes defining the ethical concerns associated with the implementation of clinical trials. To these, an additional four themes were added through documentary review. Of the four, I exclude privacy and confidentiality concerns from use in my framework, as these two concerns do not pose an uncertainty, and can be alleviated through the implementation of simple procedures. Payment for participation is primarily associated with undue influence, which, in terms of policy and strategy can be addressed in a manner similar to coercion. These two are thus combined into one element. Thus, combining the themes identified through literature review with those identified through documentary review, we are left with 10 areas of concern, which will be categorized as endogenous or systemic uncertainties. Endogenous uncertainties are then further classified as issues with potential for adverse selection, moral hazard or corruption. Finally, I propose possible mechanisms for converting each uncertainty into measurable risks. It is important to note that the causes of each of these uncertainties and the possible mechanisms for



addressing these uncertainties are derived from the literature review presented in chapter 2.

### **5.1. Endogenous uncertainties**

#### **EU1 – Adverse Selection: Are one or more of the players causing a therapeutic misconception?**

As noted in chapter 2, therapeutic misconception occurs when a potential subject does not understand that the true purpose of the clinical trial is to test the experimental product, and not to provide a beneficial treatment. Thus, subjects face an uncertainty regarding some characteristics (reasoning, beliefs, etc.) associated with the goals of the pharmaceutical company and the CRO. The pharmaceutical company or the CRO can create therapeutic misconception, especially when the treating physician is also the clinical trial investigator. This can be intentional or inadvertent. Intentional therapeutic misconception can be a result of adverse selection when: i) recruitment and consent materials developed by the pharmaceutical company do not clearly distinguish between standard of care treatment and experimental treatment; ii) recruitment and consent processes established by the CRO blur the lines between standard of care treatment and experimental treatment; or iii) the clinical trial investigator does not clearly relay the difference between a clinical trial and clinical care to the subject. Unintentional therapeutic misconception can be a result of hopefulness or deference to authority on the part of the subject.

Possible mechanisms for converting this uncertainty into measurable risk include:

- i) As identified through literature review, therapeutic misconception is more likely to occur in individuals with lower levels of education and lower incomes. Thus, the pharmaceutical company and the CRO can reduce this uncertainty for the subject by assessing the probability of causing a therapeutic misconception based on demographic information about the targeted subject population and their relationships with the research team members, if any, and then using this assessment to inform their recruitment and consent strategies.
- ii) Pharmaceutical company may provide well-defined acceptable protocols for recruitment and consent processes for each clinical trial,

including the category of individuals who may obtain informed consent.

- iii) Separate the roles of a treating physician from a non-treating physician within the recruitment, screening and consent processes. For example, a treating physician may determine potential subject's eligibility to participate in a clinical trial and may recommend the trial to the potential subject. However, a non-treating physician, who is part of the research team, would obtain consent and "remain available to answer additional questions during the trial" (Morin, Rakatansky, Riddick, Jr, & et al., 2002).
- iv) Pharmaceutical company, CRO and the government may all implement education initiatives to educate and inform the public about the purpose and importance of clinical trials, as well as the rights of clinical trial subjects. The government can leverage civil society organizations to raise public awareness of the role of clinical trials and participating subjects, and the rights of the subjects.

EU2 – Adverse Selection: Are one or more of the players not considering available alternatives adequately?

"To enable a rational choice about participating in the research study, subjects should be aware of the full range of options available to them" (United States Food and Drug Administration, 2011). Adverse selection may occur if the pharmaceutical company does not provide the CRO with complete information about the range of alternatives, or the CRO does not provide complete information about the range of alternatives to the ethics committee and the subjects.

Possible mechanisms for converting this uncertainty into measurable risk include:

- i) Pharmaceutical company provides as complete a picture of available alternatives as possible to the CRO.
- ii) CRO takes locally available alternatives into consideration, and develops a comprehensive list of available alternatives for consideration by the ethics committee.
- iii) Ethics committee considers the comprehensive list provided by the CRO in light of what is truly available to the subject population, and finalizes a consent document based on this assessment.

- iv) The subject is clearly informed of all available alternatives during the informed consent process by the research team.
- v) The ethics committee and the CRO may consider having an independent subject advocate available during the informed consent process who may help the subject in understanding complex alternatives when appropriate, without serving as a barrier to the research.

EU3 – Adverse Selection: Are the recruitment and informed consent processes adequately informing the subjects about their participation in research?

“Respect for persons requires that subjects, to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to them. This opportunity is provided when adequate standards for informed consent are satisfied” (Ryan et al., 1979).

Adverse selection during the recruitment and informed consent processes may occur if: i) subjects are not fully informed of the purpose, procedures, experimental nature, risks, alternatives, and other relevant information about their participation in a clinical trial; ii) subject is recruited or subject consent is obtained under external influence, and thus it is not voluntary; iii) subjects are provided information about the clinical trial in language or context that they do not comprehend; or iv) there has been inadequate assessment of the cognitive ability of the subject.

Possible mechanisms for converting this uncertainty into measurable risk include:

- i) Regulatory agency establishes recruitment and informed consent standards.
- ii) Regulatory agency establishes standards for recruitment and enrollment of cognitively impaired subjects in clinical trials.
- iii) The pharmaceutical company can also set standards that would be acceptable to them on a protocol-by-protocol basis.
- iv) The CRO and the ethics committee ensure that the research team is not only scientifically, but also culturally and linguistically, qualified in order to best assess the language, literacy and cultural context of the subject population.

- v) The ethics committee requires a consent monitor or subject advocate to participate in the informed consent process so as to ensure that the subject comprehends what is being explained.

#### EU4 – Adverse Selection: Are any of the players exerting undue influence?

Potential subjects may decide to participate in a clinical trial and therefore agree to enroll in a clinical trial because they are faced with undue influence exerted upon them by one of the other players. This can occur in many ways, for example: i) the potential subject may be induced during the informed consent process if the potential benefits of participation are more clearly delineated or accentuated and the potential risks of participation are masked; or ii) potential subject may feel undue influence to enroll in the clinical trial if the payment for participation is sufficiently large; or iii) potential subjects may agree to participate because of their deference to authority to a medical professional who may be recruiting them or obtaining their consent.

Possible mechanisms for converting this uncertainty into measurable risk include:

- i) Clear guidance on acceptable methods of recruitment and informed consent by the regulatory agency, given the local cultural context.
- ii) Clearly defined acceptable methods of recruitment and informed consent processes within the sponsor's protocol.
- iii) Clearly defined acceptable methods of recruitment and informed consent processes, which are customized to the local cultural context, within the ethics committee approved protocol.
- iv) Adequate implementation of the approved recruitment and informed consent processes by the CRO.
- v) Educational initiatives by the government and the civil society regarding the experimental nature of clinical trials and the rights of clinical trial subjects.

#### EU5 – Moral Hazard: How will the trial be monitored such that adverse events and unanticipated problems can be managed effectively?

Given the experimental nature of clinical trials, it is expected that the trials will involve some risk of adverse events, expected or unexpected, and unanticipated problems. Risk of harm to subjects can be heightened when one

or more players experience a moral hazard. Moral hazard may occur if: (i) the CRO does not report accurately or completely one or more of the adverse events and/or unanticipated problems to the ethics committee or to the sponsor; ii) the ethics committee does not perform adequate analysis of the reported adverse events and/or unanticipated problems; iii) the sponsor does not perform adequate analysis of the reported adverse events and/or unanticipated problems; and/or iv) CRO does not take required action based on the ethics committee's or the sponsor's analysis.

There may also be a moral hazard problem arising from the actions of the subjects themselves. The area of monitoring is heavily dependent on the collection of accurate information from the subjects themselves. Therefore, if the subjects do not report some or all of the adverse events or unanticipated problems that they experience, whether it be due to lack of understanding of what is happening to them or due to self-doubt or embarrassment, the adverse event and unanticipated problem reporting and analysis system will break down. Thus, the ethics committee and the sponsor will not be able to perform adequate or sufficient analysis, which in turn would negatively impact the payoffs of the other subjects as well as the pharmaceutical company.

Possible mechanisms to deal with this uncertainty are:

- i) Well-defined requirements for adverse event and unanticipated problems reporting and analysis by the regulatory agency.
- ii) Clearly defined monitoring procedures for adverse event and unanticipated problems within the sponsor's protocol.
- iii) Clearly defined monitoring procedures for adverse event and unanticipated problems within the ethics committee approved protocol, including the customization of the procedures to the local subject population's cultural and traditional context.
- iv) Adequate implementation of the monitoring procedures by the CRO.
- v) Clearly defined process for ethics committee review of reported adverse events and unanticipated problems, and its communication of resulting analysis and actions required to the CRO.
- vi) Establishment of a Data Safety Monitoring Board with clearly defined monitoring procedures.
- vii) Sponsor having a well established process for analyzing and disseminating resulting information and needs for action to all CROs.

EU6 – Corruption: Is one or more player acting under the influence of an existing conflict of interest?

Corruption, in the implementation of clinical trials can come in one of many forms: i) the pharmaceutical company may decide to conduct a clinical trial in a country due to easy access to the subject population it is seeking without truly intending to commercialize the product in that country; ii) the reviewer at the regulatory agency may have either a financial conflict of interest or a conflict of commitment that is related to the clinical trial at hand, and therefore s/he may approve the trial regardless of its merit; iii) the ethics committee reviewer may have either a financial conflict of interest or a conflict of commitment that is related to the clinical trial at hand, and therefore s/he may approve the trial regardless of its ethics; iv) a member of the research team within the CRO may coerce potential subjects into participation due to the possibility of a personal gain from the outcome of the trial; and/or v) the CRO may deviate from the approved protocol in an effort to speed up or to ensure its profit through a favorable outcome of the trial.

Possible mechanisms to minimize the risk arising from this uncertainty are:

- i) The publication of national healthcare priorities by the government, which would then be used to allow clinical trials that fall within the national priorities and therefore reduce the chance of trials that may not ultimately benefit the local population.
- ii) Clearly defined and well-implemented requirements for disclosure and management of conflicts of interest of each member of the research team within the CROs by the sponsor.
- iii) Well-established rules for disclosure and management of conflicts of interest of reviewers within the regulatory agency.
- iv) Well-established rules for disclosure and management of conflicts of interest of reviewers within the ethics committee.
- v) Implementation of mechanisms for monitoring of the CROs by the sponsors to ensure that the CROs are following the approved protocol.

## **5.2. Systemic Uncertainties**

### **SU1: Who bears the cost of subject participation?**

A clinical trial involves a number of procedures, some of which may be considered part of standard of care, while others may be conducted purely for research purposes. Sponsors/pharmaceutical companies sometimes pass the cost of standard of care procedures to the subjects or their third party payer. However, third party payers may not be willing to cover such cost for individuals taking part in a clinical trial or may cover up to a pre-defined maximum amount.

As observed through documentary review of regulations and guidelines in section 2 of chapter 2, the United States regulations indicate that subjects ought to be informed of any costs that they will incur as a result of their participation during the informed consent process. However, the regulations do not include any indication of considerations for passing costs to subjects. The remaining regulatory and guidance documents reviewed are silent on this issue. Hence, there exists a systemic uncertainty.

Given that the regulations do not establish whether subjects can bear any cost of participation in a clinical trial, the question of whether cost may be passed to the subjects is addressed on a trial-by-trial basis. Thus, prior to negotiating a clinical trial contract, the issue of whether there will be cost borne by the subjects is not clear to all players. There is, a priori, an uncertainty associated with this issue. There is additional uncertainty faced by the subjects, as third party payers may or may not cover the subject's portion of the cost of participation. Often times, this information is not available to the subjects until they have already enrolled in the clinical trial and participated in procedures, the cost of which is in question.

Possible mechanisms for addressing this challenge are:

- i) Guidance from regulatory agencies on what types of costs could reasonably be passed to clinical trial subjects or under which circumstances costs could reasonably be passed to the subjects.
- ii) Established regulations on what types of costs resulting from clinical trials must be covered by either the national healthcare payment system or the third party payer system.

- iii) Adequate assessment of the costs being passed to subjects and/or their third party payer by the ethics committee, and resulting determinations regarding the appropriateness of the proposal based on an understanding of the subject population.

#### SU2: Who bears the cost of treatment for injury?

Concern has been voiced in the research ethics literature that under U.S. federal regulations U.S. sponsors, particularly the NIH, are not required to provide compensation for the treatment of research-related injury for trial participants or to allow grant funds to be used by investigators for appropriate insurance. This is problematic in developing country contexts because most participants are unlikely to have health insurance, resulting in overburdened and under-resourced health systems in many developing countries being responsible for providing care and treatment for research-related injury (Mamotte, Wassenaar, & Singh, 2013).

As opposed to the United States, “many European countries mandate the provision of clinical-trials insurance, through which subjects are often covered regardless of fault” (Steinbrook, 2006). As an emerging clinical trial market, India struggled with this issue, and passed an amendment to its Drugs and Cosmetics Rules in 2013, which required the sponsor (pharmaceutical company or other) to pay for long term medical care of subjects who were injured, without any qualifiers. This raised significant concerns regarding the liability borne by the sponsors, and increasing number of sponsors suspended their clinical trial interests in India (Ghooi, 2013; PTI, 2013; Seethalakshmi, 2013). These regulatory variations illustrate the complexity of this issue and the importance of finding a delicate balance between protecting clinical trial subjects and allowing for the clinical trials to take place.

As observed through documentary review of regulations and guidelines in section 2 of chapter 2, the issue of treatment for injury is addressed in the regulatory and guidance documents in one of two ways: i) some of the documents indicate that treatment for injury should or must be provided; or ii) others indicate that subjects should simply be informed whether treatment for injury will be provided. Given the globalization of clinical trials, these variations may have very practical implications on the implementation of clinical trials. Thus, there is a systemic uncertainty.



The following measures can be considered to address this uncertainty:

- i) Clear requirements from regulatory agencies on how treatment for injury should be handled given the local healthcare environment.
- ii) Adequate assessment and determinations by the ethics committee regarding the appropriateness of the proposal for how injuries will be handled based on an understanding of the subject population.

### SU3: Should there be compensation for injury?

The topic of whether clinical trial subjects should be compensated for research related injury or death beyond the cost of treatment for research related injury is absent from current literature. The assumption is that this issue is highly dependent on cultural context. Individualistic societies, such as the United States, do not have an expectation of compensation for injury beyond that of the cost of treatment for such injury and, in rare circumstances, limited cost of missed employment. This cultural expectation extends into the United States regulations, in which the only requirement is that the subject be informed of compensation for research related injury, if any (United States Food and Drug Administration, 1981, amended 2011). However, this may be a more complex issue in societies where the individual exists within the context of his/her family, tribe or society. In such societies, the greater familial, tribal or societal unit may be dependent upon the health and welfare of the individual (Guess, 2004). As such, an injury to or death of an individual may have significant economic impact on the welfare of the larger unit. To address this issue, India, for example, established an independent expert committee to devise a formula for determining appropriate compensation in case of a serious adverse event or death occurring during clinical trials (Drugs Controller General (India), 2013).

As observed through documentary review of regulations and guidelines in section 2 of chapter 2, the issue of compensation for injury is addressed in the regulatory and guidance documents in a manner similar to the issue of treatment for injury, causing a similar systemic uncertainty.

Possible mechanisms for converting this uncertainty into measurable risk are therefore also similar, and include:

- i) Clear requirements from regulatory agencies on when and to what extent compensation for injury should be provided given the local cultural context.
- ii) Adequate assessment and determinations by the ethics committee regarding the appropriateness of the proposal for when and to what extent compensation for injuries will be provided based on an understanding of the subject population.

#### SU4: Should end of trial care be provided and to whom?

End of trial care, as discussed here, and in the documents analyzed, refers to the provisions for providing continuous experimental treatment to a clinical trial subject in case it proved beneficial to the subject, but it is not commercially available. As observed through documentary review of regulations and guidelines in section 2 of chapter 2, 3 of the 7 regulatory and guidance documents indicate that end of trial care ought to be provided where it is proven beneficial to the subjects. However, none of these provide any further guidance on considerations for when this should be made available or considered beneficial, and how this should be implemented. The others remain silent on this issue. Thus, there exists a systemic uncertainty, and to deal with it, the following can be proposed:

- i) Regulations that define the responsibilities for assessing whether end of trial care may be appropriate and beneficial to one or more subjects post-trial.
- ii) Regulatory mechanisms for allowing and monitoring expanded access or compassionate use protocols.
- iii) Guidance from regulatory agency on when it may be appropriate to implement expanded access or compassionate use protocols.
- iv) Negotiated agreements between the pharmaceutical company and the government that define the strategy for transition from expanded access or compassionate use protocols to commercial availability of the drug should it prove beneficial at the end of all phases of clinical experimentation.

#### SU5: Who will cover the cost of end of trial care?

Although 3 of the 7 regulatory and guidance documents reviewed address the issue of making end of trial care available, none of the documents address who should be responsible for the cost of this care. The issue of cost is clearly related to the issue of providing care, and is therefore, being included here as the final systemic uncertainty.

Possible mechanisms for converting this uncertainty into measurable risks include:

- i) Guidance from regulatory agency regarding the reasonable distribution of financial responsibilities for end of trial care.
- ii) Negotiated agreements between the pharmaceutical company and the government that define: i) the party(ies) responsible for the cost of end of trial care; and ii) the duration for which the responsible party(ies) must cover the cost of end of trial care.

The endogenous and systemic uncertainties identified above are combined to arrive at a framework, which can be used to evaluate governance of clinical trials. The framework is provided in table 4 below.

Table 4: Framework for Evaluating Governance of Clinical Trials

<b>Type of Uncertainty</b>	<b>Player facing uncertainty</b>	<b>Origin of uncertainty</b>	<b>Mechanisms for managing uncertainty</b>
EU1 – Adverse Selection: Are one or more of the players causing a therapeutic misconception?	Subject	Sponsor; CRO	Regulatory requirements; sponsor, CRO & IRB/EC policies and procedures; educational initiatives
EU2 – Adverse Selection: Are one or more of the players not considering available alternatives adequately?	Subject	Sponsor; CRO	Regulatory requirements; communication and transparency amongst all players; subject advocate
EU3 – Adverse Selection: Are the recruitment and informed consent processes adequately informing the subjects about their participation in research?	Subject	Sponsor; CRO	Regulatory requirements; sponsor, CRO & IRB/EC policies and procedures; subject advocate
EU4 – Adverse Selection: Are any of the players exerting undue influence?	Subject	Sponsor; CRO	Regulatory requirements and guidelines; sponsor, CRO & IRB/EC policies and procedures; educational initiatives
EU5 – Moral Hazard: How will the trial be monitored such that adverse events and unanticipated problems can be managed effectively?	Subject	Government; sponsor; CRO	Regulatory requirements and sponsor, CRO & IRB/EC policies and procedures addressing monitoring, reporting, analysis and resultant action based on adverse events & unanticipated problems

EU6 – Corruption: Is one or more player acting under the influence of an existing conflict of interest?	All players	One or more of the players	National agenda; Regulatory requirements and sponsor, CRO & IRB/EC policies and procedures addressing disclosure and management of conflicts of interest; procedures for sponsor monitoring CRO
SU1: Who bears the cost of subject participation?	All players	Systemic	Contractual clauses; regulatory requirements and guidelines; sponsor, CRO and IRB/EC policies & procedures
SU2: Who bears the cost of treatment for injury?	All players	Systemic	Contractual clauses; regulatory requirements and guidelines; sponsor, CRO and IRB/EC policies & procedures
SU3: Should there be compensation for injury?	All players	Systemic	Contractual clauses; regulatory requirements and guidelines; sponsor, CRO and IRB/EC policies & procedures
SU4: Should end of trial care be provided and to whom?	Subject	Systemic	Regulatory requirements and mechanisms; negotiated agreements
SU5: Who will cover the cost of end of trial care?	All players	Systemic	Regulatory requirements and mechanisms; negotiated agreements

\* Source: author's creation

## **6. An Illustrative Example**

To illustrate the complexity and the interdependency of the relationships and interactions amongst the many players involved in the implementation of a clinical trial, and to demonstrate how ethical violations may occur as a result of inadequate decision-making in the face of uncertainties, I will use the example of a group of HIV/AIDS clinical trials sponsored by the US National Institute of Allergy and Infectious Diseases (NIAID).

### **6.1. The Case**

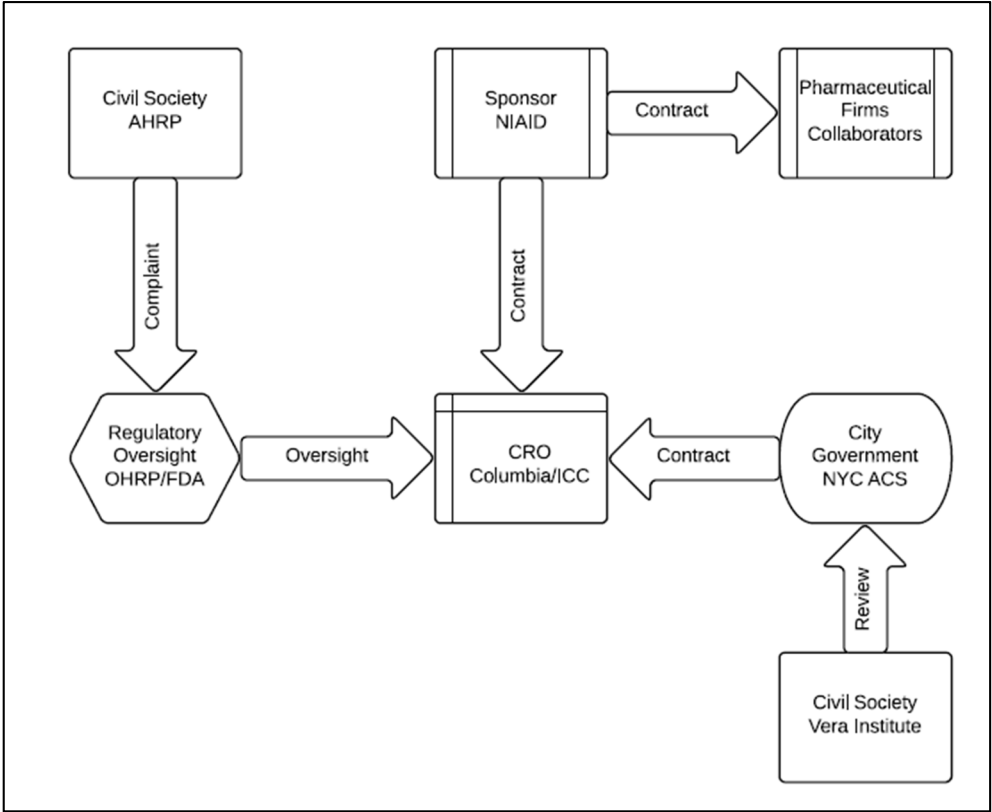
In March 2004, a civil society organization called Alliance for Human Research Protection (AHRP) filed a complaint with the US federal regulatory oversight agencies, Office for Human Research Protections (OHRP) and FDA, alleging that “federal regulations for the protection of children as research subjects have been seriously violated in federally funded HIV research...” involving “drug experiments conducted on infants and children who were under the guardianship of New York City (NYC) Agency for Children’s Services (ACS) and living at Incarnation Children’s Center (ICC), a foster care facility under contract with ACS” (Sharav, 2004). ICC is an outpatient clinic for HIV-positive children and a sub-unit of the Columbia University Pediatric AIDS Clinical Trials Unit. Additionally, ICC works collaboratively with Harlem Hospital Pediatric AIDS Program.<sup>17</sup> The fact that the children were living at ICC, a sub-unit of Columbia University, and that Columbia University was a research site for the implementation of these trials, raises concerns regarding possible conflicts of interest (EU6). The relationships amongst the various players in this case study is illustrated in figure 5 below.

The allegation of violations of federal regulations involved a group of HIV/AIDS clinical trials sponsored by NIAID, an agency of the United States government under its AIDS Clinical Trials Group (ACTG) Network. “The ACTG established and supports the largest Network of expert clinical and translational investigators and therapeutic clinical trial units in the world, including sites in resource-limited countries. These investigators and units serve as the major resource for HIV/AIDS research, treatment, care, and training/education in their communities” (AIDS Clinical Trials Group).

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<sup>17</sup> <http://liamscheff.com/wp-content/uploads/2008/11/incarnation-childrens-center.htm>

Figure 5: Illustration of a Case Study to Demonstrate Complex Relationships of Players Involved in a Clinical Trial



\* Author’s creation based on case study

The complaint listed eight clinical trials. According to ClinicalTrials.gov<sup>18</sup> registry, one of the trials was withdrawn prior to any subject enrollment. Therefore, we will focus on the remaining seven trials. Of the seven trials, two involved pharmaceutical industry collaboration: one with Genentech and MicroGene Sys Inc; and another with Lederle-Praxis Biologicals (United States National Institutes of Health, 2012). Each of the seven trials was conducted at a large number of study sites across the United States. ClinicalTrials.gov lists ICC, Columbia IMPACT Clinical Research Site and/or Harlem Hospital as a study location for each of the seven trials.

<sup>18</sup> <http://clinicaltrials.gov/ct2/home>

The complaint identified the following specific allegations of non-compliance with federal regulations:

- i) Research was not related “to the status of the children as wards” (Sharav, 2004). According to federal regulations, wards of the state may only be included in research that is: “(1) Related to their status as wards; or (2) Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards” (United States Department of Health and Human Services, 1983).
- ii) The wards of state were not “protected by a personal advocate... not associated in any way with the research, the investigator(s), or the guardian organization” (Sharav, 2004). Federal regulations require that, when research involving wards of state is approved by an IRB, “the IRB shall require appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian” (United States Department of Health and Human Services, 1983).
- iii) Individual consent was not obtained (Sharav, 2004). Federal regulations require “that adequate provisions are made for soliciting the permission of each child's parents or guardian” (United States Department of Health and Human Services, 1983). The regulations require individual parental permission and do not permit group consent. According to the complaint by AHRP, the ACS guidelines allowed for group consent of children under its guardianship by stating, "Once the hospital and ACS have executed an agreement for the trial, ACS consents to enrollment of all children who fall within the parameters of the approved protocol; provided that the child's parents consents (if parental rights have been terminated such parental consent is not necessary)."

As a result of these allegations, OHRP conducted inquiries of Columbia University Medical Center between March 2004 and February 2005. In May 2005, OHRP issued a determination of non-compliance, citing three failures, which were related to inadequacy of the recruitment and informed consent processes (EU3) and the possibility of undue influence (EU4), as follows (Cooper, 2005):



- i) “failure of the IRB to obtain sufficient information regarding the selection of wards of the state and foster children as research subjects”;
- ii) “failure of the IRB to obtain sufficient information regarding the process for obtaining permission of parents or guardians for wards of the state or foster children”;
- iii) “When some or all of the subjects (e.g., children) are likely to be vulnerable to coercion or undue influence, additional safeguards”... must be in place... “to protect the rights and welfare of these subjects... OHRP finds... a failure of the IRB to obtain sufficient information regarding such safeguards with respect to the enrollment of wards of the state or foster children.”

The OHRP required very specific corrective actions to be taken. After several rounds of communications, OHRP accepted corrective actions implemented by Columbia University Medical Center in its determination letter of February 17, 2006 (Cooper, 2006).

Separately, the New York City ACS requested independent review of the “issues related to the enrollment and monitoring of New York City foster children in clinical trials related to ... HIV...” by Vera Institute of Justice (Ross & Lifflander, 2009), an independent non-profit “center for justice policy and practice”<sup>19</sup>. Vera Institute issued its report in January 2009, which absolved ACS of most of the more serious allegations. However, the report included the disclaimer:

*...citing confidentiality laws, the New York State Department of Health (NYSDOH) refused multiple requests from Children’s Services that it use its supervisory authority to allow Vera Institute of Justice 3 staff from Vera or Children’s Services to review clinical trial research or medical records. This limited Vera’s review in several ways, including the ability to fully document the frequency and severity of toxicity (side effects), the individual outcomes of trial*

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<sup>19</sup> <http://www.vera.org/about-us>

*participation for the children in the review, and the existence of valid, signed informed consent documents.*

As a result, the AHRP made a statement on January 27, 2009 that “Denial of access to the primary records effectively undermined the validity of the Vera Institute Investigation” (Sharav, 2009). The Vera Institute’s report resulted in changes in the ACS’s “policies regarding foster children’s participation in future clinical trials” (Stein & Stainback, 2009).

## **6.2. Ethics of the Case Study**

It may be recalled that the terms *ethics* and *ethical conduct*, as used in this thesis, refer only to the principles identified as necessary for the protection of human subjects of research within the international guidelines for protection of human subjects of clinical trials, within the clinical trial literature and within the regulations for protection of human subjects of various countries, and *ethical concern*, as used in this thesis, refers to concerns about inadequate protection of human subjects of clinical trials. According to the above definitions, a number of the ethical concerns incorporated in the framework are raised through this example. There is a real or, at least, perceived, conflict of interest (EU6) of the clinical trial investigators. The ICC administration represents both the research interests of Columbia University as the parent organization, as well as the interests of the subjects who are under its guardianship. Without the presence of external independent advocates, as mandated by the regulations, it is unclear which interest was prioritized and for what reason. There is also a presence of therapeutic misconception (EU1) in this case, given that the subjects were in the care of the research site. The conflict of interest of the same individuals providing consent, while also being the guardians for the children subjects, creates a perception for the subjects that this is in their best interest and part of their standard care. Further, the children experienced undue influence (EU4) for participation, as they expect that their caretakers, who are also their guardians, would prioritize the child’s best interest. Finally, subjects were not adequately informed about their participation in the trial (EU3), as the subjects were not given the benefit of individual informed consent by their parent/guardian, a child assent, or an independent child advocate. Given that the independent investigative body was denied access to primary records, that ACS subsequently modified its policies and that Columbia University implemented corrective actions to strengthen its clinical trial oversight

procedures, it can be deducted that conflicts of interest of several of the players contributed to increased therapeutic misconception, undue influence and lack of respect for persons during the implementation of these clinical trials. It is expected that the modified policies and procedures of these organizations will result in more effective risk management in future trials.

## 7. In Terms of Maximizing Subject Welfare While Promoting Innovation

Given the overarching question of this thesis, I now summarize how each of the uncertainties identified above may directly impact subject welfare and/or innovation in table 5 below.

Table 5: Impact of Uncertainties on Subject Welfare & Innovation

Type of Uncertainty	Subject Welfare	Innovation
EU1 – Adverse Selection: Are one or more of the players causing a therapeutic misconception?	Subject does not have sufficient information to make informed decision about participation in trial	None
EU2 – Adverse Selection: Are one or more of the players not considering available alternatives adequately?	Subject does not have sufficient information to make informed decision about participation in trial	None
EU3 – Adverse Selection: Are the recruitment and informed consent processes adequately informing the subjects about their participation in research?	Subject does not have sufficient information to make informed decision about participation in trial	None
EU4 – Adverse Selection: Are any of the players exerting undue influence?	Subject does not have sufficient information to make informed decision about participation in trial	None

EU5 – Moral Hazard: How will the trial be monitored such that adverse events and unanticipated problems can be managed effectively?	Subject may be at increased risk of harm from participation	Inaccurate safety data will negatively impact overall analysis of safety and effectiveness of investigational drug
EU6 – Corruption: Is one or more player acting under the influence of an existing conflict of interest?	Subject may be at increased risk of harm due to another player's conflicted actions	Conflict of some of the players may result in improper implementation of trial, which may then result in invalid results
SU1: Who bears the cost of subject participation?	Subject may bear unexpected costs, which may negatively affect subject's financial status and insurance status	If pharmaceutical company bears significant financial burdens, it will leave the market
SU2: Who bears the cost of treatment for injury?	Subject may bear unexpected costs, which may negatively affect subject's financial status and insurance status	If pharmaceutical company bears significant financial burdens, it will leave the market
SU3: Should there be compensation for injury?	Subject and/or dependents may experience financial loss from inability to return to work	If pharmaceutical company bears significant financial burdens, it will leave the market
SU4: Should end of trial care be provided and to whom?	If experimental treatment is beneficial to subject, subject may be harmed by discontinuing it	Innovation may be promoted through end of trial care as more data from expanded use can be collected
SU5: Who will cover the cost of end of trial care?	Subject may bear unexpected costs, which may negatively affect subject's financial status and insurance status	If pharmaceutical company bears significant financial burdens, it will leave the market

## 8. Conclusion

Drug development via the clinical trial process is important and necessary in order to provide for quality healthcare of individual patients. It is also of vital importance to public health. However, there is a potential for a conflict of interest between the “commercial interests of the industry and the public health interests of patients” (Abraham, 2002). As observed in chapter 1 and as illustrated through the case study in section 6 above, conflicting goals of the various players involved in the implementation of clinical trials result in ethical violations. These conflicting agendas could be the cause for a social dilemma. Social dilemmas are “conflicts between short-term self-interest and long-term collective interest” (van Lange, Joireman, Hardisty, & van Dijk). In this chapter, I analyzed the roots of the emergence of such social dilemmas by developing a framework with the following elements: i) clinical trial as a process involving games along each step of the process; ii) strategic problems of adverse selection and moral hazard in principal-agents with asymmetric information; iii) strategic problems of corruption involving sets of players; iv) systemic problems in the form of an absence of clear rules or presence of multiple rules for conflict resolution.

The framework presented in this chapter allows us to evaluate the regulatory systems and the institutional policies and procedures that together form the governance of clinical trials by reducing the endogenous and systemic uncertainties caused by problems of adverse selection, moral hazard, corruption, absence of clear rules or presence of multiple rules. In section 5, I outline the possible mechanisms for converting the endogenous and systemic uncertainties into measurable risks. The objective of using this framework and considering the mechanisms proposed would then be to convert the uncertainties involved in the clinical trial process into measurable risks, and then to contain these risks such that harm to clinical trial subjects is minimized.

## **CHAPTER 4: CLINICAL TRIAL OVERSIGHT IN THE UNITED STATES**

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The US drug regulatory agency, the FDA, is the best resourced in the world, and is renowned for subjecting the pharmaceutical industry to stringent regulatory checks, because it must operate in a relatively transparent environment dependent on considerable legislative oversight by Congress and judicial review in the courts (Abraham, 2002).

Therefore, for the purpose of this thesis, the United States clinical trial oversight system is being used as the model against which the emerging markets' oversight systems are being benchmarked.

In this chapter, I will first present the United States oversight system, and I will then explore whether this model system provides adequate protection for human subjects while allowing for new drug innovation through the clinical trial process. The focus of this thesis is clinical trials of innovative new drugs “that serve previously unmet medical needs or otherwise significantly help to advance patient care and public health” (United States Food and Drug Administration Center for Drug Evaluation and Research, 2014). Adequate protection of human subjects will be measured by determining whether and to what extent the regulatory oversight system is able to convert the endogenous and systemic uncertainties identified in chapter 3 into measurable risks. Whether the regulatory oversight system allows for innovation is evaluated based on whether the mechanisms for converting said uncertainties into risks support the implementation of clinical trials within the given market or if they serve as barriers to the implementation of clinical trials within the given market.

### **1. Oversight in Practice**

Two government agencies within the United States Department of Health and Human Services are primarily responsible for the regulatory oversight of clinical trials in the United States. These are the Food and Drug Administration (FDA) and the Office for Human Research Protections (OHRP). Both agencies, the FDA and the OHRP, require review of proposed research by an Institutional Review Board (IRB), which is responsible for the ethical and regulatory review of the research.

## 1.1. FDA

The FDA regulations apply to all clinical investigations that propose to introduce drugs, biologics or devices to subjects within the United States or that propose to deliver drugs, biologics or devices to subjects for introduction into the United States interstate commerce (United States Food and Drug Administration, 1981, amended 2013a). Investigational drugs may not be used unless the sponsor first obtains an Investigational New Drug (IND) exemption from the FDA. In addition, approved drugs being used in an investigational manner also require that the sponsor obtain an IND prior to its use in a clinical trial. A checks and balances method is used to ensure that this requirement is fulfilled. This system holds the sponsor, investigators and the IRB all responsible for ensuring that the sponsor has obtained an IND prior to the use of an investigational drug or an approved drug in an investigational manner in a clinical trial.

## 1.2. OHRP

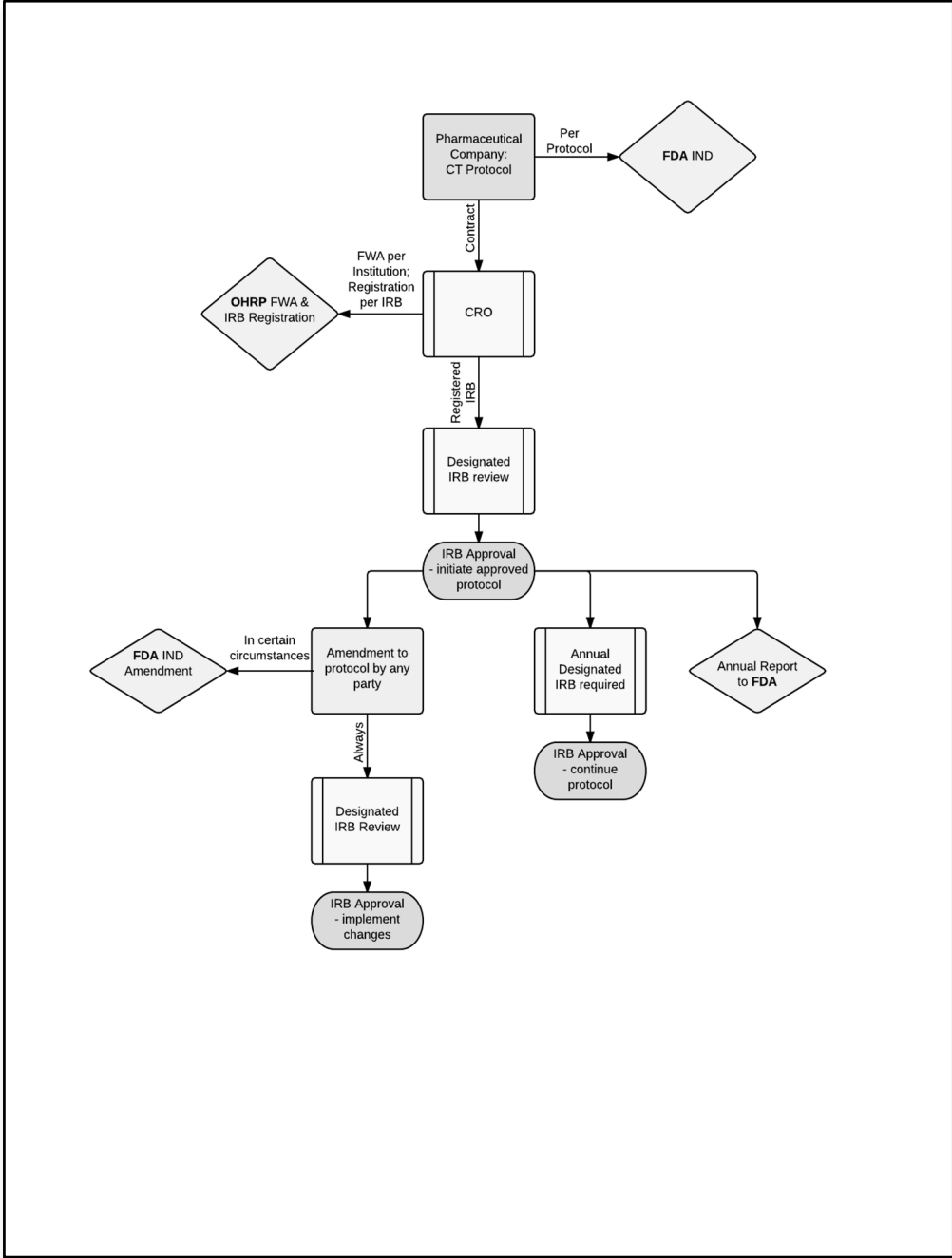
OHRP regulations apply to research involving human subjects that is “conducted, supported or otherwise subject to regulation by any federal department or agency” (United States Department of Health and Human Services, 1991, amended 2009). Figure 6 below outlines the approval process for a clinical trial.

## 1.3. Enforcement Mechanisms

The regulatory oversight approach used by both the FDA and the OHRP is based on the *theory of responsive regulation*, which is

*...centrally concerned with designing regulatory institutions and processes which stimulate and respond to the regulatory capacities which already exist within regulated firms, attempting to keep regulatory intervention to the minimum level necessary to secure the desired outcomes, but while retaining the capacity to intervene more (in terms of more stringent enforcement or the introduction of a more interventionist regime) (Scott, 2004).*

Figure 6: Clinical Trial Approval Process in the United States



\* Author’s creation



This approach places the law at the apex of the regulatory enforcement pyramid, and relies on institutions<sup>20</sup> and processes already in place within regulated firms to ensure compliance. In such a system, the regulators interact with the regulatees primarily through education and advice, until and unless there is evidence to suspect non-compliance. At this point, the regulators escalate enforcement to warning letters, civil or criminal penalties and ultimately to sanctions (Scott, 2004).

Following the responsive regulation approach, both FDA and OHRP have issued regulations for the oversight of clinical trials and research involving human subjects, which are supplemented with a large number of guidance documents. It is then the responsibility of the regulated institution to implement institutional policies and procedures to comply with the regulations. Though neither agency is directly involved in the day-to-day oversight or enforcement of clinical trials, both exercise escalating levels of enforcement power. Figure 7 below illustrates the regulatory oversight system.

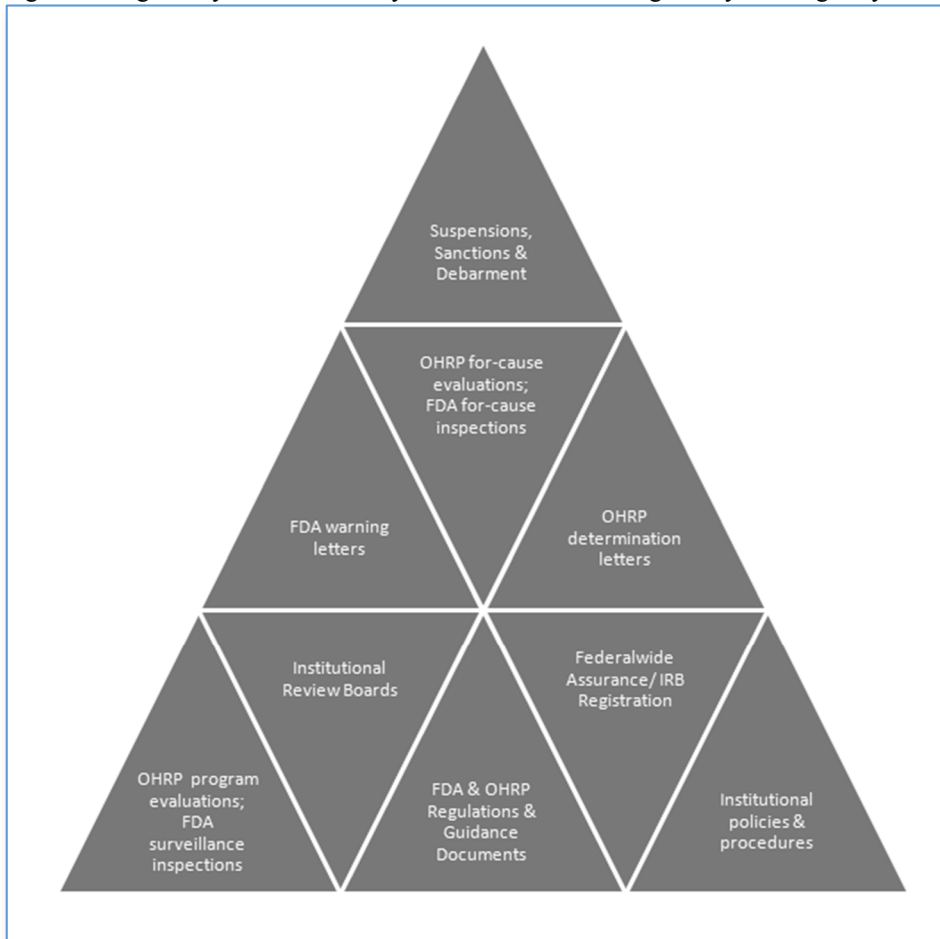
continuing non-compliance to the appropriate agency(ies) (United States Department of Health and Human Services, 1991, amended 2009; United States Food and Drug Administration, 1981, amended 2013b).

Another enforcement mechanism used at the base of the enforcement pyramid is periodic review of the regulated institutions by the federal agency to ensure that the institution is operating in compliance with federal regulations.

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<sup>20</sup> For the purpose of this chapter, the term “institution” refers to contract research organizations.

Figure 7: Regulatory Enforcement Pyramid Based on US Regulatory Oversight System



\* Author's creation

At the bottom of the enforcement pyramid reside the Federalwide Assurance (FWA) and the Institutional Review Board (IRB) registration. Every institution that is engaged in federally supported or conducted human subject research is required to file a FWA with OHRP, which serves as the institution's written assurance that it will comply with relevant federal regulations. Both the FDA and the OHRP mandate that institutions to which their respective regulations are applicable have a designated IRB, which reviews and approves proposed research or clinical trial, and ensures that the research complies with the regulations. Each designated IRB is required to be registered with the OHRP, and has responsibility to report serious or

OHRP conducts Not-For-Cause Compliance Oversight Evaluations as well as For-Cause Compliance Oversight Evaluations. Not-for-cause compliance oversight evaluations are conducted in the absence of substantive allegations or indications of noncompliance. For-cause evaluations occur, at OHRP's discretion, in response to OHRP's receipt of substantive written allegations or indications of non-compliance with the HHS regulations.

These evaluations may result in no findings, or they may result in one or more of the following outcomes:

- OHRP recommends improvements to the institution's human subject protection policies and procedures, such as better documentation of actions or communications in IRB protocol records, or clearer description of operational details in IRB written procedures. The institution is free to implement these recommendations or not.
- OHRP determines that the institution's policies and procedures for protecting human subjects in general are not in compliance with one or more requirements of the HHS regulations, or that the IRB review (or IRB records related to the review) or conduct of one or more specific research projects are not in compliance with one or more of the requirements of the HHS regulations. In these circumstances, OHRP requires that the institution develop and implement corrective actions.
- OHRP determines that there is noncompliance with the HHS regulations and, as a result, restricts or attaches conditions to its approval of the institution's FWA based on the nature and scope of the institution's noncompliance. Despite such restrictions or conditions, OHRP may allow some or all research projects to which the FWA applies to continue while the institution satisfies the terms of the restriction or conditions placed upon OHRP's approval of the institution's FWA (United States Department of Health and Human Services, 2009a).

The FDA conducts Surveillance Inspections as outlined below (United States Department of Health and Human Services Food and Drug Administration, 2006). These Inspections may or may not result in identification of non-compliance.

### **1.3.1. FDA Inspections of clinical investigators (CRO)**

FDA conducts announced and unannounced inspections of clinical investigator sites (United States Department of Health and Human Services, 2010). The inspections may be:

- to verify the accuracy and reliability of data that has been submitted to the agency;
- as a result of a complaint to the agency about the conduct of the study at a particular investigational site;
- in response to sponsor concerns;
- upon termination of the clinical site;
- during ongoing clinical trials to provide real-time assessment of the investigator's conduct of the trial and protection of human subjects;
- at the request of an FDA review division; and
- related to certain classes of investigational products that FDA has identified as products of special interest in its current work plan (i.e., targeted inspections based on current public health concerns).

An FDA inspection may result in: i) no findings; ii) findings of regulatory non-significance, in which case the FDA may issue an *Informational or Untitled Letter*; or iii) findings of *regulatory significance*, in which case the FDA issues a *Warning Letter*.

If the FDA finds that an “investigator has repeatedly or deliberately failed to comply with applicable regulatory requirements or has deliberately or repeatedly submitted false information to the sponsor or FDA in any required report”, the FDA will start a process for disqualifying the investigator from receiving investigational new drugs or biologics.

### **1.3.2. FDA Inspections of institutional review boards (IRB)**

FDA conducts two types of inspections of IRBs: surveillance inspections to review the overall operations and procedures of the IRB; and directed inspections of an IRB's review of specific clinical trial(s), which are generally in response to a complaint, clinical investigator misconduct, or safety issues pertaining to a trial or site (United States Department of Health and Human Services, 2006b).

Similar to the inspections of clinical investigator sites, an FDA inspection of an IRB may result in: i) no findings; ii) findings of deviations from the requirements of statutes and regulations for which voluntary corrective actions would be sufficient, in which case the FDA may issue an Informational or Untitled Letter; or iii) findings of serious deviations from applicable statutes and regulations, in which case the FDA issues a Warning Letter. Warning letters to IRBs require prompt corrective action.

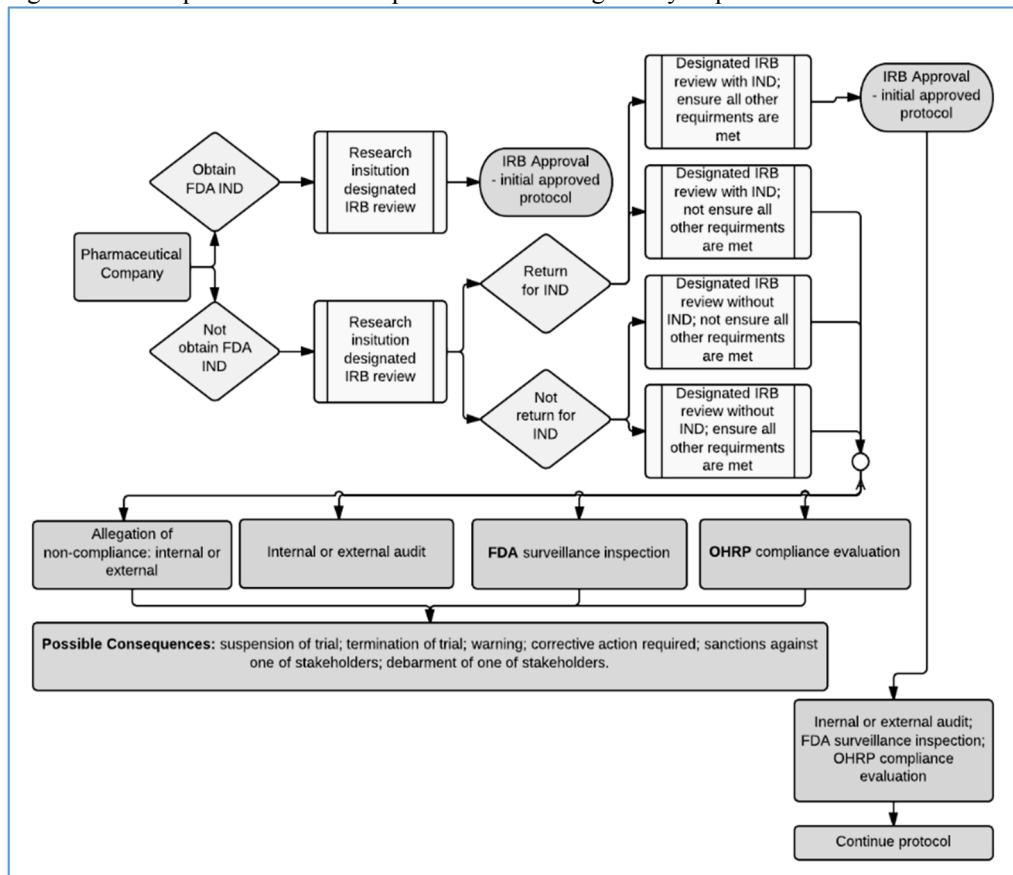
If an IRB is determined to be in non-compliance, the investigation may result in a letter to the IRB and its institution, requiring a response within a specified time. The response must describe the corrective actions that will be implemented by the IRB and its institution. In such instances, until satisfactory corrective action has been implemented, the FDA may take any of the following actions:

- Withhold approval of new studies that are conducted at the institution or reviewed by the IRB;
- Direct that no new subjects be added to ongoing studies;
- Terminate ongoing studies when doing so would not endanger the subjects;
- Notify relevant State and Federal regulatory agencies and other parties with direct interest in the Agency's action of the deficiencies in the operation of the IRB in instances when the apparent noncompliance creates a significant threat to the rights and welfare of human subjects

“If the FDA finds that an IRB or its institution has refused or repeatedly failed to comply... and the non-compliance adversely affects the rights and welfare of the human subjects, the FDA may initiate proceedings to disqualify an IRB or the institution” (United States Department of Health and Human Services Food and Drug Administration, 2006).

Figure 8 depicts possible non-compliance with these regulations and related consequences.

Figure 8: Consequences of non-compliance with US regulatory requirements



\* Author's creation based on US regulatory oversight system

## 2. Whether and to What Extent are Endogenous and Systemic Uncertainties Addressed in US Regulations?

In chapter 3, I identified endogenous and systemic uncertainties associated with the clinical trial process. In this section, I address whether and to what extent the US regulations address these uncertainties.

## **2.1. Endogenous Uncertainties**

### EU1 – Adverse Selection: Are one or more of the players causing a therapeutic misconception?

The US regulations do not directly address therapeutic misconception. However, OHRP has interpreted the regulatory requirement of providing the subjects with “a description of any benefits to the subject or to others which may reasonably be expected from the research” in the informed consent<sup>21</sup> as implying that benefits shall not be exaggerated (Borrer, 2002; United States Department of Health and Human Services). Both agencies assign the responsibility of appropriately interpreting and applying the regulations to the designated IRB.

As such, the US regulations do not provide a clear mechanism for converting this uncertainty into calculable risk, and thus does not allow for prevention of adverse selection caused by therapeutic misconception.

### EU2 – Adverse Selection: Are one or more of the players not considering available alternatives adequately?

The FDA and OHRP regulations list “disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject”<sup>22</sup> as a required element of informed consent. However, the regulations do not address requirements for consideration of all available alternatives within the local market by any of the players.

As such, the US regulations do not provide any mechanisms for converting this uncertainty into calculable risk, and thus do not allow for prevention of adverse selection caused by misinformation about available alternatives.

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<sup>21</sup> 21 CFR 50.25(a)(3),  
<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=50.25>  
45 CFR 46.116 (a)(3),

<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.116>

<sup>22</sup> 21 CFR 50.25,  
<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=50.25>  
45 CFR 46.116, <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.116>

### EU3: Adverse Selection: Are the recruitment and informed consent processes adequately informing the subjects about their participation in research?

Both the FDA and OHRP require that legally effective informed consent be obtained from each subject or a legally authorized representative prior to enrolling them in a clinical trial, list a set of basic required elements and additional elements when applicable for inclusion in the informed consent document and require that “information that is given to the subject or the representative shall be in language understandable to the subject or the representative”<sup>23</sup>.

With respect to recruitment of subjects, the OHRP is silent. However, in its guidance, FDA advises that it “expects IRBs to review the advertising to assure that it is not unduly coercive and does not promise a certainty of cure beyond what is outlined in the consent and the protocol.”<sup>24</sup>

Assessment of subject comprehension is not addressed in either agency’s regulations.

As such, the US regulations do require and/or recommend several mechanisms for converting this uncertainty into calculable risk, and thus partly allow for ways to prevent adverse selection during the recruitment and consent processes.

### EU4 – Adverse Selection: Are any of the players exerting undue influence?

Both the FDA and the OHRP regulations state, “An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence.”<sup>25</sup> It is then the responsibility of the investigators and the IRB to

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<sup>23</sup> 21 CFR 50.20,  
<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=50.20>  
45 CFR 46.116, <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.116>  
<sup>24</sup> <http://www.fda.gov/RegulatoryInformation/Guidances/ucm126428.htm>

<sup>25</sup> 21 CFR 50.20,  
<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=50.20>  
45 CFR 46.116, <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.116>



“be vigilant about minimizing the possibility for coercion and undue influence” (United States Department of Health and Human Services).

As such, the US regulations do not define any mechanisms by which this uncertainty could be converted into a calculable risk, and adverse selection through undue influence may be prevented.

EU5 – Moral Hazard: How will the trial be monitored such that adverse events and unanticipated problems can be managed effectively?

The FDA holds the sponsor responsible for reviewing and evaluating “evidence relating to the safety and effectiveness of the drug as it is obtained from the investigator”<sup>26</sup>; for reviewing and evaluating information regarding safety of a drug obtained from foreign sponsors or regulatory agencies; and for reporting this information in the form of IND safety reports to both the FDA and the participating investigators within specified time frames.<sup>27</sup> FDA also published a set of guidelines addressing the “roles, responsibilities and operating procedures of Data Monitoring Committees” to assist the sponsors in making decisions regarding when a data safety monitoring committee would be necessary and how it should function (United States Department of Health and Human Services, 2006a).

For ongoing monitoring of all FDA-regulated products, the FDA hosts MedWatch<sup>28</sup>. MedWatch is a safety information and adverse event reporting system, which allows all parties to report safety information, including adverse events, related to all FDA-regulated products. This information is then processed, and the FDA publishes news, medication alerts, recall information and labeling changes via: i) its web site; ii) subscription to MedWatch e-list, available to the public at large; iii) MedWatch Twitter followers; and iv) MedWatch RSS feed.

The OHRP holds the IRB responsible for having “written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and

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<sup>26</sup> 21 CFR 312.56,

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.56>

<sup>27</sup> 21 CFR 312.32,

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.32>

<sup>28</sup> <http://www.fda.gov/Safety/MedWatch/default.htm>

the department or agency head of (i) any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB.<sup>29</sup>” The OHRP also provides its own Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events (United States Department of Health and Human Services, 2007).

As such, the US regulations do require and/or recommend several mechanisms for converting this uncertainty into calculable risk, and thus allow for ways to prevent moral hazard caused by ineffective monitoring of adverse events and unanticipated problems.

EU6 - Corruption: Is one or more player acting under the influence of an existing conflict of interest

In the US, there is no national agenda that allows for prioritization of clinical trials. However, the National Institutes of Health’s (NIH) research prioritization may serve as a guide to identifying public health needs (National Institutes of Health, 2013). Though the NIH prioritization does not have a direct relationship to clinical trials of investigational drugs, it does have an indirect impact on clinical trials since NIH supports a significant amount of fundamental and translational research which may result in the development of new molecular entities that are then used to develop investigational drugs.

The first party amongst whom conflicts of interest must be disclosed and managed is the government oversight body who reviews the scientific protocol and gives approval to proceed with the clinical trial. In the US, this body is the FDA. The FDA review team consists of FDA staff from its various offices, as well as consultants and special government employees (advisory committee members) as needed (Center for Drug Evaluation and Research, 2013). The FDA addresses conflict of interest of consultants and special government employees. “Participation of members with potential conflicts of interest generally would occur under narrow circumstances where the potential conflict is minimal and the member's expertise is necessary to afford the committee essential expertise.” To assess this balance, the FDA

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<sup>29</sup> 45 CFR 46.103, <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.103>

uses a published algorithm, which “sets out the questions and considerations to address in a step-wise manner” (United States Department of Health and Human Services, 2008).

FDA also addresses the possible conflicts of interest of the investigator conducting the clinical trial. FDA requires disclosures of a defined set of “disclosable financial interests and arrangements” of the clinical investigator, sub-investigators, their spouses and dependent children. These include compensation by sponsor, proprietary interest, equity interest and significant interest. Depending on the nature of the disclosed conflict, the FDA may take a number of actions, ranging from audits and/or requests for additional data to refusal to use data toward agency action (United States Department of Health and Human Services, 2013).

Additionally, both the FDA and the OHRP regulations state that an “IRB may require that information, in addition to that specifically mentioned in... [the regulations], be given to the subjects when in the IRB's judgment the information would meaningfully add to the protection of the rights and welfare of subjects<sup>30</sup>. OHRP has interpreted this to include information regarding any conflicts of interests of the investigators (United States Department of Health and Human Services, 2004).

Both the FDA and OHRP regulations require that, “No IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB”.<sup>31</sup> It is then the institution and the IRB's responsibility to implement policies and procedures to identify, mitigate and manage conflicts of interests to ensure that the disclosed conflicts do not “compromise the protection of research subjects” (United States Department of Health and Human Services, 2004).

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<sup>30</sup> 21 CFR 56.109(b),

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=56.109>;

45 CFR 46.109(b), <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.109>

<sup>31</sup> 21 CFR 56.107(e),

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=56.107>

45 CFR 46.107(e), <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.107>

As such, the US regulations do require and/or recommend several mechanisms for converting this uncertainty into calculable risk, and thus allow for ways to prevent corruption caused by conflicts of interest.

## **2.2. Systemic Uncertainties**

### **SU1: Who bears the cost of subject participation?**

Regulations for both agencies state that, when appropriate, subjects should be informed of “any additional costs to the subject that may result from participation in the research”<sup>32</sup>. Additionally, the FDA requires sponsors to obtain prior FDA approval for charging subjects for the cost of investigational drugs. This approval may be granted if the trial and the use of the investigational drug meet the criteria defined in the FDA regulations<sup>33</sup>. Other costs, such as the cost of standard of care provided during the clinical trial, are not addressed in the regulations.

As such, the US regulations do not define any cost/payment models or responsibilities by which this uncertainty could be converted into a calculable risk.

### **SU2: Who bears the cost of treatment for injury?**

As a required element of informed consent, the regulations for both agencies state that subjects should be given “an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained”<sup>34</sup>.

The FDA further provides guidelines regarding the investigator’s responsibilities toward the subjects of a clinical trial. Specifically, the FDA

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<sup>32</sup> 21 CFR 50.25,

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=50.25>

45 CFR 46.116, <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.116>

<sup>33</sup> 21 CFR 312.8,

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.8>

<sup>34</sup> 21 CFR 50.25,

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=50.25>

45 CFR 46.116, <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.116>

considers the investigator responsible for i) “Providing reasonable medical care for study subjects for medical problems arising during participation in the trial that are, or could be, related to the study intervention”; and ii) “Providing reasonable access to needed medical care, either by the investigator or by another identified, qualified individual (e.g., when the investigator is unavailable, when specialized care is needed)”. (United States Department of Health and Human Services, 2009b)

Although the US regulations indicate that subjects should be informed of any treatment for injury that may be provided, and that reasonable care ought to be provided, they do not define any cost/payment models or responsibilities by which this uncertainty could be converted into a calculable risk.

#### SU3: Should there be compensation for injury?

As noted above, a required element of informed consent, per US regulations is that subjects should be given “an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained”<sup>35</sup>.

Although the US regulations indicate that subjects should be informed of any compensation for injury that may be provided, they do not provide any algorithms or responsibilities by which this uncertainty could be converted into a calculable risk.

#### SU4: Should end of trial care be provided and to whom?

Although the US regulations do not address any requirements for providing end of trial care where it may be beneficial to the clinical trial subject(s), the US regulatory system does have defined mechanisms in place by which expanded access to investigational drugs may be provided.

The regulations do not define any requirements or responsibilities for converting this uncertainty into a calculable risk.

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<sup>35</sup> 21 CFR 50.25,

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=50.25>

45 CFR 46.116, <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.116>

### SU5: Who will cover the cost of end of trial care?

The US regulations are silent on this issue, and therefore, do not provide any mechanisms for converting this uncertainty into a calculable risk.

Table 6 below provides a summary of the above analysis.

Table 6: Endogenous and Systemic Uncertainties Addressed in US Regulations

<b>Uncertainties</b>	<b>US Regulatory Requirements</b>
<u>EU1 – Adverse Selection: Are one or more of the players causing a therapeutic misconception?</u>	<ul style="list-style-type: none"><li>- Silent</li></ul>
<u>EU2 – Adverse Selection: Are one or more of the players not considering available alternatives adequately?</u>	<ul style="list-style-type: none"><li>- Disclosure required</li><li>- Mechanisms to address uncertainty <b>not</b> provided</li></ul>
<u>EU3: Adverse Selection: Are the recruitment and informed consent processes adequately informing the subjects about their participation in research?</u>	<ul style="list-style-type: none"><li>- Mechanisms to address uncertainty provided</li></ul>
<u>EU4 – Adverse Selection: Are any of the players exerting undue influence?</u>	<ul style="list-style-type: none"><li>- Not permitted</li><li>- Mechanisms to address uncertainty <b>not</b> provided</li></ul>
<u>EU5 – Moral Hazard: How will the trial be monitored such that adverse events and unanticipated problems can be managed effectively?</u>	<ul style="list-style-type: none"><li>- Mechanisms to address uncertainty provided</li></ul>

EU6 - Corruption: Is one or more player acting under the influence of an existing conflict of interest	<ul style="list-style-type: none"> <li>- Mechanisms to address uncertainty provided</li> </ul>
SU1: Who bears the cost of subject participation?	<ul style="list-style-type: none"> <li>- Disclosure required</li> <li>- Mechanisms to address uncertainty <b>not</b> provided</li> </ul>
SU2: Who bears the cost of treatment for injury?	<ul style="list-style-type: none"> <li>- Disclosure required</li> <li>- Mechanisms to address uncertainty <b>not</b> provided</li> </ul>
SU3: Should there be compensation for injury?	<ul style="list-style-type: none"> <li>- Disclosure required</li> <li>- Mechanisms to address uncertainty <b>not</b> provided</li> </ul>
SU4: Should end of trial care be provided and to whom?	<ul style="list-style-type: none"> <li>- Requirements and responsibilities not delineated</li> <li>- Mechanisms by which other players may choose to address uncertainty provided</li> </ul>
SU5: Who will cover the cost of end of trial care?	<ul style="list-style-type: none"> <li>- Silent</li> </ul>

### 3. Modus Operandi of Regulatory Enforcement: An Empirical Study

Section 1 above describes the clinical trial regulatory oversight system in the US, and section 2 provides an analysis of the US regulations to determine whether the endogenous and systemic uncertainties under question are addressed in the US regulations. I now put these together to determine whether the enforcement mechanisms in place are effective in their implementation within the US regulatory oversight system.

First, I had to establish the total number of clinical trials of investigational drugs receiving oversight from FDA and OHRP. I used the [clinicaltrials.gov](http://clinicaltrials.gov) database to obtain data on number of trials for this study, as it is the most comprehensive database of clinical trials of both publicly and privately funded clinical trials that require oversight by the FDA. The FDA requires that all clinical trials be registered with [clinicaltrials.gov](http://clinicaltrials.gov) and holds the sponsor and the CRO conducting the research responsible for ensuring that this occurs.

A search of the [clinicaltrials.gov](http://clinicaltrials.gov)<sup>36</sup> database using the search criteria, intervention = drugs, location = United States, and received from 01/01/2009 to 12/31/2013, yields a total of 21,869 clinical trials registered during the five year period. Given that the FDA started requiring registration of all clinical trials in 2007 to be certified within the application to the FDA, this number is expected to be a relatively accurate representation of the clinical trials conducted under a FDA issued IND during the 2009-2013 time period. To base my evaluations on as accurate a number of clinical trials as possible, the analysis for this study is conducted using enforcement data for years 2009-2013.

To evaluate the oversight of IRBs, I obtained information about registered IRBs from the OHRP IRBs and FWAs database<sup>37</sup>, since this is the official database of registered IRBs and institutions with FWAs. According to this database, a total of 2,592 actively registered IRBs review FDA-regulated research. Of these, 792 are non-US IRBs.

For the purpose of this study, I have made some assumptions due to limitations of the data that is available. Below is a list of the assumptions and the implications of making these assumptions.

- I am assuming one clinical investigator per clinical trial. Given the possibility that each trial may take place at multiple sites, this may be a conservative number. However, it does account for the lead investigator for each trial.

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<sup>36</sup> <http://clinicaltrials.gov/ct2/home>

<sup>37</sup> <http://ohrp.cit.nih.gov/search/search.aspx?styp=bsc>



- To account for the number of registered IRBs, I am using the current numbers according to the OHRP web site as of January 2014. Thus, I am assuming that the number of registered IRBs did not change significantly from 2009 to 2014.

### **3.1. Enforcement Actions**

#### **3.1.1. Routine and For-Cause Evaluations by Regulatory Agency (Base & Middle of the Enforcement Pyramid)**

##### **3.1.1.1. OHRP**

OHRP determination letters<sup>38</sup>, were used to determine the number of evaluations performed by the agency. OHRP issued 102 letters during the 2009-2013 time period. Since many of the letters were follow-up letters to an institution regarding a previously issued determination letter, I filtered the letters to arrive at 66 independent determinations letters. Of the 66, 32 determination letters were specific to research that did not involve clinical trials of drugs. Therefore, for the purpose of this research, a total of 34 determination letters, and therefore, 34 institutions are being considered.

With respect to these 34 institutions, the OHRP conducted a total of 23 routine program evaluations, of which 21 were located in the US and 2 located outside of US during the 2009-2013 evaluation period. In addition, 1 evaluation was performed in response to a subject complaint within the US; 9 evaluations of US institutions were performed in response to allegations of non-compliance; and 1 evaluation of a foreign institution was performed in response to allegations of non-compliance. Given that a total of 2,592 IRBs are registered as reviewing FDA regulated research, the OHRP performed routine evaluations of 1% of the total registered IRBs; and for-cause evaluations of 0.42% of the total registered IRBs.

Of the thirty-four evaluations, 10, or 29.4%, did not involve any concerns and required no further actions. The remaining 24, or 70.6%, of the institutions received a total of 65 citations. 2 citations involved systematic concerns involving the institutions' entire human research protection program. The remaining 63 citations involved either non-compliance by the PI or the IRB.

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<sup>38</sup> <http://www.hhs.gov/ohrp/compliance/letters/index.html>

## PIs

Of the 63 citations, 5, or 8%, involved non-compliance by the PI. Of these, 4 citations involved paramount non-compliance, where PIs started the research or implemented changes to the research without prospective IRB approval, or did not provide the IRB complete and accurate information. 1 citation involved a PI who did not follow the IRB approved protocol.

## IRBs

Of the 63 citations, IRBs received 58, or 92%. 6 of these citations were of paramount non-compliance, where the IRB either did not conduct a continuing annual review as required or granted an approval without obtaining sufficient information. 27 citations were a result of deficiencies in IRB operations, including: i) lack of SOPs, inadequate SOPs or SOPs not being followed; ii) inappropriate or inaccurate application of regulations by the IRB; iii) absence of quorum during IRB meeting; and iv) inadequate IRB membership. 11 citations were due to the IRB's approval of inadequate informed consent document or procedures, with 1 of these involving incomplete information about available alternatives, 1 involving incomplete information regarding the cost of participation and 1 involved IRB approval of a consent document that included coercive language. 10 citations were due to inadequate recordkeeping. 3 citations were a result of IRB's approval of research involving vulnerable populations, including children, pregnant women and prisoners, without giving adequate consideration to the required additional protections for these populations, thus potentially placing these subjects at additional risk. 1 citation was issued because the IRB did not follow its own policy on unanticipated problems.

### **3.1.1.2. FDA**

During the same period, FDA Center for Drug Evaluation and Research inspected a total of 1,893 clinical investigators and a total of 480 IRBs (United States Department of Health and Human Services, 2014). Given that the total number of clinical trials during this time period was 21,869, and assuming one clinical investigator per trial, the FDA inspected 9% of clinical investigators. With regard to IRBs registered as conducting FDA regulated research, the FDA inspected 19% of the registered IRBs.

FDA warning letters are published on the FDA web site<sup>39</sup>. A search of the FDA warning letters using the search criterion, “clinical trial,” yields a total of 20 warning letters issued during the 2009-2013 time period. Of these, 2 are related to device studies, 2 are related to studies of dietary supplements, 1 is related to an animal drug, and 2 are concerning labeling and misbranding. The remaining 13 are related to clinical trials of drugs for humans, and therefore, this number is being used as the total number of warning letters for the purpose of this study. Of the 13, 10 warning letters were issued to clinical investigators, of which 1 was also a sponsor, 2 to IRBs and 1 to a sponsor.

A second search was conducted to identify any letters missed using the criteria for search described above. This time, I browsed the letters by subject. 4 additional warning letters issued to clinical investigators were identified; 1 additional letter to an investigator, who is also the sponsor, was identified; 2 additional letters to sponsors were identified; 1 warning letter to a CRO was identified; and letters to 3 additional IRBs were identified.

### Sponsors

5 sponsors were cited by the FDA during the 5 year period. These 5 sponsors received a total of 16 citations. Of the 16 citations, 1 citation involved paramount non-compliance, where the sponsor failed to obtain an IND prior to use of an investigational drug in a clinical trial. 8 citations were directly related to monitoring or safety concerns. 4 of the citations involved procedural non-compliance issues. 1 citation involved a failure to obtain prior FDA approval for charging subjects for an investigational drug. 1 sponsor was cited for failure to disclose conflict of interest, and the final citation involved record-keeping concerns.

### CRO / Clinical Investigators

1 CRO and 15 clinical investigators were cited by the FDA during the five year period. This group was issued a total of 48 citations. Of the 48 citations, 4 citations involved paramount non-compliance, where prospective IRB approval was not sought, either initially, prior to implementing changes or at annual continuing review. 29 of these citations were related to monitoring and safety concerns, or concerns related to not conducting the trial in

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<sup>39</sup> <http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm>

accordance with the approved protocol. 9 citations involved a failure to obtain adequate informed consent. 6 citations involved procedural non-compliance issues.

### IRBs

5 IRBs were cited by the FDA during this five-year period. A total of 17 citations were issued to the 5 IRBs. 1 citation was of paramount concern where the IRB failed to review the clinical trial annually. 6 citations were due to the IRB's lack of adequate standard operating procedures (SOPs). 3 citations involved a failure by the IRB to ensure adequate informed consent. An additional 3 citations were related to inadequate documentation by the IRB. 2 citations involved the IRB's failure to apply the regulations accurately. 1 citation was a failure of an IRB member to recuse from discussion due to a conflict of interest. The final citation involved insufficient membership on the IRB.

## **3.1.2. Suspensions, Disqualifications & Debarment by Regulatory Agency (Top of the Enforcement Pyramid)**

### **3.1.2.1. OHRP**

OHRP considers much of the information regarding this highest level of enforcement actions against an investigator or institution to be confidential (United States Department of Health and Human Services, 2009a). However, determinations letters are generally issued for each of these types of actions, and published in a redacted manner. There was no determination letter during the 2009-2013 time period that indicated actions at this level.

### **3.1.2.2. FDA**

In cases where the FDA identifies repeated and/or deliberate serious non-compliance, it conducts clinical investigator disqualification proceedings, which may result in investigator disqualification actions<sup>40</sup>.

According to the FDA Clinical Investigators – Disqualifications Proceedings database<sup>41</sup>, 12 *Notices of Initiation of Disqualification Proceedings and*

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<sup>40</sup> <http://www.fda.gov/ICECI/EnforcementActions/default.htm>

*Opportunity to Explain* were issued during the 2009-2013 time period. 10 of these investigators were subsequently disqualified, and 2 were restricted. “A disqualified clinical investigator is not eligible to receive investigational drugs, biologics, or devices, and is not eligible to conduct any clinical investigation that supports an application for a research or marketing permit for products regulated by FDA”.<sup>42</sup> A restricted investigator receives lesser sanctions than disqualification in an agreement with the FDA.

Investigator restrictions and disqualifications were a result of the following: 12 actions were taken because the investigator did not follow the protocol as written. 10 actions were taken due to inadequate or inaccurate case histories. 9 actions were due to false reporting to the FDA or the sponsor. 7 were due to inadequate supervision of the clinical trial. 5 were due to inadequate drug disposition records. 4 were due to inadequate informed consent. 2 were due to a failure to report unanticipated problems to the IRB. 1 was due to a failure to protect the rights, safety and welfare of subjects. The final 1 was due to the investigator changing the protocol without IRB approval.

There is a lack of sufficient data publicly available on the causes of debarment.

#### **4. Assessment of the US Regulatory Oversight System**

To evaluate the effectiveness of the US regulatory oversight system, each of the following components of the enforcement pyramid must be considered: i) OHRP evaluations & FDA surveillance inspections; ii) IRB performance; iii) sufficiency of regulations; and iv) institutional policies and procedures.

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<sup>41</sup><http://www.accessdata.fda.gov/scripts/sda/sdNavigation.cfm?sd=clinicalinvestigatorsdisqualificationproceedings>

<sup>42</sup> <http://www.fda.gov/ICECI/EnforcementActions/ucm321308.htm#database>

#### **4.1. OHRP Evaluations & FDA Surveillance Inspections**

As noted in section 3.1.1 above, during the 2009-2013 time period, the OHRP evaluated less than 1.5% of the registered IRBs, while the FDA inspected 19% of the registered IRBs. Additionally, the FDA inspected 9% of the clinical investigators. The common rule of thumb for auditing for patient safety in clinical environments is approximately 10% of the cases (Duke University School of Medicine, 2016). Given this standard, OHRP evaluation rate of less than 1.5% of IRBs is not effective. FDA's 19% surveillance rate is effective for IRB monitoring, and its investigator surveillance rate of 9% comes close. Thus, I conclude that FDA surveillance inspection system is effective in monitoring IRBs and clinical investigators. However, OHRP evaluation system is not effective in providing oversight of human subject research. At the overall US regulatory system level, since the FDA has oversight over all clinical trials, I conclude that the overall monitoring system is effective.

#### **4.2. IRB Performance**

IRB performance is being evaluated based on the results of OHRP evaluations of IRBs and FDA surveillance inspections of IRBs. As noted in section 3.1.1 above, 70.6% of OHRP evaluations resulted in citations. Of the total citations, 92% were issued to IRBs. 20.8% of the relevant FDA warning letters were issued to IRBs. Thus, the overall effectiveness of IRBs may be questionable.

Let's now assess whether and to what extent the IRBs are effective in addressing the endogenous and systemic uncertainties in question. This again is based on the data obtained through OHRP's and FDA's public records for the purpose of the study presented in section 3 above. The citations to IRBs break down as shown in Table 7.

Table 7: Regulatory Agency Issued Citations to IRBs Under Their Purview

<b>Citation</b>	<b>Number of Citations</b>	<b>Related Uncertainty</b>
Lack of review	6 – OHRP 1 - FDA	All uncertainties
Deficient review	27 – OHRP 2 - FDA	All uncertainties
Lack of adequate SOPs / insufficient membership	7 - FDA	All uncertainties
Approval of inadequate informed consent	11 - OHRP 3 - FDA	EU3
Inadequate record keeping	10 – OHRP 3 - FDA	Unknown
Inadequate consideration of vulnerable populations	3	All uncertainties
Did not follow policy for unanticipated problems	1	EU5
Involvement of a reviewer with a conflict of interest	1	EU6

\* Based on author's calculations

To explain the relationships of the noted uncertainties:

- The absence of an IRB review or a deficient IRB review implies that the IRB does not consider any of the uncertainties. Therefore, in each of these cases, the IRB did not address how any of the uncertainties could be converted into a calculable risk based on which decisions can be made.
- Lack of adequate SOPs impacts adequate review, which in turn implies that the IRB does not sufficiently consider any of the uncertainties. Insufficient membership is combined with this citation category, since SOPs should require sufficient membership.
- When an IRB approves an inadequate informed consent, the inadequacy of the informed consent increases the possibility of adverse selection.

- Absent adequate records, whether the IRB considered any of the uncertainties or conducted an adequate review would be unknown.
- When the vulnerability, whether physical, psychological, social or economic, of a subject population is not considered, the uncertainties faced by the subject population cannot be sufficiently considered.
- When IRB policy for managing unanticipated problems is not followed, the IRB becomes a source of moral hazard.
- The involvement of a reviewer with a conflict of interest creates uncertainty based on corruption.

Given the high percentage of IRBs cited, and the significant number of citations made due to overall insufficiencies in review, I conclude that the IRB oversight system may not be efficient. Of course, this is based on a small sample of IRBs, and future studies to conduct systemic evaluations of larger sample sizes across US are warranted.

#### **4.3. Sufficiency of Regulations**

Based on the evaluation presented in section 2 above, the US regulatory requirements for addressing the uncertainties in question can be summarized as follows:

- Endogenous uncertainties: the US regulations are silent with respect to one endogenous uncertainty; address but do not define mechanisms for conversion of 2 of the endogenous uncertainties; and address and define mechanisms for conversion of 3 of the endogenous uncertainties.
- Systemic uncertainties: the US regulations are silent with respect to one systemic uncertainty; address but do not define mechanisms for conversion of 3 of the systemic uncertainties; and do not address but have a mechanism in place to convert 1 uncertainty should one of the other players choose to address it.

Thus, in terms of whether the US regulations sufficiently address the endogenous and systemic uncertainties present in the clinical trial process, though some uncertainties are addressed sufficiently, most require additional regulatory input.



#### 4.4. Institutional Policies and Procedures

Institutional policies and procedures apply to sponsors and CROs, which are inclusive of PIs/clinical investigators. Institutional policies and procedures are also being evaluated based on the results of OHRP evaluations and FDA surveillance inspections. As noted in section 3.1.1 above, 70.6% of OHRP evaluations resulted in citations. Of the total citations, 8% were issued to PIs. 79% of the relevant FDA warning letters were issued to one of these institutions. A breakdown of these citations is provided in table 8 below.

Table 8: Regulatory Agency Issued Citations to Institutions Under Their Purview

Citation	Number of Citations	Related Uncertainty
Lack of IRB review	4 – OHRP 4 – FDA	All uncertainties
Not follow approved protocol / inadequate monitoring	1 – OHRP 47 - FDA	All uncertainties
Lack of IND	1 - FDA	All uncertainties
Failure to obtain approval to charge subjects	1 – FDA	SU1
Failure to disclose conflict of interest	1 – FDA	EU6
Inadequate record keeping	1 – FDA	Unknown
Failure to obtain adequate informed consent	9 – FDA	EU3

To explain the relationships of the noted uncertainties:

- The absence of an IRB review or a deficient IRB review implies that the IRB does not consider any of the uncertainties. Therefore, in each of these cases, the IRB did not address how any of the uncertainties could be converted into a calculable risk based on which decisions can be made.
- Not following the approved protocol, and not providing adequate monitoring affect the complete implementation of a clinical trial

protocol, and thus implies that the institution did not sufficiently consider any of the uncertainties.

- Not obtaining an IND is the equivalent of not obtaining a review by the regulating agency. Thus, this also implies that none of the uncertainties were adequately addressed.
- Failure to obtain approval to charge the subjects becomes the source of uncertainty for all other players.
- The involvement of an institutional member with a conflict of interest creates uncertainty based on corruption.
- Absent adequate records, whether the institution considered any of the uncertainties or implemented the trial in accordance with the protocol is unknown.
- Failure to obtain adequate informed consent increases the possibility of adverse selection.

Based on this small sample size, it appears that significant improvement is warranted at the institutional levels. As with the assessment of IRB performance above, future studies to conduct systemic evaluations of larger sample sizes are warranted.

## **5. Conclusion**

The aim of this chapter was to determine whether the US regulatory oversight system provides adequate protection for human subjects while promoting new drug innovation through the clinical trial process. Based on the assessments above, I conclude that there are many gaps in the regulatory requirements, and needs for improvements at the levels of the IRBs and the institutional policies and procedures of the sponsors and the CROs. Given US' responsive regulatory approach, there is significant reliance on IRBs and institutional policies and procedures for adequate oversight of clinical trials, and deficiencies in these institutions' policies can negatively impact both subject welfare and clinical trial success.

At a more specific level, the needs for improvement in the US regulatory oversight system based on the assessments made in section 4 and their related impact on subject welfare and/or innovation are outlined in table 9 below.

Given the above, I conclude that the US regulatory oversight system as a whole favors innovation over subject welfare.

**Table 9: US Regulatory Oversight System's Impact on Subjects Welfare and Innovation**

<b>Uncertainty</b>	<b>Level at which improvement is required</b>	<b>Impact on subject welfare and/or innovation</b>
EU1 – Adverse Selection: Are one or more of the players causing a therapeutic misconception?	<ul style="list-style-type: none"> <li>- Regulatory</li> <li>- IRB</li> <li>- Institution</li> </ul>	<ul style="list-style-type: none"> <li>- Negative impact on subject welfare</li> <li>- No direct impact on innovation</li> </ul>
EU2 – Adverse Selection: Are one or more of the players not considering available alternatives adequately?	<ul style="list-style-type: none"> <li>- Regulatory</li> <li>- IRB</li> <li>- Institution</li> </ul>	<ul style="list-style-type: none"> <li>- Negative impact on subject welfare</li> <li>- No impact on innovation</li> </ul>
EU3 – Adverse Selection: Are the recruitment and informed consent processes adequately informing the subjects about their participation in research?	<ul style="list-style-type: none"> <li>- IRB</li> <li>- Institution</li> </ul>	<ul style="list-style-type: none"> <li>- Negative impact on subject welfare</li> <li>- No impact on innovation</li> </ul>
EU4 – Adverse Selection: Are any of the players exerting undue influence?	<ul style="list-style-type: none"> <li>- Regulatory</li> <li>- IRB</li> <li>- Institution</li> </ul>	<ul style="list-style-type: none"> <li>- Negative impact on subject welfare</li> <li>- No impact on innovation</li> </ul>
EU5 – Moral Hazard: How will the trial be monitored such that adverse events and unanticipated problems can be managed effectively?	<ul style="list-style-type: none"> <li>- IRB</li> <li>- Institution</li> </ul>	<ul style="list-style-type: none"> <li>- Negative impact on subject welfare</li> <li>- Negative impact on innovation through inaccurate analysis of trial outcomes</li> </ul>
EU6 – Corruption: Is one or more player acting under the influence of an existing conflict of interest?	<ul style="list-style-type: none"> <li>- IRB</li> <li>- Institution</li> </ul>	<ul style="list-style-type: none"> <li>- Negative impact on subject welfare</li> <li>- Negative impact on innovation through possible improper implementation of trial &amp; therefore invalid</li> </ul>

		results
SU1: Who bears the cost of subject participation?	<ul style="list-style-type: none"> <li>- Regulatory</li> <li>- IRB</li> <li>- Institution</li> </ul>	<ul style="list-style-type: none"> <li>- Negative impact on subject welfare</li> <li>- Positive impact on innovation, as pharmaceutical company is free to make any decision as long as it discloses its decision</li> </ul>
SU2: Who bears the cost of treatment for injury?	<ul style="list-style-type: none"> <li>- Regulatory</li> <li>- IRB</li> <li>- Institution</li> </ul>	<ul style="list-style-type: none"> <li>- Negative impact on subject welfare</li> <li>- Positive impact on innovation, as pharmaceutical company is free to make any decision as long as it discloses its decision</li> </ul>
SU3: Should there be compensation for injury?	<ul style="list-style-type: none"> <li>- Regulatory</li> <li>- IRB</li> <li>- Institution</li> </ul>	<ul style="list-style-type: none"> <li>- Negative impact on subject welfare</li> <li>- Positive impact on innovation, as pharmaceutical company is free to make any decision as long as it discloses its decision</li> </ul>
SU4: Should end of trial care be provided and to whom?	<ul style="list-style-type: none"> <li>- Regulatory</li> <li>- IRB</li> <li>- Institution</li> </ul>	<ul style="list-style-type: none"> <li>- Negative impact on subject welfare</li> <li>- Neutral with respect to innovation, as post-trial data may be beneficial but not always necessary</li> </ul>
SU5: Who will cover the cost of end of trial care?	<ul style="list-style-type: none"> <li>- Regulatory</li> <li>- IRB</li> <li>- Institution</li> </ul>	<ul style="list-style-type: none"> <li>- Negative impact on subject welfare</li> <li>- Positive impact on innovation, as pharmaceutical company is free to make any decision as long as it discloses its decision</li> </ul>

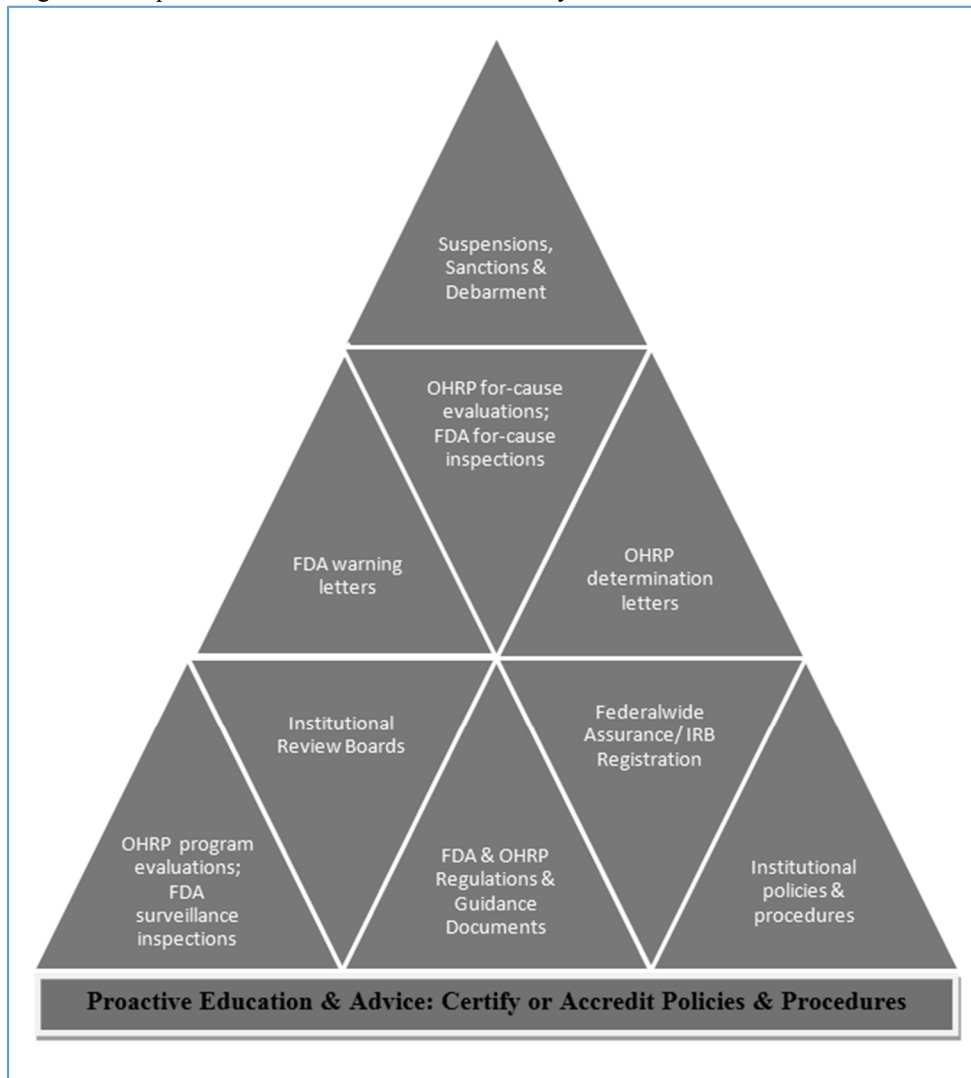
## 6. Recommendation

Given that there is significant dependence on IRB and institutional policies and procedures for effective oversight of clinical trials, and given that many of the shortcomings identified through OHRP evaluations and FDA inspections are at the IRB and institutional level, I suggest that there is a need for evaluation of IRB and institutional policies and procedures prior to their implementation.

Currently, the regulatory agencies simply inform all stakeholders of any regulatory requirements, and expect that the sponsors, CROs and IRBs will implement these requirements effectively. The only policy feedback that these institutions typically receive is in the form of a determination or warning letter, and as part of a corrective action plan following an OHRP evaluation or an FDA surveillance inspection. Though effective in gaining timely response and change when necessary, these methods are perceived as a threat by the receiving institution. The simple fact that the outcome of the evaluations and inspections are publicly available results in organizations acting in fear of reputational damage and not necessarily with the interest of all stakeholders in mind.

Looking at this from an institutional theory perspective, one may argue that, in light of the external pressure to implement corrective actions required by a governing agency, these organizations may enter into survival mode by placing a high value on “conformity with the institutional environment and the advisability of adhering to external rules and norms” (Oliver, 1991). Development and implementation of comprehensive policies and procedures that are tailored to an institutional context could not be created under such high-pressure conditions. Thus, the question becomes whether organizations should design their policies and procedures to simply align with that which has traditionally been accepted by the governing agencies, irrespective of how well these align with organizational goals and priorities; or, if organizations should strategically adapt their policies and procedures to comply with the requirements of the regulatory agencies, while ensuring that these are consistent with organizational objectives. Since the latter approach would serve both parties most effectively, I conclude that the US regulatory oversight system have an additional layer below the current base of the pyramid, which allows for a prospective rather than responsive method of is demonstrated in figure 9.

Figure 9: Proposed Modification to Enforcement Pyramid for the US



\* Author's creation

One mechanism for accomplishing this would be to introduce a process of certifying or accrediting institutional policies and procedures for the oversight of clinical trials in advance of their implementation. Essentially, the goal of this layer would be to provide active organization-level guidance and advice prior to allowing the organization to participate in the conduct of clinical trials.

## **CHAPTER 5: INDIA AS AN EMERGING CLINICAL TRIAL MARKET**

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Given the excessive costs of R&D associated with clinical trials in recent years, there has been a trend toward globalization of clinical trials, specifically, a shift of phase III clinical trials from traditional regions (North America and Western Europe) to emerging regions (Eastern Europe, Latin America, Asia, Middle East and Africa) (Thiers et al., 2008). This movement is due to a number of factors, including: i) lower cost per research subject; ii) large subject populations who are easily accessible; iii) availability of treatment naïve subject populations; iv) faster recruitment across wider demographics; and v) local government support and local endorsements by key opinion leaders (Cekola, 2007; Kelleher, 2004-2005; Shah, 2003). According to Cruickshank, et al (2006), conducting a clinical trial outside of the United States and Western Europe costs 30-65% less, depending on the country, and may be completed 6-7 months faster. As a result, the pharmaceutical company benefits from low costs, faster return on investment and longer patent protection. The public may also benefit from an earlier access to the medicine.

Another reason for the globalization of clinical trials is the growing recognition of the importance of conducting clinical trials on the local population from a scientific and ethical perspective, and the often related regulatory requirement. Most governments require one or more phases of the clinical trial associated with a given drug to be conducted locally prior to granting approval to market the drug. Scientifically, this is important as genetic/ethnic backgrounds “play a large part in determining how people respond to particular therapies (PriceWaterhouseCoopers, 2007).” Ethically speaking, it is important to demand that clinical trials in a given country are focused on the disease burden of the local population. “Research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research (Ryan et al., 1979).”

Among the emerging countries, the largest percentage of clinical trials conducted outside the United States and Europe are in Africa and Asia (Glickman et al., 2009; United States National Institutes of Health, 2012). A.T. Kearney conducted an evaluation to identify the most attractive countries for outsourcing clinical trials. The criteria used for ranking country attractiveness were size and availability of patient pool, cost efficiency,

relevant expertise, regulatory conditions and infrastructure and environment. Based on their analysis, India is the second most attractive country to offshore clinical trials, followed by Russia in the number one spot (Bailey, Cruikshank, & Sharma, 2012).

Given its number two spot as the site of choice for clinical trials, and considering the absence of the language barrier associated with the number one site (Russia), this research will focus on India as a case study representative of the emerging markets. This chapter aims to address the questions: i) What are the strengths and weaknesses of India as a clinical trial market, and what, if any, challenges does it face in the oversight of clinical trials?; ii) Whether the current oversight system provides adequate protection for human subjects while allowing for new drug innovation through the clinical trial process?; and iii) How does India's governance of clinical trials compare to the governance of clinical trials in the United States, as described in chapter 4.

## **1. Evolution of Clinical Trials in India**

### **1.1. Historical Perspective**

Unlike the serendipitous origins of clinical trials in the traditional markets described in Chapter 1, India's history of clinical trials originated with the establishment of Indian Research Fund Association (IRFA) in 1911, which was later renamed Indian Council of Medical Research (ICMR) in 1949 (Bhatt, 2010). IRFA was established by the Indian Government to provide sponsorship and coordination of medical research (Indian Council of Medical Research). The establishment of IRFA was India's first step toward the development of a local medical research industry.

India's first set of regulations governing drugs and cosmetics, The Drugs and Cosmetics Act of 1940 went into effect in 1947. However, the focus of these regulations was limited to the import, manufacture, distribution and sale of drugs and cosmetics (Imran, Najmi, Rashid, Tabrez, & Shah, 2013). The conduct of clinical trials was not yet on India's radar.

The Indian Patents Act of 1970 established process patents, prior to which there had been a product patent system established under the British rule. As Ramani and Maria (2005) explain, by the end of 1960s, population had grown, but domestic industrial capabilities were very limited and Western



multinationals in India sold essential drugs at unaffordable prices. Thus, they explain:

There were two possible solutions to this health care emergency. Either medicine could be imported in large quantities as essential commodities or incentives could be provided for the development of the local pharmaceutical industry. The Indian Government opted for the latter solution.

Following the strategy adopted earlier by Japan, China, Russia and Eastern Europe and Southern Europe, the existing IPR, the Indian Patent and Design Act of 1911 was changed. From 1970 onwards, instead of according product patents, the new IPR regime began to recognize only process patents. Initially, this was not opposed by the Western multinationals, as they did not view the Indian market to be capable of producing threatening competitors (Ramani & Guennif, 2012; Ramani & Maria, 2005).

This concept of process patents resulted in the ability to “copy still-patented drugs by slightly altering” the production process. Thus, the Indian Patents Act of 1970 was the leading force behind the Indian generic drugs market boom. An unanticipated outcome of the Indian Patents Act of 1970 and the generic drugs market boom was that it became a barrier to introduction of innovative products by the global pharmaceutical industry into India (Imran et al., 2013). Indian consumers revealed themselves to be price sensitive rather than brand loyal, as was the case in Latin America; and the price competition provided by Indian firms proved to be a strong disincentive for any multinational that wished to sell in India at prices sold in the high income countries (Ramani & Guennif, 2012).

Intellectual property discussions at the Uruguay Round of the General Agreement on Tariffs and Trade (GATT) provoked concern and uncertainties amongst the Indian generic drugs market (Nair, 2008). After much national debate and discussion, India signed the agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS) in 1994, which went into effect in 2005 (Imran et al., 2013; Nair, 2008). During this interval between 1994 and 2005, India amended The Patents Act three times in order to comply with the terms of the TRIPS agreement (World Intellectual Property Organization).

These changes in India’s patent laws resulted in an influx of contract research organizations and drug discovery by pharmaceutical industry (Nair, 2008).

India soon became an attractive clinical trials market, and the government tried to respond with efforts to bring Indian clinical trial standards to meet the international standards. The Central Ethical Committee of ICMR issued India's first *Ethical Guidelines for Biomedical Research on Human Participants* in 2000, which were later revised in 2006. From a regulatory perspective, the oversight of conduct of clinical trials was first addressed in the June 2005 revisions to Drugs and Cosmetics Act, which incorporated ICMR's ethical guidelines and Good Clinical Practices (GCP) guidelines into regulations governing the protection of human subjects of clinical trials (Bhatt, 2010; Imran et al., 2013). The evolution of India's regulatory oversight of clinical trials is depicted in figure 10 below.

Figure 10: Evolution of Clinical Trial Oversight in India

Indian Research Fund Association (IRFA) Established	Drugs and Cosmetics Act of 1940 goes into effect	IRFA renamed Indian Council of Medical Research (ICMR)		ICMR issues 1st Ethical Guidelines for Biomedical Research on Humans	Drugs & Cosmetics Act Revised; inclusion of Indian GCP	ICMR Ethical Guidelines Revised	Amendments to the Drugs & Cosmetics Act: Rules 122 DAB; 122 DAC; & 122 DD
1911	1947	1949	1970	2000	2005	2006	2013
Indian Patents Act				India's Agreement on TRIPS goes into effect			

\* Author's creation

\* Data source: (Bhatt, 2010; Imran et al, 2013)

## 1.2. India as a Global Destination for Clinical Trials

The globalization of clinical trials combined with India's signing of the TRIPS agreement, the implementation of ICMR's ethical guidelines, and the revised Drugs and Cosmetics Act were seen by many as the stepping stones for making India a global destination for clinical trials. The clinical trials market in India was slated to enjoy an expected growth rate of over 30% during 2010-2012 (Gupta & Padhy, 2011). However, contrary to this projection, the upward trend of outsourced clinical trials in India started to stagnate in 2011 (Karmarkar, 2012). According to Matthew (2012), "The number of new trials (in India) grew from 115 in 2005 to 234 in 2008, though it remained almost flat at 260, 246 and 254, respectively, in the years that followed". Similarly, the Boston Consulting Group's 2005 projection that the

Indian clinical trials market would hit \$1 billion by 2011 fell short, as it placed the 2011 market size at \$498 million (Matthew, 2012).

Some attributed this downward trend to increased concerns regarding the ethical conduct of clinical trials in India (Bhan, 2012; Glickman et al., 2009; Kelleher, 2004-2005; Petryna, 2005; Shah, 2003). These ethical concerns included exploitation of populations for whom clinical trials may be the only means for obtaining healthcare; lack of truly informed consent from populations who may not have an understanding of the experimental state or nature of drugs being offered nor of the alternatives available to them; conduct of clinical trials related to diseases that do not disproportionately affect the population of India; and acceptance of ethically compromised experimental design due to lower standards of healthcare as compared to the developed countries (Matthew, 2012; Politzer & Krishnan, 2012).

Alternately, some scholars suggested that this downward trend might be a result of shortcomings in two areas of the regulatory system. First, it could be because of capacity constraints, i.e. the regulatory capabilities are such that India was not able to handle an increasing volume of clinical trials. For instance, Karmarkar (2012) suggests that the downward trend may be a result of delays caused by a lengthy regulatory approval process. The lengthy approval process, in turn, was a result of insufficient resources. Second, it could be due to the quality of regulatory capabilities, especially with respect to sufficiently protecting the interests of clinical trial subjects. Politzer and Krishnan (2012) raised concerns about the “regulatory failures” resulting from “lapses in the functioning of so-called ethical committees”.

### **1.3. Challenges Faced by an Emerging Market**

Increase in conduct of clinical trials in India was accompanied by “extensive media coverage, both in India and abroad... with serious, documented cases of poor, illiterate citizens including children of India being used as ‘guinea pigs’” (Joshi, 2012). In addition, the Ministry of Health and Family Welfare reported that “a total of 1,514 subjects have died in the years 2008 to August 2010 during clinical trials” (Ranjit Roy Chaudhury Expert Committee, 2013). Media reports of unethical conduct and a large number of deaths of subjects in clinical trials led the non-governmental organization, Swasthya Adhikar Manch, to file a public interest litigation. The Supreme Court of India requested information regarding the clinical trials conducted in India, including subject deaths and compensation for injury from the Ministry of

Health and Family Welfare in October 2012, and in the absence of receiving the requested data, the court gave a “clear call for accountability” in January 2013 (Vaidya, 2013).

This call from the Supreme Court triggered significant changes in regulations governing clinical trials, effectively altering the clinical trial environment in India. The 2013 changes in the Indian regulations and their impact are discussed in greater detail in section 3 below.

## **2. Regulatory Oversight System in Place Through 2012: An Empirical Study**

To better understand the significant concerns raised by scholars and media, as well as to identify the challenges faced by the Indian regulatory agencies in the oversight of clinical trials, I conducted a study to evaluate the regulatory framework for oversight of clinical trials in India in 2012. The study was completed prior to the Indian government’s publication of the amendments to its regulations in 2013. For this study, I used two methods: i) documentary analysis of the existing regulations and related literature analysis; and ii) semi-structured interviews with government representatives, pharmaceutical company representatives, contract research organization representatives, researchers and civil society representatives. Findings from my 2012 study are included in this section.

### **2.1. Documentary and Literature Analysis**

For the purpose of documentary analysis, I identified India’s regulatory architecture at the time through a review of the web sites for India’s Ministry of Health and Family Welfare, India’s Central Drugs Standard Control Organization and Indian Council of Medical Research, and verified this information in interviews with Indian government officials. No additional oversight bodies were identified by the Indian government officials, or through Google search or Google Scholar search for India’s oversight of clinical trials.

#### **2.1.1. Oversight System in Place through 2012**

The Ministry of Health and Family Welfare’s (MHFW) Drugs and Cosmetics Act and Rules (Ministry of Health and Family Welfare, 2005) is the primary legislation governing clinical trials in India. The Central Drugs Standard Control Organization (CDSCO) is the regulatory agency responsible for

enforcing this legislation. Through 2012, the only tool used by the CDSCO to govern clinical trials was a set of guidelines, Good Clinical Practices (GCP) for Clinical Research in India (Central Drugs Standard Control Organization). Though the Indian Council of Medical Research (ICMR) formulates, coordinates and promotes biomedical research in line with India's national health priorities, and does not have a governing role per se, the guidelines issued by ICMR, Ethical Guidelines for Biomedical Research on Human Participants (Indian Council of Medical Research, 2006), were the primary document providing rules for ethical conduct of clinical trials in India, and was used as a reference and guide by the CDSCO in its enforcement.

As noted in chapter 1, an effective oversight system must include:

- (i) The scientific design of the clinical trial must be consistent with sound research design, such that the trial will yield valid data in a most effective manner;
- (ii) The proposed procedures do not unnecessarily expose subjects to risk; and potential benefits outweigh the potential risks;
- (iii) The clinical trial must be monitored in order to ensure compliance with applicable regulations and ethical guidelines; and
- (iv) Consequences of non-compliance and rewards for ensuring compliance must be considered (Baram, 2001; Califf et al., 2003).

As demonstrated in previous chapters, these 4 elements of oversight can be addressed through regulatory oversight, ethics committee review to ensure protection of human subjects of clinical trials, and institutional policies and procedures of the sponsors and CROs to implement clinical trials in a scientifically valid manner that also protect the subjects of clinical trials.

#### **2.1.1.1. Regulatory Oversight**

As noted in section 1.3 above, serious concerns regarding adequate regulatory oversight of clinical trials were raised in 2012-2013. The Department-Related Parliamentary Standing Committee on Health and Family Welfare, charged with evaluating "the functioning of the Central Drugs Standard Control Organization" (Department-Related Parliamentary Standing Committee on Health and Family Welfare, 2012) cited lack of enforcement in a number of areas, including:

- a) Per Indian GCP (Central Drugs Standard Control Organization), “If the drug is already approved/marketed in other countries, phase III data should generally be obtained on at least 100 patients distributed over 3-4 centres primarily to confirm the efficacy and safety of the drug in Indian patients when used as recommended in the product monograph for the claims made.” However, the Parliamentary Standing Committee reported, “In the case of 11 drugs (28%) Phase III clinical trials mandated by Rules were not conducted.”
- b) Clinical trials were conducted on fewer than recommended number of subjects and/or sites.
- c) Required expert opinions were not sought.
- d) Phase III clinical trials are expected to be conducted in subjects representing the major ethnic groups in India. However, this has not been adequately considered when approving clinical trial sites.

The Parliamentary Standing Committee also cited CDSCO for lack of transparency of the clinical trial and drug approval processes; and an absence of mechanisms for post-approval monitoring of both clinical trials and post-marketing surveillance.

### **2.1.1.2. Ethics Committee Review**

Literature and documentary review revealed three areas of concern related to the ethics committee review of clinical trials in India through 2012: i) uncertainties regarding the qualifications of the ethics committees; ii) lack of enforcement of ethics committee review; and iii) inadequate ethics committee reviews.

#### **Uncertainties regarding the qualifications of ethics committees**

India had numerous ethics committees. However, the regulations did not provide, and therefore the ethics committees were not established, based on: i) any required criteria for their qualifications; ii) any required criteria for their standard operating procedures; iii) any required criteria for their approval of clinical trials; or iv) any required reporting of non-compliance with CDSCO and ICMR guidelines or ethics committee approved protocol. Data regarding the exact number of ethics committees in operation in India in 2012 was not available; however, a 2008 survey by the Indian Council of Medical Sciences identified *at least* 71 institutions with ethics committees at that time (Mathur & Muthuswamy, 2008). According to the Association for

the Accreditation of Human Research Protection Programs (AAHRPP), Inc.'s web site<sup>43</sup>, only 3 institutions in India had been accredited by AAHRPP at the time. Additionally, there was no mechanism in place to identify, track, educate and monitor these ethics committees.

Literature also revealed growing concerns regarding the quality of reviews performed by the existing ethics committees, including: a) non-compliance with the MHFW's regulations; b) lack of adequate training; c) inadequate or absent standard operating procedures; d) inadequate or absent record keeping; e) lack of consideration for members' conflicts of interest; f) insufficient monitoring; g) absence of standard operating procedures; and h) lack of sufficient resources, such as neutral meeting space (Bavdekar & Thatte, 2008; Desai, 2012; Kadam & Karandikar, 2012). These concerns were reinforced by the United States Department of Health and Human Services in its October 15, 2012 Determination Letter issued to the Tata Memorial Hospital, in which Tata Memorial Hospital was cited for related failures by its Institutional Review Board (Ethics Committee) (Borror, 2012).

#### Lack of enforcement of ethics committee review

The ICMR guidelines state, "It is *mandatory* (italicized for emphasis) that all proposals on biomedical research involving human participants *should* (italicized for emphasis) be cleared by an appropriately constituted Institutional Ethics Committee." The statement itself is confusing in that it claims that ethical review is mandatory, while using the suggestive term, "should". The MHFW required that all clinical trials receive approval from an ethics committee prior to their initiation. The CDSCO Guidelines recommended "the sponsor and/or investigator *should* (italicized for emphasis) seek the opinion of an independent Ethics Committee..." Since the only regulating body that granted an official approval for the conduct of clinical trials in India was the CDSCO, this recommendation did not have the backing of an enforcement mechanism to require receipt of approval by an ethics committee. According to the former Deputy Director General of ICMR and currently a Course Director for ICMR's Bioethics Education for India, Dr. Nandini Kumar<sup>44</sup>, CDSCO's approval letters, at the time of the study,

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<sup>43</sup> <http://aahrpp.org/learn/find-an-accredited-organization>

<sup>44</sup> Telephone interview on November 8, 2012

reminded the sponsors and investigators that they should obtain an ethics committee approval, without any further verification. CDSCO did not have a mechanism in place to require the submission of ethics committee approval prior to issuing its approval for conduct of a clinical trial.

### Inadequate ethics committee reviews

Srivastava (2010) identifies another cause of ineffective, and sometimes lack of, ethics review based on local culture. Indian culture gives significant deference to the authority of the physician. As such, Indian physicians are not accustomed to oversight of their role as a physician, regardless of whether it is for clinical care or research purposes. Srivastava identifies the following related concerns: a) physicians “view ethics as a hindrance to their research ideas taking final shape”; b) “fear of disclosing their intellectual pursuits”; and c) “fear of disapproval and encroachment on their academic freedom”. According to Srivastava, these issues can be resolved with adequate education and training in bioethics, which would result in a greater appreciation of ethical oversight.

#### **2.1.1.3. Consequences of Inadequate Oversight**

In the absence of adequate regulatory and ethics committee oversight, the influx of clinical trials into India posed a significant threat of exploitation of the Indian population, especially given the socio-economic vulnerability of some of its populations. Srivastava notes that “eight Indian states account for more poor people than 26 of the poorest African nations combined” (Srivastava, 2010). This threat was already realized in a number of cases where trials were suspended by the Indian government after they had already been initiated and safety or other concerns were brought to light primarily by the Indian civil society. Examples include:

- a) Research involving the administration of human papilloma virus (HPV) vaccine to 2,300 girls in Andhra Pradesh and Gujarat. The vaccine was administered to young girls from “poor and disadvantaged social groups” without adequate scientific justification and absent appropriate informed consent (Mattheij et al., 2012; Shenoi, 2012).
- b) Several clinical trials conducted by the Bhopal Memorial Hospital and Research Center have been suspended, as they involved the testing of unapproved (for research or standard



of care) drugs on victims of the “Bhopal gas tragedy”, using inappropriate consent procedures and resulting in 14 deaths (Politzer & Krishnan, 2012; Shenoi, 2012).

- c) Suspension of multicenter phase III clinical trials of the diabetes drug, ragaglitazar, “when animal studies reported urinary bladder tumours in rats” (Bagale, Joshi, & Kadam, 2011; Maiti & Raghavendra, 2007).
- d) National Human Rights Commission (NHRC) of India’s investigation into the enrollment of 200 mentally ill subjects without adequate informed consent in the city of Indore, state of Madhya Pradesh, “concluded that this indicated ‘complete ineffectiveness of regulatory controls’” (Chowdhury, 2013). Several such incidences in the same state resulted in a ban on all new trials by a committee of the state government (Yee, 2012).

## **2.2. Expert Interviews**

To validate the concerns identified from documentary and literature analysis, I conducted semi-structured interviews with representatives of United States and Indian government; global pharmaceutical companies with presence in India; contract research organizations with presence in India; and Indian researchers and civil society.

### **2.2.1. Interview Methodology**

This interview study involved the use of qualitative semi-structured interviews. The final number of interviews was determined as the study progressed, depending on when saturation was reached and no new challenges or barriers were identified. I concluded the study with a total of thirteen interviews.

“In studies that use semi-structured interviews that are analysed using content analysis, sample size is often justified on the basis of interviewing participants until ‘data saturation’ is reached” (Francis et al., 2010). Francis et al (2010) developed a two-step process for establishing data saturation. First, one must “specify a minimum sample size for initial analysis.” The goal of the initial analysis is to identify common themes, leading to data saturation. The second step is to identify “how many more interviews will be conducted without new ideas emerging”, thus establishing a stopping criterion. Francis

et al point out that, when interview studies are conducted to obtain “content validity”, as is the case in my study, “the appropriate sample size is a function of the purpose of the study and the complexity, range and distribution of experiences or views of interest, rather than of the statistical parameters used in quantitative research.” They go on to prove these principles using two studies. The first Francis et al study, a “study of clinical behaviour of healthcare professionals, had an initial sample size of 10, with a stopping criterion of 3. At the 10 interview mark, there were no new shared beliefs for two interviews.” Interview 13 revealed a new belief, and saturation was reached at 14 interviews. The second Francis et al study on “the acceptability of a potential genetic screening service” had an initial sample size of 17 and a stopping criterion of 3. Data saturation was reached at 17 interviews.

Given that the scope of my interviews was very narrow, essentially to establish the strengths and weaknesses or challenges of the oversight of clinical trials in India at the time of the interviews, I established an initial sample size of 13, with the pre-established stopping criterion of 3 should there remain any new ideas or thoughts after the initial 13 interviews. No new themes emerged after the 10<sup>th</sup> interview, thus saturation was reached at 10 samples. I included a few experts from the US in order to obtain a more objective internal and external perspective, and to see whether there are any initial differences in perception from within and outside India. However, the majority of the subject population was from within India. The 13 interviewees included:

- 2 government officials from the US, of which one was physically located in the US and the other in India
- 2 government officials from India
- 1 researcher from the US
- 3 researchers from India, one of whom is also part of Indian civil society and the other two also play a role in the Indian government
- 1 ethics committee member from India
- 1 civil society representative from India
- 1 pharmaceutical industry representative from US; and
- 2 pharmaceutical industry representatives from India

Potential interviewees were identified using snowball sampling through professional networks and word of mouth.

*(Snowball sampling) technique offers real benefits for studies which seek to access difficult to reach or hidden populations. Snowball sampling can be applied... as an 'informal' method to reach a target population. Snowball sampling is used most frequently to conduct qualitative research, primarily through interviews (Atkinson & Flint, 2001).*

The population I was trying to reach falls in the “difficult to reach” category, for the following reasons: government officials are often hesitant to discuss shortcomings of the regulatory systems, as they may be implicated as the cause of the shortcomings or may face repercussions from the body that employs them; pharmaceutical company representatives and CRO representatives are often hesitant to discuss oversight of clinical trials due to chance of revealing proprietary information; and ethics committee members are hesitant to discuss their review processes, both due to reputational implications about the committee on which they sit and the potential of revealing confidential information. Thus, trust through familiarity with the interviewer or their social network is important in accessing these populations. Researchers in this area are few, and due to their busy schedules, familiarity with the person contacting them significantly increases their responsiveness.

The interviewees were approached via email and LinkedIn invitations, and interviewees were asked to name additional contacts within the categories of individuals being interviewed. Interviews were conducted telephonically. I used a pre-defined interview script, which was used as a guide. Follow-up questions were then asked based on individual responses. The interviewees were first asked open-ended questions to identify the top three strengths and weaknesses of India as a clinical trial market. They were then asked to rate, on a five-point scale, the efficiencies and transparency of CDSCO’s approval and safety monitoring procedures; and the effectiveness, qualifications and transparency of the ethics committees in India with whom they have had interactions. These ratings were then followed by additional open-ended questions to obtain the respondent’s views on anticipated barriers to the implementation of imminent changes in the Drugs and Cosmetics Rules;

whether the government has sufficient resources to provide adequate human subject protection; and whether and what role civil society may play in protecting human subjects. The interviews were recorded in a notebook, and then transcribed into an Excel sheet, which was used to code the responses. Due to the manageable size of the data set, the data was analyzed in Excel, using tables and color-coding by the author.

## 2.2.2. Interview Results

Upon completion of the 13 interviews, it was clear that no new themes were emerging, and there was great consensus amongst the respondents. Therefore, I concluded the interviews with the 13.

### 2.2.2.1. Strengths and Weaknesses of India as a Clinical Trial Market

Each of the respondents was asked to identify the top three strengths and the top three weaknesses of India as a clinical trial market.

#### Strengths of India as a Clinical Trial Market

When asked to identify the top three strengths of India as a clinical trial market, 85% of the respondents identified large treatment naïve population as one of the top three strengths. Available infrastructure and qualified investigators were the second most commonly identified strength, identified by 62% of the respondents. The third most commonly identified strength was low cost, by 31% of the respondents. The identified strengths are outlined in table 10 below.

Table 10: Strengths of India as a Clinical Trial Market Identified Through Expert Interviews

<b>Top Three Strengths</b>	<b>#s</b>	<b>Total</b>	<b>%</b>
Large treatment naïve population	11	13	85%
Infrastructure / Qualified PIs	8	13	62%
Low Cost	4	13	31%
Diverse Population	3	13	23%
Modified Regulations	3	13	23%
Easy Recruitment due to direct benefit	3	13	23%

As noted in the introduction of this chapter, faster recruitment across diverse demographics is often cited in literature as one of the reasons for moving clinical trials to an emerging market. However, none of the respondents identified this as a strength. On the contrary, one Indian researcher, who is also active in Indian civil society, highlighted that this may constitute a weakness by stating:

*Many people have no insurance and no money; therefore, there is more systemic pressure to look for alternatives; this combined with doctors looked at as demigods who people believe have the patient's best interest in mind results in quick recruitment. There is a conflict of interest because the PI has the best interest of the clinical trial in mind, but is recruiting his/her own patients; therefore, there is a therapeutic misconception.*

### Weaknesses of India as a Clinical Trial Market

India's regulatory architecture was the most common weakness of India as a clinical trial market identified by 77% of the respondents. The second most common weakness identified was a lack of awareness and education by 62% of the respondents. The third most common weakness identified was social disparity resulting in ethical concerns by 38% of the respondents. Table 11 below lists the weaknesses identified by the respondents.

Table 11: Weaknesses of India as a Clinical Trial Market Identified Through Expert Interviews

<b>Top Three Weaknesses</b>	<b>#s</b>	<b>Total</b>	<b>%</b>
Regulatory Architecture	10	13	77%
Lack of awareness & education	8	13	62%
Recently modified regulations	5	13	38%
Social disparity / ethics	5	13	38%
Infrastructure / Qualified Pis	4	13	31%
Conflict of interest	2	13	15%

Indian government officials responded to the concerns regarding the regulatory architecture by stating:

*Clinical trials is a very new phenomenon; India previously produced generics only; the oversight system is new and we didn't have an elaborate system to handle this before - until 9 months ago - it was a very straightforward system - you ask for approval, you get approval; then NGOs went to UN with a cry regarding exploitation and the Supreme Court took it very seriously, and said that we must get the house in order; so, last 9 months, we amended the rules and made stricter rules.*

We have made elaborate arrangements, but how we will implement these is unsure; we have not yet had sufficient time to evaluate the impact on what is happening in the field.

#### **2.2.2.2. Regulatory Oversight of Clinical Trials**

Regarding the regulatory oversight of clinical trials, three themes emerged as most prominent (each identified by 46% of respondents): i) regulations and guidelines are issued but not applied or not applied consistently or effectively; ii) reforms are taking place that are giving a positive direction and increased quality and accountability; and iii) there is a lack of effective safety monitoring, both on the part of the government and the ethics committees.

##### **Inconsistent or ineffective regulatory enforcement**

Though 46% of the respondents agreed that there is inconsistent or ineffective application of the regulations, the perceived reasons for this inconsistency or ineffectiveness varied.

From outside India, a representative of the US government noted, “lack of resources is one component of... that lack of enforcement.” However, a US researcher observed:

*[It is] not a matter of resources; they already have representatives of the government in all the regions;*

*they need more of the consistent hammering down of principles of the law; checking whether laws are applied; local representatives should be taking regular screening.*

The perceived reasons for the ineffective enforcement within India differed from those outside. An Indian ethics committee member identified the source of the problem to be the Drug Controller General's (DCG) office:

*DCG India is the first gatekeeper, who is understaffed and extremely corrupt. The reviewers for DCG have conflicts.*

The ethics committee member further observed:

*[There is a lack of] sincere effort to protect our people. The government talks only about market potential, but not about protections of the people.*

An Indian researcher and civil society member indirectly concurred with this statement by stating that it is not a matter of lack of resources; rather:

*If there is political will, it will create funds; wealth can be generated; it is not a poor government.*

### Reforms moving in positive direction

A member of the Indian pharmaceutical industry was supportive of the new reforms and stated that the reforms "are giving positive direction and increasing the quality and accountability; they will hold all stakeholders responsible." A member of the US pharmaceutical industry concurred, "the process is becoming more efficient now; in the past, it was very bureaucratic." A researcher, who is also a member of the Indian government noted that, with "increased oversight, there is increased ... possibility of compliance." Another member of the Indian government expects reforms to continue in a positive direction, as increased resources are dedicated to the reforms:

*We went from having 12 inspectors to 140 now, and the proposed number is 1400. The government has*

*dedicated 3,000 crore rupees to restructure & reorganize this in a 5-year plan (2012-2017) and to have total 2500 people.*

### Lack of effective safety monitoring

Regarding safety monitoring, Indian researchers stated:

*Safety monitoring is almost not there; they [the government] do not have inspectors to visit sites; media & civil society reports result in scandals & only those clinical trials are audited & some suspended; no others are audited.*

*Until recently, adverse events were being reported per requirements; but it was not clear what happened after they were reported.*

Though majority of the interviewees agreed that the reforms are moving in a positive direction, first impressions of inspections that started to increasingly take place in response to the Supreme Court's ruling were not very positive. An Indian researcher, who is also a member of the Indian government, indicated that "inspections are now increasingly happening... but the implementation is not consistent." A member of an Indian ethics committee noted:

*They did one visit for only one particular study, though they didn't explain why they chose the study. The audit report they gave us was very vague and didn't have anything specific. They need to get trained on how to audit. The controller from the local level was not trained on how to do an audit, and didn't ask a lot of the questions that I think would be relevant.*

A member of the Indian pharmaceutical industry noted that the reporting aspect of safety monitoring is now effective, "but other areas like protecting the public through analysis and outcome is not effective."



### **2.2.2.3. Ethical Oversight of Clinical Trials**

When asked about their experiences with and perceptions of ethics committees in India, 31% of the interviewees believed that the ethics committees were effective, with another 31% stating that they did not know whether the ethics committees were effective. Effectiveness of the ethics committees was considered significantly varied by 23% of the respondents. Ethics committee members, with whom the respondents interacted, were considered qualified by 46% of the interviewees, and 54% of the interviewees believed that the ethics committees in India with which they interacted had a transparent process.

### **2.2.2.4. Implementation of Proposed Changes**

A total of 54% of the interviewees indicated that they foresee problems with the implementation of changes being proposed by the government. The theme of inconsistent or ineffective enforcement that originated during the discussion on regulatory enforcement resurfaced during the discussion on possible barriers to implementation of changes. Interviewees expressed concern that, though the regulations may change, they may not be implemented in an effective way. For example, an Indian researcher who is also a member of Indian civil society, and a member of the Indian pharmaceutical company both consider the requirements of the ethical committee registration system to be “barebones.” They noted that, although the ethics committees were already being registered, it was simply a registration system, with no system for accountability or verification of quality standards.

### **2.2.2.5. Role of Civil Society**

An overwhelming 85% of the interviewees concurred that civil society can play a positive role in the protection of human subjects of clinical trials. There was agreement amongst the interviewees that the role of the civil society should be to raise public awareness and education regarding the purpose and the ethics of clinical trials, and regarding subjects’ rights. Interviewees also concurred that civil society should function as subject advocate. Though majority of the interviewees indicated that civil society can play such a role, 46% agreed that civil society was not playing a positive and constructive role at the time of the interviews. The interviewees’ perceptions of civil society and the reasons for believing that civil society was not playing a positive role varied: i) they have their own agenda; ii) they sensationalize

the problems; iii) they are not transparent with information that is the basis for the concerns they raise; and iv) they have misperceptions about the need for clinical trials.

### **2.2.3. Discussion**

Based on documentary and literature analysis, I had identified shortcomings in both regulatory oversight and ethics committee reviews of clinical trials in India under the system in place through 2012, resulting in exploitation of vulnerable populations. Interview respondents validated this.

The interview respondents also raised concerns that directly relate to some of the endogenous and systemic uncertainties under study. Specifically, the following uncertainties are identified as areas of concern in the quotes presented above:

- EU1 – Adverse Selection: Are one or more of the players causing a therapeutic misconception?
- EU4 – Adverse Selection: Are any of the players exerting undue influence?
- EU5 – Moral Hazard: How will the trial be monitored such that adverse events and unanticipated problems can be managed effectively?
- EU6 – Corruption: Is one or more player acting under the influence of an existing conflict of interest?

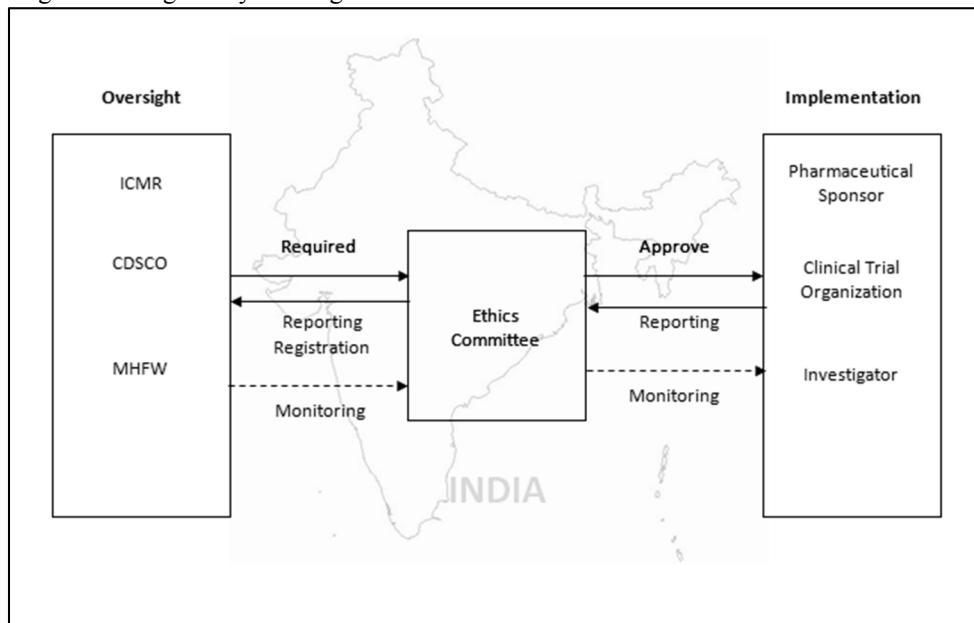
## **3. Current Regulatory Architecture**

Section 2 gives insight into the regulatory framework in place through 2012, and perceptions regarding the imminent changes in regulatory framework. In this section, I will describe the current regulatory architecture; outline the regulatory changes introduced in 2013; and provide an analysis of the current regulations in terms of the regulatory considerations of endogenous and systemic uncertainties.

As noted in the previous sections, the MHFW's Drugs and Cosmetics Act and Rules are the primary legislation governing clinical trials in India. The CDSCO is the regulatory agency responsible for enforcing this legislation. Though the ICMR formulates, coordinates and promotes biomedical research in line with India's national health priorities, and does not have a governing

role per se, the guidelines issued by ICMR influence both the MHFW's formation of legislation and CDSCO's regulatory oversight. Figure 11 below provides an overview of the regulatory oversight of clinical trials in India.

Figure 11: Regulatory Oversight in India



\* Author's creation based on Indian regulatory oversight system

2013 was a landmark year for India's clinical trial market, with a significant overhaul of the regulatory requirements for the oversight of clinical trials in India. Three critical amendments to the Drugs and Cosmetics Rules went into effect in 2013: i) Rule 122 DAB<sup>45</sup>, published on January 30, 2013 addressed compensation in case of injury or death during clinical trials; ii) Rule 122 DAC<sup>46</sup>, published on February 1, 2013, established conditions for approval to conduct clinical trials, including requirements for clinical trials to be conducted in compliance with approved protocols, in compliance with the requirements of the Act, in accordance with Good Clinical Practice Guidelines and only after approval from an ethics committee; and iii) Rule 122 DD<sup>47</sup>, published on February 8, 2013, required registration of ethics

<sup>45</sup> <http://cdsco.nic.in/writereaddata/GSR%2053%28E%29%20dated%2030.01.2013.pdf>

<sup>46</sup> <http://cdsco.nic.in/writereaddata/GSR%2063%28E%29%20dated01%2002.2013.pdf>

<sup>47</sup> <http://cdsco.nic.in/writereaddata/G.S.R%2072%28E%29%20dated%2008.02.2013.pdf>

committees and established composition requirements for ethics committees. In addition, on April 2, 2013, the Directorate General of Health Services Office of Drugs Controller General issued a memo, which formalized the clinical trial monitoring process. By means of the memo, the Directorate General required all zonal offices of CDSCO to maintain “records of the details of names, qualification etc. of Investigators, and clinical trial sites falling under their jurisdiction and also constitute Expert Committees to conduct clinical trial inspections” (Singh, 2013). Once the CDSCO has had sufficient time and opportunity to implement and enforce these newly established regulations, their effectiveness can be evaluated in future research.

The current regulatory environment, including all regulatory changes implemented in 2013, will be used in this section to evaluate the oversight of clinical trials in India in terms of the endogenous and systemic uncertainties and risks identified in chapter 3.

### **3.1. Regulatory Considerations of Endogenous and Systemic Uncertainties**

In chapter 3, I identified the endogenous and systemic uncertainties associated with the conduct of clinical trials. In chapter 4, I evaluated whether and to what extent these uncertainties are addressed within the US regulatory system. In this section, I will evaluate whether and to what extent these uncertainties are addressed in the current Indian regulatory system. Given the ICMR and GCP guidelines are not enforceable, this section will focus on regulatory requirements only.

EU1 – Adverse Selection – Are one or more of the players causing a therapeutic misconception?

The Indian regulations do not address therapeutic misconception.

EU2 – Adverse Selection: Are one or more of the players not considering available alternatives adequately?

Indian regulations are silent on the consideration of available alternatives.

EU3 – Adverse Selection: Are the recruitment and informed consent processes adequately informing the subjects about their participation in research?

The Drugs and Cosmetics Rules, require voluntary written informed consent from the subject or legal representative, and hold the ethics committee responsible for ensuring the adequacy of the informed consent process. In addition to the requirement of obtaining effective informed consent, the MHFW issued an Order on November 19, 2013 (Directorate General of Health Services, 2013b) requiring “audio-visual recording of the informed consent process of each trial subject, including the procedure of providing information to the subject and his/her understanding on such consent... while adhering to the principles of confidentiality.”

With respect to the inclusion of children, the regulations indicate that parent or legal guardian consent must be obtained, and that the assent of the child must be obtained to the extent possible. With respect to adults with diminished cognitive ability, the regulations refer to consent from legal representative of the subject. However, who may serve in that capacity is unclear. A search of indiankanoon.org, which is a database of all laws, judgments and acts issued by the Indian government, yielded only one possibly relevant definition of *legal representative*. This is within The Mental Health Act of 1987<sup>48</sup>, which assigns mental health decision-making responsibilities to a relative or friend. The term, “friend”, is not defined; however, the term, “family”, is defined as “any person related to the mentally ill person by blood, marriage or adoption.” Whether this applies to consent for participation in a clinical trial is unclear. In a presentation, Dr. Ravindran, Professor of Medicine and Medical Ethics at St. John’s Medical College Bangalore, concluded, “There is a need for clear guidance on the identification of persons who are legally authorized to provide informed consent on behalf of incompetent adults” (Ravindran).

EU4 – Adverse Selection: Are any of the players exerting undue influence?

The Indian regulations are silent on the issue of coercion.

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<sup>48</sup> <http://indiankanoon.org/doc/185191195/>

EU5 – Moral Hazard: How will the trial be monitored such that adverse events and unanticipated problems can be managed effectively?

Indian regulations require the investigator to report all serious and unexpected adverse events to the sponsor and the ethics committee; the sponsor is then responsible for reporting these to the CDSCO.

Ongoing monitoring has been formalized with the regulatory changes of 2013. Rule 122 DAC adds additional requirements, notably: i) CDSCO officers may inspect clinical research sites at any time, with or without prior notice; and ii) the inspecting officers may issue a warning letter detailing any deficiencies, recommend that the study be rejected or discontinued, suspend or cancel the clinical trial permission, or debar the investigator(s) or sponsors. The site inspection described in Rule 122 DAC was further defined in a memorandum from the Directorate General of Health Services issued on April 26, 2013, which requires that zonal expert committees and drug inspectors must inspect the clinical trial sites in their zone at least once per year (2013a). At the central level, the Office of Drugs Controller General has formulated an expert committee to review all serious adverse events of deaths to determine whether the reported death was related to the clinical trial (2014).

EU6 - Corruption: Is one or more player acting under the influence of an existing conflict of interest?

Similar to the US, there is no nationally defined agenda that allows for prioritization of clinical trials. However, the ICMR's "research priorities coincide with the National health priorities". Though the ICMR prioritization does not have a direct relationship to clinical trials of investigational drugs, it can be used as a guide by the CDSCO with respect to which clinical trials to approve, since much of the fundamental research conducted or sponsored by ICMR is focused on reducing "the total burden of disease and to promote health and well-being of the population" (Indian Council of Medical Research).

Rule 122 DD<sup>49</sup> requires conflict of interest disclosure and management for the ethics committee members. Additionally, it is noted that members of the

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<sup>49</sup> <http://cdsco.nic.in/writereaddata/G.S.R%2072%28E%29%20dated%2008.02.2013.pdf>

Independent Expert Committee for review of deaths should not have any conflicts of interest (Office of Drug Controller General (India), 2014) and that members of the panel of experts for evaluation of applications for clinical trials should not have any conflicts of interest (Directorate General of Health Services, 2012). However, the Rule does not discuss the specific processes for disclosure and management of possible conflicts of interest of the ethics committee members or the expert committee members. Thus, it is not clear how the risk of conflict of interest associated with these committee members are minimized or managed. The regulations do not address the conflicts of interests of the research team members.

#### SU1: Who bears the cost of subject participation?

Indian regulations are silent on whether subjects can bear any cost of participation.

#### SU2: Who bears the cost of treatment for injury? and SU3: Should there be compensation for injury?

The 2013 Rules 122 DAB and 122 DAC require the sponsors to provide free medical management in case of an injury occurring to a clinical trial subject (Rule 122 DAB (1)), as well as financial compensation (Rule 122 DAB (2) & (3)). An injury is considered related to the clinical trial if it occurs due to: adverse effects of investigational products; departure from approved protocol, scientific misconduct or negligence; failure of investigational product to provide intended therapeutic effect; administration of placebo providing no therapeutic benefits; or concomitant medication administered as part of approved protocol (Rule 122 DAB (5)).

Further, according to Rule 122 DAB, the sponsor and the investigator are responsible for reporting all injuries to the ethics committee and the licensing authority, and in case of deaths, to the expert committee. The ethics committee, and in case of deaths, the expert committee, makes recommendations regarding the cause of injury and the compensation to the licensing authority, who then makes the final determinations. It is unclear whether and to what extent this newly introduced process will be able to convert this uncertainty into a measurable risk.

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SU4: Should end of trial care be provided and to whom?

Indian regulations are silent on this issue.

SU5: Who will cover the cost of end of trial care?

Indian regulations are silent on this issue.

Table 12 below provides a summary of the above analysis.

Table 12: Endogenous and Systemic Uncertainties Addressed in Indian Regulations

<b>Uncertainty</b>	<b>Indian Regulatory Requirement</b>
EU1 – Adverse Selection: Are one or more of the players causing a therapeutic misconception?	- Silent
EU2 – Adverse Selection: Are one or more of the players not considering available alternatives adequately?	- Silent
EU3: Adverse Selection: Are the recruitment and informed consent processes adequately informing the subjects about their participation in research?	- Mechanisms to address uncertainty provided
EU4 – Adverse Selection: Are any of the players exerting undue influence?	- Silent
EU5 – Moral Hazard: How will the trial be monitored such that adverse events and unanticipated problems can be managed effectively?	- Mechanisms to address uncertainty provided
EU6 - Corruption: Is one or more player acting under the influence of an existing conflict of interest	- Mechanisms to address uncertainty provided
SU1: Who bears the cost of subject participation?	- Silent
SU2: Who bears the cost of treatment for injury?	- Mechanisms to address uncertainty provided
SU3: Should there be compensation for injury?	- Mechanisms to address uncertainty provided
SU4: Should end of trial care be provided and to whom?	- Silent
SU5: Who will cover the cost of end of trial care?	- Silent



### 3.2. Impact on Subject Welfare and Innovation

Given the very recent changes in Indian regulations, it is not possible to perform an objective evaluation of the implementation of these regulations and their real impact on subject welfare and/or innovation. Once sufficient time to implement all the new changes has passed, future studies to assess the effectiveness of these changes may be conducted. For now, I present a preliminary assessment of the regulatory requirements as written, and their possible impact on subject welfare and/or innovation. The impact is outlined in table 13 below.

Table 13: Impact of Indian Regulatory Oversight on Subjects Welfare and Innovation

<b>Uncertainty</b>	<b>Impact on subject welfare and/or innovation</b>
EU1 – Adverse Selection: Are one or more of the players causing a therapeutic misconception?	<ul style="list-style-type: none"> <li>- Negative impact on subject welfare</li> <li>- No impact on innovation</li> </ul>
EU2 – Adverse Selection: Are one or more of the players not considering available alternatives adequately?	<ul style="list-style-type: none"> <li>- Negative impact on subject welfare</li> <li>- No impact on innovation</li> </ul>
EU3: Adverse Selection: Are the recruitment and informed consent processes adequately informing the subjects about their participation in research?	<ul style="list-style-type: none"> <li>- Required mechanisms may promote subject welfare</li> <li>- Requirement for audio-visual recording may become barrier to innovation if subjects are not agreeable to being recorded</li> </ul>
EU4 – Adverse Selection: Are any of the players exerting undue influence?	<ul style="list-style-type: none"> <li>- Negative impact on subject welfare</li> <li>- No impact on innovation</li> </ul>
EU5 – Moral Hazard: How will the trial be monitored such that adverse events and unanticipated problems can be managed effectively?	<ul style="list-style-type: none"> <li>- Required mechanisms may promote subject welfare</li> <li>- Required mechanisms may promote innovation</li> </ul>
EU6 - Corruption: Is one or more player acting under the influence of an existing conflict of interest	<ul style="list-style-type: none"> <li>- Requirement to disclose conflicts of interest may promote subject welfare; however, lack of defined mechanisms for disclosing and managing these may negatively impact subject welfare.</li> <li>- Requirement to disclose conflicts of interest may promote</li> </ul>

	innovation; however, lack of defined mechanisms for disclosing and managing these may negatively impact innovation.
SU1: Who bears the cost of subject participation?	<ul style="list-style-type: none"> <li>- Negative impact on subject welfare</li> <li>- Negative impact on innovation</li> </ul>
SU2: Who bears the cost of treatment for injury?	<ul style="list-style-type: none"> <li>- Positive impact on subject welfare</li> <li>- Negative impact on innovation due to very broad definition of “related” injury, which exposes sponsors to expansive costs</li> </ul>
SU3: Should there be compensation for injury?	<ul style="list-style-type: none"> <li>- Positive impact on subject welfare</li> <li>- Negative impact on innovation due to very broad definition of “related” injury, which exposes sponsors to expansive costs</li> </ul>
SU4: Should end of trial care be provided and to whom?	<ul style="list-style-type: none"> <li>- Negative impact on subject welfare</li> <li>- Neutral with respect to innovation, as post-trial data may be beneficial but not always necessary</li> </ul>
SU5: Who will cover the cost of end of trial care?	<ul style="list-style-type: none"> <li>- Negative impact on subject welfare</li> <li>- Positive impact on innovation, as pharmaceutical company is free to make any decision as long as it discloses its decision</li> </ul>

Given the above, I conclude that there are many areas in which the Indian regulatory requirements must be further improved if a balance of subject welfare and innovation is to be reached.

## **4. India-US Comparison**

Chapter 4 describes the governance of clinical trials in the US, and the present chapter, thus far, describes the governance of clinical trials in India. In this section, I will compare the oversight of clinical trials in the two countries.

### **4.1. Effective Oversight**

At the beginning of chapter 1, I identified the 4 elements of effective oversight that allow for an acceptable risk/benefit ratio for the design and conduct of a clinical trial: i) sound research design to yield valid data, which requires adequate scientific review by regulatory agency approving conduct of trial; ii) protection of human subjects of trial through adequate ethics committee oversight; iii) adequate monitoring of clinical trials; and iv) consequences of non-compliance and reward for compliance.

#### **Regulatory oversight**

In the US, the FDA “is responsible for approving the use of the Investigational New Drug (IND) application, which must be submitted by the sponsor to the FDA for all clinical trials involving new drugs or biological products. The FDA's primary objectives in reviewing an IND are, in all phases of the investigation, to ensure the safety and rights of participants, and in Phases 2 and 3, to help ensure the quality of the scientific drug evaluation is sufficient to permit evaluation of the drug’s effectiveness and safety.” (National Institute of Allergy and Infectious Diseases, 2014).

In India, “The Drugs Controller General of India (DCGI) is responsible for reviewing, evaluating, and approving clinical trial applications for an unregistered medicine, and for any new indication or dosage regimen of a registered medicine. All new clinical trial applications in India must be evaluated in regard to the following parameters: assessment of risk versus benefit to the patients; innovation vis-à-vis existing therapeutic option; unmet medical need in the country” (National Institute of Allergy and Infectious Diseases, 2014).

Both countries’ regulatory review requires assessment of the risk/benefit to the subjects, and the safety and effectiveness of the investigational drug.

However, India adds the consideration of therapeutic options and medical needs of the country.

An important aspect of the regulatory oversight process is the transparency of its process, which allows all players to understand the decisions being made and the effectiveness of the process itself. Respective agencies of both countries have published their policies and procedures with regard to the approval process for conducting a clinical trial / obtaining an investigational new drug (IND) exemption, as well as safety monitoring requirements and processes on their public web sites.

Though not directly related to the clinical trial approval process, both countries also require registration of clinical trials in a national database. Clinicaltrials.gov in the US is publicly available<sup>50</sup>, and data accessible for search. The Clinical Trials Registry – India subscribes to World Health Organization’s International Clinical Trials Registry Platform<sup>51</sup>, through which a user can perform searches for data on registered clinical trials in India. These databases provide information regarding individual clinical trials, their trial sites, and varying degrees of trial specific data. Indirectly, these databases can provide information regarding trials that have been approved.

US FDA rolled-out an agency-wide transparency initiative in 2010<sup>52</sup>. Thus far, the initiative has led to increased transparency with regard to safety monitoring, as noted in the safety monitoring sub-section above. Though Indian CDSCO posts safety alerts on its web site<sup>53</sup>, a searchable database is not available.

FDA transparency with respect to individual clinical trial approval status is limited. For example, as of the end of 2014, the IND Activity Reports<sup>54</sup> only provide data through 2008. However, data on the drugs being used in clinical

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<sup>50</sup> <http://clinicaltrials.gov/>

<sup>51</sup> <http://www.who.int/ictrp/en/>

<sup>52</sup> <http://www.fda.gov/aboutfda/transparency/default.htm>

<sup>53</sup> <http://www.cdscn.in/forms/SearchMore.aspx?Id=33>

<sup>54</sup>

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/>

trials, and therefore granted an IND, is publicly available within [clinicaltrials.gov](http://clinicaltrials.gov) database for all registered trials. Real time data on individual IND approval times and processes is not readily available. India publishes current list of drugs approved for use in clinical trials<sup>55</sup>.

### Ethics committee review for protection of human subjects

Both US and India rely on independent oversight bodies (IRB/ethics committee) to provide initial and ongoing oversight for protection of human subjects, as defined in the respective regulations. Both countries also require that only those IRBs/ethics committees who have registered with the national IRB/ethics committee registration system review clinical trials. The ethics committee review process in the two countries has similar aims and serves similar functions.

FDA requires that only those IRBs that are registered with OHRP review FDA-regulated research. Ethics committee registration became mandatory in India in February 2013. Respective agencies of both countries provide information about the registered IRB/ethics committee on their respective web sites.

Both countries depend on institutional policies to define the requirements for IRB/ethics committee member training, and IRB/ethics committee monitoring. In addition to institutional monitoring, both countries have defined policies and procedures for agency monitoring of IRB/ethics committee through routine evaluations and inspections.

### Standard mechanisms for safety monitoring

Respective agencies of both countries have established criteria and timelines for reporting of adverse events during the conduct of a clinical trial, and both also have regulatory bodies that ultimately receive and process this information. US also employs ongoing monitoring of regulated products through MedWatch<sup>56</sup>, an online safety information and adverse event reporting system, which allows for adverse events to be reported, processed and resulting information to be published for public access. India currently

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<sup>55</sup> <http://cdsco.nic.in/forms/SearchMore.aspx?Id=11>

<sup>56</sup> <http://www.fda.gov/Safety/MedWatch/>

does not have a comparable mechanism for making safety and adverse event information readily available. Finally, US has an extensive post marketing monitoring program.

In 2010, India introduced a pharmacovigilance program<sup>57</sup>, allowing for a post marketing monitoring system that “monitor(s) the safety of medicine information from many sources to “include spontaneous adverse drug reaction (ADR) reporting mechanism, medical literature published worldwide, action taken by regulatory authorities in other countries.” India currently does not analyze the reported adverse events internally; rather, these are “sent to WHO-Uppsala Monitoring Centre (UMC) for analysis and signal detection”. (National Coordination Centre: Indian Pharmacopoeia Commission, 2013)

Unlike in the US, where post-marketing monitoring is incorporated into the Med Watch system, there is no similar system for dissemination of the safety information to the public in India.

#### **4.2. Endogenous and Systemic Uncertainties**

Another point of comparison is the manner in which the two countries’ regulatory agencies address the endogenous and systemic uncertainties faced by the various players. Table 14 below provides a side-by-side comparison of whether the two countries’ regulations address these uncertainties. Based on this comparison, I make the following conclusions: i) though the US regulations make requirements related to some of the endogenous uncertainties that are not addressed in the Indian regulations, they do not provide mechanisms for addressing the uncertainties or for converting them into calculable risks; therefore, the US and Indian regulations are comparable with respect to their ability to address endogenous uncertainties; ii) the Indian regulations address systemic uncertainties more clearly compared to the US regulations.

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<sup>57</sup> [http://www.ipc.gov.in/PvPI/pv\\_home.html](http://www.ipc.gov.in/PvPI/pv_home.html)

Table 14: Comparison of US & Indian Regulatory Requirements

<b>Uncertainties</b>	<b>US Regulations</b>	<b>Indian Regulations</b>
EU1 – Adverse Selection: Are one or more of the players causing a therapeutic misconception?	- Silent	- Silent
EU2 – Adverse Selection: Are one or more of the players not considering available alternatives adequately?	- Disclosure required - Mechanisms to address uncertainty <b>not</b> provided	- Silent
EU3: Adverse Selection: Are the recruitment and informed consent processes adequately informing the subjects about their participation in research?	- Mechanisms to address uncertainty provided	- Mechanisms to address uncertainty provided
EU4 – Adverse Selection: Are any of the players exerting undue influence?	- Not permitted - Mechanisms to address uncertainty <b>not</b> provided	- Silent
EU5 – Moral Hazard: How will the trial be monitored such that adverse events and unanticipated problems can be managed effectively?	- Mechanisms to address uncertainty provided	- Mechanisms to address uncertainty provided
EU6 - Corruption: Is one or more player acting under the influence of an existing conflict of interest	- Mechanisms to address uncertainty provided	- Mechanisms to address uncertainty provided

SU1: Who bears the cost of subject participation?	<ul style="list-style-type: none"> <li>- Disclosure required</li> <li>- Mechanisms to address uncertainty <b>not</b> provided</li> </ul>	- Silent
SU2: Who bears the cost of treatment for injury?	<ul style="list-style-type: none"> <li>- Disclosure required</li> <li>- Mechanisms to address uncertainty <b>not</b> provided</li> </ul>	- Mechanisms to address uncertainty provided
SU3: Should there be compensation for injury?	<ul style="list-style-type: none"> <li>- Disclosure required</li> <li>- Mechanisms to address uncertainty <b>not</b> provided</li> </ul>	- Mechanisms to address uncertainty provided
SU4: Should end of trial care be provided and to whom?	<ul style="list-style-type: none"> <li>- Requirements and responsibilities not delineated</li> <li>- Mechanisms by which other players may choose to address uncertainty provided</li> </ul>	- - Silent

## 5. Discussion and Conclusions

At the beginning of this chapter, I asked three questions. I thus address these questions based on the findings of my studies presented above.

### 5.1. What are the strengths and weaknesses of India as a clinical trial market, and what, if any, challenges does it face in the oversight of clinical trials?

Literature review and expert interviews both revealed that the strengths of India as a clinical trial market are large treatment naïve population, available infrastructure and qualified investigators, and low cost. Literature also identifies faster recruitment as a strength. However, experts who were interviewed argue that, though faster recruitment is great for innovation, as it allows for quicker conclusions to the clinical trials, it might be a result of conflicts of interest of the physician recruiters, therapeutic misconception and undue influence. I, therefore, conclude that, prior to the 2013 regulatory changes, the characteristics that made India a strong clinical trial market were also the source of several endogenous uncertainties, and the manner in which these uncertainties were being addressed at the time favored innovation over



subject welfare. This question then switches to the question of whether the regulatory overhaul of 2013 introduces mechanisms to convert these endogenous uncertainties into measurable risks. I address this in section 5.2 below.

Literature review and expert interviews both revealed that the weaknesses of India as a clinical trial market are its regulatory architecture, lack of awareness and education of the public and potential subjects, and social disparity. These findings were further supported by the results of both literature review and expert interviews that highlighted more specific concerns regarding ineffective regulatory oversight and the ineffectiveness of the ethics committee reviews. The weaknesses thus are also the challenges faced by the oversight system. I will answer the question of what, if any, challenges does the Indian oversight system face by answering whether the regulatory overhaul of 2013 addressed the two primary shortcomings identified by the empirical study.

### Regulatory Oversight

One of the concerns identified regarding regulatory oversight was that even when the regulations include certain requirements, such as expert opinions and subject diversity, these were not being implemented or enforced by the CDSCO during its review process. The primary reason for this was identified as a lack of dedicated resources. According to its Targets/Roadmap/Capacity Building: 2013-2020 plan (Central Drugs Standard Control Organization, 2012), CDSCO plans to significantly increase its staff and the number of experts at both the central and zonal levels. In addition, the CDSCO plans to establish a National Drug Regulators Training Academy for ongoing education of the regulators.

Another concern regarding regulatory oversight was the lack of transparency of the clinical trial and drug approval processes. Again, the CDSCO plans to implement an e-governance system to not only improve the processing of clinical trial application and the monitoring of clinical trials, but also to increase transparency of its processes (Central Drugs Standard Control Organization, 2012). In the interim, the CDSCO has introduced additional

features on its web site, such as daily dispatch details and calendar of expert committee meetings<sup>58</sup>.

The final concern regarding regulatory oversight was a lack of effective safety monitoring. The 2013 regulatory reforms introduced significant changes in this area. The CDSCO established new rules regarding the reporting of serious adverse events, and introduced subject matter expert panels to review such events (Office of Drugs Controller General (India), 2014). In addition, Rule 122 DAC introduced requirements for inspections and enforcement mechanisms such as warning letters, suspensions and debarment. The 2010 Guidance on Clinical Trial Inspection (Directorate General of Health Services, 2010) has now been highlighted as a resource for all inspectors.

Whether these plans will materialize, and whether these, along with the changes already made, will be sufficient to ensure adequate regulatory oversight must be evaluated by future research.

### Ethics Committee Oversight

One area of concerns regarding ethics committee oversight of clinical trials was the qualifications of the ethics committee members, particularly with respect to bioethics and familiarity with regulatory requirements. Rule 122 DD sets forth the requirements for the composition of an ethics committee and requires ethics committees to be registered with the licensing authority. The *System for Prescreening of the Applications for Registration of Ethics Committees* indicates that a “preliminary scrutiny of the applications” takes place to ensure compliance with the requirements set forth in Rule 122 DD. The Rule defines the basic professional or non-professional qualifications of the ethics committee members, and states that “members *should* (italicized for emphasis) be conversant with the provisions of clinical trials...” as required by the applicable regulations and Good Clinical Practices. In addition, the CDSCO issued a *Checklist for Submission of Applications for Registration of Ethics Committee*<sup>59</sup>, which indicates that applications should

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<sup>58</sup> <http://www.cdsco.nic.in/forms/SearchMore.aspx?Id=3>

<sup>59</sup>

<http://www.cdsco.nic.in/writereaddata/CHECKLIST%20FOR%20SUBMISSION%20192013.pdf>

include “documents, *if any* (italicized for emphasis), that the members of the committee are conversant...” Though the regulations suggest that members be conversant in GCP and regulatory requirements, they do not require education and training of ethics committee members with respect to biomedical ethics or regulatory requirements. Thus, it is unlikely that the changes implemented thus far will address this concern.

Another area of concern was the enforcement of the ethics committee review requirement, i.e. verification of whether an ethics committee, in fact, reviewed the given clinical trial. The recently published *Clinical Trial and New Drugs Application* checklist includes checkboxes for identification of ethics committee and inclusion of ethics committee approval. It is unclear how this requirement would be enforced, since neither the regulations nor the checklist require actual verification of the ethics committee review, initially, or on an ongoing basis. Whether the expected increase in clinical trial inspections and reliance on institutions to self-regulate will prove to be an effective mechanism for ensuring ethics committee review must be evaluated by future research.

A third concern regarding the ethics committee oversight was the inadequacy of the review by the ethics committees. Ethics committees are required to submit their standard operating procedures (SOPs) with their request for registration. The degree of scrutiny given to the individual SOPs is yet to be determined. The level of review of these SOPs will determine the degree of their effectiveness. This must also be evaluated in future research. In addition to the review of the SOPs prior to their implementation, the effective implementation of the approved SOPs must also be monitored. Although Rule 122 DD indicates that an ethics committee’s registration may be suspended or canceled if there is evidence of non-compliance by the ethics committee, mechanisms for monitoring ethics committees are not defined. Finally, the concern of inadequate ethics committee review overlapped with the concern regarding the qualification of ethics committee members, specifically that the adequacy of the reviews was lacking because the members were not sufficiently trained in bioethics and regulatory requirements. This issue has yet to be resolved.

## **5.2. Whether the current oversight system provides adequate protection for human subjects while allowing for new drug innovation through the clinical trial process?**

As noted in section 3 above, additional improvements in the Indian clinical trial oversight system are required in order to balance subject welfare and innovation. With respect to half of the endogenous and systemic uncertainties involved in the clinical trial process, the current Indian regulations are either silent or do not provide mechanisms to convert the uncertainty into measurable risk.

The uncertainties that are addressed and for which mechanisms for implementation have been provided relate to informed consent process (EU3), trial monitoring (EU5), conflicts of interest (EU6), cost of treatment for injury (SU2) and compensation for injury (SU3). However, as observed in section 3 above, the balance of uncertainties in these areas has shifted, and the new requirements may result in a negative impact on innovation.

## **5.3. How does India's governance of clinical trials compare to the governance of clinical trials in the United States, as described in chapter 2.**

India has adopted the US model of oversight of clinical trials. Both countries have issued regulations and guidelines for oversight of clinical trials. Both countries have regulatory bodies (US FDA and Indian CDSCO) that grant approval to conduct clinical trials of specific experimental treatments; and both countries rely on the ethics committees (IRB in US) to ensure ethical and compliant implementation of clinical trials.

Both countries rely heavily on IRB/EC and institutional policies and procedures for effective oversight that ensures protection of clinical trial subjects. Whereas the US has a federalwide assurance system, which binds the institutions to a commitment to regulatory and ethical compliance, Indian ethics committee registration system requires the ethics committees to submit its SOPs to the licensing authority at the time of requesting registration. Given both countries' reliance on IRB/EC and institutional oversight, both would benefit from prospective institutional policy review, education and advice, as recommended in section 6 of chapter 4.

There are opportunities for improvement in the regulatory oversight of clinical trials in both countries, if subject welfare and promotion of innovation were to be balanced. The framework presented in this thesis can be used as a guide toward establishing mechanisms for maximizing subject welfare and avoiding barriers to innovation by oversight system in both countries.

## CHAPTER 6: INDUSTRY'S ROLE IN MAXIMIZING SUBJECT WELFARE

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The business of drug development, by definition, has twofold motives: the altruistic motive of developing drugs for the benefit of public health; and the commercial motive of making a profit. There has been considerable debate about which of these seem to be the primary motivator for the industry:

*Scarcely a day goes by... without some story or other in the media about pharmaceutical products and practices. On the one hand, newspaper headlines boast new breakthrough 'wonder drugs'. On the other hand, stories of drug crises or controversies are regularly rehearsed in the media, thereby stirring fear and fascination in the public mind as to the power of pharmaceuticals and the industry that markets and manufactures them. Clearly pharmaceuticals have an important role to play in the alleviation of human suffering and the saving of lives. They are also, however, the source of much controversy, contestation and conflict, not simply in terms of their development, testing and marketing, but in terms of their very meaning and consumption (Williams, Gabe, & Davis, 2008).*

Much of the literature related to ethical conduct of clinical trials by the pharmaceutical companies focuses on conflicts of interest (Fisher, 2008; Lexchin, Bero, Djulbegovic, & Clark, 2003; Montaner, O'Shaughnessy, & Schechter, 2001; Williams et al., 2008), informed consent process (Bhutta, 2004; Strause, 2013) and discussions about the party responsible for ethical and moral responsibilities (Adobor, 2012; Schüklenk, 2000). However, there is a gap in literature in that the issue of how to balance industry interests with public interests is not thoroughly discussed. This then is the focus of this chapter, wherein I will address the industry's responsibility and efforts in maximizing welfare while promoting innovation. I will do this by answering the following questions: i) to what extent do international standards establish industry players' responsibility toward protection of clinical trial subjects? ii) how and to what extent do the industry players address the endogenous and systemic uncertainties identified in chapter 3?; iii) what challenges do the

industry players face in the protection of clinical trial subjects?; and iv) what are the possible tradeoffs for maximizing subject welfare while promoting innovation, and where is the mutually benefitting balance?

## **1. Industry Players**

The pharmaceutical industry performs research and development toward new drug development, and produces and markets drugs. For the purpose of this research, two key players are being considered: the pharmaceutical companies and the contract research organizations (CRO). Pharmaceutical companies can be divided into brand developers and generic manufacturers. The brand manufacturers perform research and development toward new drugs, and produce and market these. The generic manufacturers “produce generic versions of brand-name drugs once they come off patent” (Long, 2014). For the purpose of this research, I will focus on the brand manufacturers’ perspective. Brand manufacturers vary by size, including large, medium and small size companies. Large pharmaceutical companies, such as Pfizer and GlaxoSmithKline, perform research and development, production and marketing functions. Medium and small size companies may perform all of these functions independently or in partnership with other companies or organizations to perform one or more of these functions. For the purpose of this research, I focus on brand manufacturers, regardless of their size, as the ethical standards and regulatory requirements do not vary by company size.

As defined in chapter 3, CRO refers to “a person (or an entity) that assumes, as an independent contractor with the sponsor, one or more of the obligations of a sponsor, e.g., design of a protocol, selection or monitoring of investigations, evaluation of reports, and preparation of materials to be submitted” for regulatory approval (United States Food and Drug Administration, 1987). In addition to the shift in the conduct of clinical trials from traditional markets to emerging markets, the clinical trial industry has moved from using academic medical centers as the CRO to contracting with private, for-profit CROs in the recent decades. “Shifting from more than 80 percent in 1990 to less than 35 percent of pharmaceutical contracts today, universities have been increasingly replaced by private-sector, for-profit research organisations”(Fisher, 2008). Therefore, the CROs being studied here are the private, for-profit CROs.

## 2. Responsibility of the Industry Players to Protect Human Subjects of Clinical Trials

When evaluating industry's efforts toward maximizing welfare while promoting innovation, it is important to first consider the ethical responsibilities for which the industry is being held responsible in current literature. Adobor concludes that the pharmaceutical company and the contract research organization "have both individual and collective responsibilities for ensuring that the ethical and moral issues... are addressed." He further concludes that, though the Declaration of Helsinki provides a "baseline for what is universally acceptable, it would probably be prudent, and more realistic, if its provisions serve as guidelines, rather than de facto rules since contextual factors may warrant modifications of some rules" (Adobor, 2012). However, in literature, when it comes to assigning responsibility for ethical conduct of clinical trials, setting the rules and evaluating whether the industry players measure up to these rules, the Declaration of Helsinki<sup>60</sup> and the International Conference on Harmonisation's Good Clinical Practices (ICH GCP)<sup>61</sup> are used as the principal standards (Adobor, 2012; Cekola, 2007; Petryna, 2005; Schüklenk, 2000).

Beyond individual papers in literature, two organizations, namely SOMO Centre for Research on Multinational Corporations<sup>62</sup> and Access to Medicine Foundation<sup>63</sup>, have taken the lead in evaluating pharmaceutical industry on its conduct of clinical trials. Wemos<sup>64</sup> has also published a number of reports on ethical conduct of clinical trials, though many of these have been in collaboration with SOMO. When evaluating the pharmaceutical industry on ethical conduct of clinical trials, these organizations use the standards defined in the Declaration of Helsinki and/or ICH GCP as the basis for their evaluation. Therefore, it is assumed that they assign responsibility for ethical conduct of clinical trials to the industry players in accordance with, and limited to the requirements of, these two documents.

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<sup>60</sup> <http://www.wma.net/en/30publications/10policies/b3/>

<sup>61</sup>

[http://www.ich.org/fileadmin/Public\\_Web\\_Site/ICH\\_Products/Guidelines/Efficacy/E6/E6\\_R1\\_Guideline.pdf](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf)

<sup>62</sup> <http://www.somo.nl/>

<sup>63</sup> <http://www.accessmedicineindex.org/>

<sup>64</sup> <http://www.wemos.nl/Eng/publications.htm>



The Access to Medicine Index 2014 evaluated clinical trial conduct as one component of the R&D subset of its rankings of the “top 20 research-based pharmaceutical companies”. “The index views compliance with ICH-GCP as a baseline for quality assurance” and “assesses whether companies comply with the” Declaration of Helsinki (Access to Medicine Foundation, 2012a).

SOMO has published several reports on the ethical conduct of clinical trials. *Ethics for Drugs Testing in Low and Middle Income Countries* analyzes “ethical aspects of phase III clinical trials conducted in low and middle-income countries for drug approval in the European Union. This study evaluates the conduct of clinical trials against the Declaration of Helsinki (Irene Schipper & Weyzig, 2008). *Putting Contract Research Organizations on the Radar* identifies the risks associated with the combination of outsourcing and offshoring of clinical trials, and how pharmaceutical companies manage these risks. Risk and risk management are both analyzed against the benchmarks of the Declaration of Helsinki and ICH GCP (van Huijstee & Schipper, 2011). Additional reports, including a report on *Examples of Unethical Trials*, also use the ethical norms defined in the Declaration and the ICH GCP as the basis for evaluation (Weyzig & Schipper, 2008).

Documents such as the Declaration of Helsinki and the ICH GCP have thus become the default benchmark for holding the industry players responsible for protecting human subjects of clinical trials.

## **2.1. Responsibility for Addressing Endogenous and Systemic Uncertainties Per International Standards**

Since the Declaration and the ICH GCP are used as the global reference for holding industry players responsible for protecting human subjects of clinical trials, I will first evaluate whether these international standards in fact establish industry players’ responsibility toward subject protection. I will do so by documenting whether these international standards address each of the endogenous and systemic uncertainties identified in chapter 3, and if so, the player these standards hold responsible for addressing the uncertainties.

In general, the Declaration of Helsinki “is addressed primarily to physicians. The WMA (World Medical Association) encourages others who are involved in medical research involving human subjects to adopt these principles” (World Medical Association, 1964). In contrast, ICH GCP addresses ethics

committees, investigators, sponsors and CROs. The GCP assigns the following overarching responsibilities to the sponsors: i) “implementing and maintaining quality assurance and quality control systems with written SOPs”; ii) “securing agreement from all involved parties to ensure direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing...”; iii) documenting “financial aspects of the trial... in an agreement between the sponsor and the investigator/institution”; iv) “selecting the investigator(s)/institution(s)” and the monitor; v) obtaining documentation from the investigator/institution of an ethics committee approval by a committee that is “organized and operates according to GCP and applicable laws and regulations”; and vi) “the ultimate responsibility for the quality and integrity of the trial data” (ICH Expert Working Group, 1996).

EU1 – Adverse Selection: Are one or more of the players causing a therapeutic misconception?

Principle 31 of the Declaration states, “The physician must fully inform the patient which aspects of their care are related to the research.”

The ICH GCP is silent on this issue.

EU2 – Adverse Selection: Are one or more of the players not considering available alternatives adequately?

This uncertainty is not addressed in either of the documents.

EU3 – Adverse Selection: Are the recruitment and informed consent processes adequately informing the subjects about their participation in research?

Principle 7 of the Declaration makes a general statement that “medical research is subject to ethical standards that promote and ensure respect for all human subjects...”

Additionally, principles 25-32 of the Declaration relate to informed consent. These focus on the physician’s responsibilities of: i) obtaining voluntary informed consent (principle 25); ii) adequately providing information about, ensuring that the subjects understand the information, and obtaining documented consent regarding the “aims, methods, sources of funding, any

possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study” and iii) making special provisions for subjects who are incapable of giving informed consent for themselves.

The ICH GCP holds the ethics committees responsible for ensuring “that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements...” The GCP then addresses informed consent more specifically in section 4.8, where it provides for the following investigator responsibilities: i) informed consent should be free of any coercion or undue influence; ii) information provided during informed consent process, orally or in writing, should not in any way require the subject or his/her legal representative to waive any legal rights; iii) the language in the informed consent should be understandable to the subjects; iv) subject’s questions should be answered before obtaining consent; and v) the use of an impartial witness when involving subjects who are unable to read.

#### EU4 – Adverse Selection: Are any of the players exerting undue influence?

Principle 25 of the Declaration states, “Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary.”

Section 3.1 of the ICH GCP states, “The IRB/IEC should review both the amount and method of payment to subjects to assure that neither presents problems of coercion or undue influence on the trial subjects.” Additionally, section 4.8 of the GCP notes that subjects should be informed that their participation in the trial is voluntary during the consent process and in the consent document. Each of these statements holds the PI or the ethics committee responsible for minimizing coercion and undue influence.

#### EU5 – Moral Hazard: How will the trial be monitored such that adverse events & unanticipated problems can be managed effectively?

Principle 23 of the Declaration holds the PI responsible for informing the ethics committee of any adverse events, and the ethics committee is then responsible for its consideration and monitoring.

Section 4.11 of the ICH GCP indicates that “All serious adverse events (SAEs) should be reported immediately to the sponsor...”; “The investigator should also comply with the applicable regulatory requirement(s)...”; and “Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor...” Section 5.17 then holds the sponsor responsible for expediting reporting of adverse drug reactions to investigators/institutions, ethics committees and regulatory authorities. Section 5.18 holds the monitor (identified by the sponsor) to verify “that the investigator provides all the required reports... and that these documents are accurate, complete, timely...”

#### EU6 – Corruption: Is one or more player acting under the influence of an existing conflict of interest?

Principle 26 notes that potential subjects should be informed of “any possible conflicts of interest.” Principle 27 of the Declaration states, “When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.”

Section 3.2 of the ICH GCP states, “Only those IRB/IEC members who are independent of the investigator and the sponsor of the trial should vote/provide opinion on a trial-related matter.”

Neither of the two guidelines address conflict of interest of the members of the government body responsible for approving the clinical trial and/or granting an investigational new drug exemption. Additionally, neither guidelines address financial conflicts of interest of the principal investigator or other members of the research team, other than to state that the subjects should be notified of any conflict.

#### SU1: Who bears the cost of subject participation?

The Declaration of Helsinki is silent on this issue. The ICH simply indicates, “The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution” (section 4.9).

## SU2: Who bears the cost of treatment for injury?

The Declaration of Helsinki is silent on these issues.

Section 4.3 of the ICH GCP indicates that the “investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events...” Of note again is section 4.9 of the ICH GCP, “The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution”. The GCP further indicates that “the sponsor should provide insurance or should indemnify... the investigator/the institution against claims arising from the trial” if required by applicable regulations; and that “the sponsor’s policies and procedures should address the costs of treatment of trial subjects in the event of trial-related injuries in accordance with the applicable regulatory requirement(s).”

## SU3: Should there be compensation for injury?

The Declaration of Helsinki is silent on these issues.

The only relevant language in the GCP is again section 4.9, “The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution”.

## SU4: Should end of trial care be provided and to whom? AND U5: Who will cover the cost of end of trial care?

Principle 34 of the Declaration states, “sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial.” Once again, relevant language in ICH GCP is in section 4.9, “The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution”.

Based on the above evaluation, I conclude that the Declaration of Helsinki and the ICH GCP have many gaps when it comes to setting the industry players’ responsibility for addressing the endogenous and systemic uncertainties involved in the clinical trial process. The minimal responsibility, per international standards, and the gaps are summarized in table 15 below.

Table 15: Players Held Responsible for Protection of Human Subjects of Clinical Trials by Declaration of Helsinki and ICH GCP

	Declaration of Helsinki	ICH GCP
EU1 – Adverse Selection: Are one or more of the players causing a therapeutic misconception?	Physician	Silent
EU2 – Adverse Selection: Are one or more players not considering available alternatives adequately?	Silent	Silent
EU3 – Adverse Selection: Are the recruitment and informed consent processes adequately informing the subjects about their participation in research?	Physician	Ethics Committee & Investigator
EU4 – Adverse Selection: Are any of the players exerting undue influence?	Physician	Ethics Committee & Investigator
EU5 – Moral Hazard: How will the trial be monitored such that adverse events & unanticipated problems can be managed effectively?	Researcher, Ethics Committee & Government	Sponsor & Investigator
EU6 – Corruption: Is one or more player acting under the influence of an existing conflict of interest?	Physician	Ethics Committee
SU1: Who bears the cost of subject participation?	Silent	Silent – contractual consideration
SU2: Who bears the cost of treatment for injury?	Silent	Sponsor, Investigator, Government
SU3: Should there be compensation for injury?	Silent	Silent – contractual consideration
SU4: Should end of trial care be provided and to whom?	Sponsor, Researchers & Government	Silent – contractual consideration
U5: Who will cover the cost of end of trial care?	Sponsor, Researchers & Government	Silent – contractual consideration

Based on the above evaluation, the pharmaceutical company, in this case the sponsor, is responsible for the following responsibilities per international standards: i) monitoring research with respect to adverse events and unanticipated problems (EU5); ii) ensuring coverage for cost of treatment for injury (SU2); and iii) provisions for end of trial care (SU4 & SU5). The CRO, which is where the physician investigator resides, is held responsible for addressing most of these uncertainties. However, the CRO is an agent of the pharmaceutical company, and it has a vested interest in meeting the pharmaceutical company's contractual requirements in order to make a profit and remain in business.

Local regulatory requirements are the next level of requirements against which the industry players are evaluated. International standards are the foundation for most regulatory requirements, and in emerging markets, the regulatory requirements initially established do not go beyond the requirements of the international standards. At the pharmaceutical company level, it is important to recognize that avoiding reputational damage is a relatively effective motivation for regulatory compliance. This responsibility of regulatory compliance is contractually passed on to the CRO as well. Yet, as noted in previous chapters, and by SOMO (Weyzig & Schipper, 2008), ethical violations in clinical trials continue to occur. Thus, it is clear that mere compliance with international ethical principles and guidelines, and local regulatory requirements is not sufficient.

What, then, is the source for establishing the industry players' responsibility toward protection of clinical trial subjects? From the perspective of corporate social responsibility, it is reasonable to expect that, being in the business of advancing public health through drug development, the industry players must take "actions that appear to further some social good, beyond the interests of the firm and that which is required by law" (McWilliams & Siegel, 2001). In case of clinical trials, it is reasonable to further expect that corporate social responsibility requires industry players to take actions beyond those not only required by law but also by international standards. Therefore, the remainder of this chapter will focus on how and to what extent the industry players address the endogenous and systemic uncertainties identified in chapter 3, and thereby take actions based on corporate social responsibility.

### **3. Industry's Role in Maximizing Subject Welfare: An Empirical Study**

In order to determine whether and to what extent industry players are making an effort to go above and beyond the international standards and the regulatory requirements for protection of human subjects of clinical trials, and to identify any challenges industry players face in protecting human subjects, I conducted an empirical study. The study and its findings are described in this section.

#### **3.1. Methodology**

This empirical study involved the use of qualitative semi-structured interviews. The final number of interviews was determined as the study progressed, depending on when saturation was reached and no new challenges or barriers were identified. I concluded the study with a total of 9 interviews. No new themes were identified after the sixth interview. Six (6) of the interviewees currently work in a global pharmaceutical company focused on branded products, two (2) currently work for a CRO and one (1) respondent has previously worked as head of operations for a pharmaceutical company and a CRO and currently works as a consultant to the pharmaceutical industry. Of the six (6) pharmaceutical company interviewees, two (2) are scientific heads of global clinical research; one (1) is head of operations for medical research; one (1) is vice president for a country campus; one (1) is head of advocacy; and the final pharmaceutical company interviewee (1) is a feasibility strategist. The two CRO representatives are both heads of clinical operations.

Potential interviewees were identified through professional networks and word of mouth using the snowball sampling method described in chapter 5. The interviewees were approached via email and LinkedIn invitations, and interviews were conducted telephonically. I used a pre-defined interview script, which was used as a guide. Follow-up questions were then asked based on individual responses. The interviewees were first asked open-ended questions related to each of the uncertainties. These questions focused on challenges, difficulties or barriers faced by the industry players and ways in which the industry players balance subjects welfare with industry interest of completing the clinical trial. These questions were followed by additional open-ended questions regarding the overarching challenges faced by industry players in protection of clinical trial subjects in general, and in emerging markets in particular; and tradeoffs for maximizing subject protection and



mutually benefitting balance. The interviews were recorded in a notebook, then transcribed into an excel sheet, which was used to analyze the responses.

### **3.2. Addressing Endogenous and Systemic Uncertainties**

#### **EU1 – Adverse Selection: Are one or more of the players causing a therapeutic misconception?**

Majority of the respondents indicated that sponsors can help minimize therapeutic misconception by writing good quality protocols, investing in education and training and providing materials or tools to the sites and the investigators. Several of the pharmaceutical company respondents noted that building relationships with the research teams, advocacy groups and communities is another important factor in minimizing the risk of therapeutic misconception. The pharmaceutical company respondents described some of their challenges and approach to overcome the challenges:

*At global development level, you make sure that the informed consent is communicated in a way that people understand. We can't control every doctor, but we make materials available not just the informed consent, but that you can work with materials that subjects can understand; in countries where literacy is not at the US level - we have to have that informed consent - but we work with special materials like storyboards. We develop materials not just to work with individual patients, but for their families and decisions with village elders. Individual consent needs to be balanced out. We would encourage this on a country-by-country level and work on the side with the doctors to take proper informed consent. It doesn't always happen.*

*We address these with advocacy groups, patients and community leaders - people working hand-in-hand with the patients. There is an opportunity and responsibility to educate and to answer all questions that are raised.*

*We don't allow centers who are not able to provide explanations of procedures, side effects and we make every effort to make sure that the patients are really aware. When patients could misunderstand, we use drawings and figures, etc. In countries like India where there are 30-40 different dialects, for example, we use booklets with figures.*

*The challenge is that we don't have direct access to the patients and rely on PIs to relay information - we assume that they are providing balanced information.*

EU2 – Adverse Selection: Are one or more of the players not considering available alternatives adequately?

Majority of the respondents indicated that they rely on the site and the PI to help identify all the available alternatives in the local environment. One respondent noted:

*We have to work with the physicians at local sites and team with the ethics committee. We try to work in areas with robust ethics committees. Ethics committees will sometimes identify something we missed. For conventional medicine, it works okay with good relations with doctors and ethics committees. I am not sure it works well at all in markets with complimentary alternative medicine. That's really the doctor's job.*

EU3 – Adverse Selection: Are the recruitment and informed consent processes adequately informing subjects about their participation in research?

Majority of the respondents concurred that ensuring respect for persons requires a good informed consent process that is ongoing, and that is supplemented with simpler consent forms and good documentation of the informed consent process. One challenge that was identified by several respondents was trying to balance the legal requirements with providing information that is important for the subjects in lay language. Challenges in ensuring effective informed consent were identified as follows:

*It involves tremendous amount of education of the sites... educating the sites is critical; it is appealing to partner with big sites with a track record for doing large clinical trials.*

*This is something we talk about all the time, but don't do well all the time. I would like to see better documentation of the process and questions being answered. I would like to see it be an ongoing process. So, on the fifth or sixth visit, it may take an extra 10 minutes to ask how are things, this is what we are doing, do you want to continue.*

*I read the consent forms and they are difficult. We try hard to balance legal aspects and need to make sure we are getting consent from patients, but 30-page legalese document is not getting informed consent. We try to make them as simple as possible and from a patient's perspective. The consent process is reviewed by the sites and the PIs; we walk through the process with them and make sure it is best for each patient. Sometimes we use videos to make it more understandable. But we use the consent form to drive the process.*

*This is a big industry problem. Informed consent has been a document over the years - a legal document. We go around this by having a 2-page summary to talk about risks, without any legalese. Companies are doing more to educate people on informed consent - some take complex informed consent and convert it into a tri-fold brochure. Some are making it available in different ways - they ask patients to take it home and discuss it with family members; provide it on an app; we send it to them electronically to look on their computer. Some study coordinators used to make a great effort to sit down with the subjects, but with the nature of medical care nowadays, this takes too much time and is not feasible like it used to be; but if don't*

*do this, it's unfair. So, we find better ways. Allow patients to take it, discuss with loved ones and then come back. We send them read only documents. Industry is talking about how to do this better. There are applications now on how to make it more user friendly in different formats and of course give patients time to consider.*

#### EU4 – Adverse Selection: Are any of the players exerting undue influence?

Two mechanisms for balancing risks of coercion and undue influence with subject recruitment were identified as equally important by majority of the respondents. First, since the sponsors are dependent on the PI and the site staff to recruit and consent subjects, the respondents emphasized the importance of the right site and PI selection followed by adequate and targeted site monitoring. Second, the respondents noted that matching the cultural understanding to the consent process, and having a transparent consent process is important in minimizing these risks.

One respondent noted that the local healthcare environment plays a large role in minimizing coercion and undue influence:

*Outside the US, socialized medicine is common - many physicians put patients on clinical trials to get them into the system quicker - is this coercion? Is it justified?*

This respondent also raised the concern that there is the perception of coercion when recruiting subjects from a lower socio-economic region, since these populations may participate in trials in order to get healthcare that they cannot otherwise afford. The respondent countered this argument:

*Perceived coercion; state of healthcare; availability of medical care in general. Do we deprive under the umbrella of ethics - there is a difference between ethics and morality? If you don't give because someone is poor, how is it better than giving because the person is poor? You have to have good protocol design, good inclusion/exclusion criteria and good informed consent*

*process; hopefully, these will manage therapeutic misconception...*

The respondent further noted that this is not only an issue in lower socio-economic regions. Rather, it also applies to socialized medicine:

*...in The Netherlands - a physician told me that some patients have to wait a long time to get into the system - so the physician puts them on clinical trials to get them into the system quicker.*

Some of the respondents also emphasized their reliance on PIs, ethics committees and other partners to help in minimizing these risks:

*We are only as good as our investigative sites and investigators who have conversations with subjects. We have certain expectations of our site staff and if they don't meet our expectations we shut them down. We have parameters in place and there are rules and regulations in place, but we can't control that. We have no way of knowing whether they are following the rules all the time.*

*Every trial is reviewed by an ethics committee - we never do any trial where this information is not reviewed by different ethics committees. We also use external companies that translate certain aspects into cultural varieties for correct understanding. Even between France and UK, there may be a different cultural understanding of a condition. This is also important when we use diaries or subjective evaluations - we are always working to match cultural understanding.*

EU5 – Moral Hazard: How will the trial be monitored such that adverse events and unanticipated problems can be managed effectively?

Majority of the respondents observed that this is one risk that the industry manages really well, and that, if there is a challenge, it is in underreporting by the subjects. Mechanisms for managing this risk include:

*We are always looking to see if AEs are identified by the PI as needed. Always checking with them if every unexpected AE is reported or not and how to convince them to do so. Sometimes the definition of AE is not well understood by the PI, and our medical experts weigh in and make correction between the medical expert and the PI who come to an agreement. One situation can be under-reporting. From statistical point of view, if AEs are equal across sites; but if the PI is saying no AEs at some sites, we are alerted and our monitors investigate what is happening and why compared to the other sites.*

*Once the events are identified and reported to the doctor, we don't have an issue. We have a lot of systems in place looking for things emerging. Safety physicians whose job is to talk to the investigators and try to understand every event. Once in the system, system works. Challenge is in area with lower socio-economic patients who don't want to admit to having an event and be withdrawn; and also cultural influences.... Some experience pain differently; some don't want to report it to the doctor; and for some it is not culturally acceptable. All you can do is look for patterns and country effects in side effects and see if there are differences. Safety and data safety monitoring committees review data every 6 months for each trial so we are fine there - data is reviewed every 6 months.*

*We educate the PIs and the patients to report any possible AEs. Lots of them are reported, and at the end*

*they are not all related, but there is underreporting so we ask them to report everything. All are then put in a database that we constantly monitor for each study - we have a scientific director who monitors these. We also match these with earlier phases of research and do surveillance using algorithm. We are always looking for a signal, then we have pharmacovigilance meetings and a forum to look for possible relations. We also organize external advisory boards who look at this. Also, we have independent monitoring boards who also monitor the study and do interim analysis for side effects and efficacy and they can stop the study for either side effects or efficacy reasons.*

*We have monitors who monitor this closely to make sure we uncover things. We do a lot more of patient diaries now to make sure we are getting signals and managing them appropriately.*

EU6 - Corruption: Is one or more player acting under the influence of an existing conflict of interest?

Rather than focus on the standard operating procedures for disclosures of conflicts by various stakeholders, the respondents were asked to focus on the larger perceived conflict of the industry's profit maximizing agenda. Specifically, the respondents were asked to address how their company balances new drug development opportunities with the healthcare priorities of the countries where they conduct the clinical trial.

The CRO respondents indicated that they simply follow the interests identified by the sponsor. The majority of the pharmaceutical company respondents indicated that this decision is based on the prevalence of the disease and the unmet needs of the population. Several of the respondents indicated that this is important because the prevalence and the unmet needs will also determine the likelihood of the drug being approved for marketing in the country. How the prevalence and unmet needs are identified varied:

*We just recently refocused and organized our global approach, which is now related to aligning our interest*

*with the talent and experience available in the markets; the assumption is that aligning with the country's niche will give us the opportunity and it should align with the interest of the country.*

*We have a fairly extreme view - we don't let commercial people near early drug development decisions. On a global basis, this is determined by science and medical need. If there is a specific medical need, and our research guys are working on a drug in that area, we will take it without consideration to market size. These decisions are based on science and medical need and figure out commercialization later. If there is medical need, the market will be there.*

#### SU1: Who bears the cost of subject participation?

Respondents were asked to describe how their company balances costs of standard of care provided during the clinical trial; the undue influence of making care available to subjects in lower socio-economic regions; and minimizing the cost of clinical trials to the company itself.

The CRO respondents concurred that they rely on the sponsor and the local regulations to determine how to address this uncertainty. Majority of the pharmaceutical industry respondents indicated that their company tries to have the subject or their third party payer cover the cost of standard of care, when allowed by the local regulations. However, if this is not possible, particularly in lower socio-economic regions, the company covers all costs of participation. Two of the seven pharmaceutical company respondents indicated that their company covers all costs of subject participation, including standard of care. Of the companies who try to pass the cost of standard of care to the subjects or their third party payer, majority expressed concern that covering the cost of standard of care may be considered unethical, as it is perceived as creating undue influence on the subjects.

Several of the pharmaceutical company respondents described the various issues they may consider in an effort to address this uncertainty on a case by case basis. Several respondents used US as an example for local considerations, where subjects or their third party payers can be charged for



standard of care. Thus, at least two of the companies represented in the interviews do not cover the cost of standard of care in the US as a standard practice. One respondent indicated that Medicare no longer covers the cost of concomitant medications for individuals participating in clinical trials. Therefore, the company must take this into consideration when budgeting for the trial.

One respondent described the internal debate resulting in this uncertainty:

*We don't routinely pay for standard of care in the US. If something is outside the protocol, we wouldn't pay for it. But if standard of care is not the same in other countries and we want patients to have the same to get clean data, we would pay for everything. We err on the side of paying for everything. We do want to keep trial costs low, but keeping it low compared to bringing a drug to market six months earlier, we would pay for it. Patients should not have to pay for anything themselves. On the other hand, some ethicists say, if patients would have to pay if they wouldn't have this, you should not pay for it because it's coercion. But then they take the risks and we feel they should get something out of it.*

Another respondent described a pharmaceutical industry initiative toward reducing this uncertainty. TransCelerate BioPharma Inc., “a non-profit organization focused on advancing innovation in research and development (R&D), identifying and solving common R&D challenges and further improving patient safety, with the goal of delivering more high quality medicines to patients, evolved from discussions at various forums for executive R&D leadership to discuss relevant issues facing the industry and solutions for addressing common challenges.”<sup>65</sup> One of its initiatives is the introduction of “Master Service Agreements” amongst participating companies, whereby the companies provide “rapid and ready supply of comparator products” to each other for use in clinical trials. According to the

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<sup>65</sup> <http://www.transceleratebiopharmainc.com/about-us/>

respondent, their company does not expect subjects to pay for any cost of participation. Rather:

*What can and should be leveraged is that the 19 companies in TransCelerate are selling each other drugs at a very reduced rate. This is a fantastic model and we should be doing this across the board outside of TransCelerate.*

#### SU2: Who bears the cost of treatment for injury?

All of the respondents indicated that the sponsor, i.e. the pharmaceutical company, covers the cost of all trial related injuries. The respondents also agreed that, when there is doubt regarding the relatedness of the injury, the company covers the cost. Thus, the interviews reveal that this may not be a real uncertainty.

#### SU3: Should there be compensation for injury?

The respondents were asked to provide their company's view on compensating for research related injury. Majority of the respondents were hesitant to address this question in great detail. The respondents indicated that if the injury was related to the trial, and the issue of compensation was raised, they would probably pay for it. One respondent explained this further:

*If we were served a document by a site that established that the injury was due to the trial, we would probably do what's asked. Nobody wants to be on the front page of the newspaper. If we are presented with it, we do it. If not, we don't.*

#### SU4: Should end of trial care be provided and to whom? and SU5: Who will cover the cost of end of trial care?

The CRO respondents noted that this is based on regulatory requirements, and where there is no regulatory requirement, they are not sure how the sponsor makes these decisions. Majority of the pharmaceutical company respondents indicated that, when there is demonstrated benefit to the subjects, they provide end of trial care in the form of extension trials, compassionate use and/or accelerated access, depending on the options available based on

local regulatory environment. Several of the respondents commented on factors that must be considered:

*If a phase II trial launches, it is invasive and trial fails, but one patient benefits, we can't manufacture it because it is never going to be approved. Companies should give a lot of thought to this.*

*In oncology, it's easier - we have extension protocols for every phase III trial. We collect long-term survival data. Many drugs that come to market that seem to be very good and impact progression once survival, but overall data show it's the same. So, it's good to have long-term data, and we generally encourage all subjects to roll over. For earlier stage trial, we tend to do the same, but you really don't know if there are benefits. By continuing to provide the drugs there may be unexpected side effects. In Brazil, this was a big issue... For a while, Brazil mandated us to provide continuing treatment, but for phase II you didn't know if they got benefit and there could be other treatment that's just as good so why would we supply it? Now in Brazil, there is enhanced role of the PI, where PI provides recommendations to national ethics committee about end of trial care. That's good, perhaps that's the way to do it, by engaging the PI more.*

*This is on an individual basis per study per compound. If there is a life threatening disease with general medical necessity and it is not possible in patient's healthcare environment for the patient to receive it after the trial, we provide it until the drug is available on market through follow-up long-term care.*

*Assessment of the PI. For us, the PI will assess.*

Table 16 below summarizes industry’s mechanisms for addressing each of the uncertainties and their respective challenges as identified by the interview respondents.

Table 16: Mechanisms for Reducing Uncertainties and Challenges Toward Protection of Human Subjects as Identified Through Expert Interviews

<b>Uncertainty</b>	<b>Mechanisms for reducing uncertainty</b>	<b>Challenges faced by industry</b>
EU1 – Adverse Selection: Are one or more of the players causing a therapeutic misconception?	<ul style="list-style-type: none"> <li>- Write good quality protocols</li> <li>- Invest in education &amp; training of CROs and community</li> <li>- Provide materials and tools to CROs</li> <li>- Build relationships with community</li> </ul>	<ul style="list-style-type: none"> <li>- Lack of control over every investigator</li> </ul>
EU2 – Adverse Selection: Are one or more of the players not considering available alternatives adequately?	<ul style="list-style-type: none"> <li>- Obtain information about local availabilities from CROs and ethics committees</li> </ul>	<ul style="list-style-type: none"> <li>- Markets with complimentary alternative medicine</li> </ul>
EU3 – Adverse Selection: Are the recruitment and informed consent processes adequately informing the subjects about their participation in research?	<ul style="list-style-type: none"> <li>- Good ongoing informed consent process and its documentation</li> <li>- Simple consent documents</li> <li>- Educating CROs</li> <li>- Use brochures, summaries, applications, computer-aided formats</li> </ul>	<ul style="list-style-type: none"> <li>- Balancing legal requirements with providing information that is important to the subjects</li> </ul>
EU4 – Adverse Selection: Are any of the players exerting undue influence?	<ul style="list-style-type: none"> <li>- Right CRO selection &amp; monitoring</li> <li>- Match cultural understanding to process</li> <li>- Good protocol design</li> </ul>	<ul style="list-style-type: none"> <li>- Local healthcare environment</li> <li>- Lack of control over CRO</li> </ul>

EU5 – Moral Hazard: How will the trial be monitored such that adverse events and unanticipated problems can be managed effectively?	<ul style="list-style-type: none"> <li>- Open communication with CRO</li> <li>- Monitoring of adverse events</li> <li>- Education of CROs and subjects</li> <li>- Subject diaries</li> </ul>	<ul style="list-style-type: none"> <li>- Underreporting by subjects or investigators</li> <li>- Cultural influences</li> </ul>
EU6 – Corruption: Is one or more player acting under the influence of an existing conflict of interest?	<ul style="list-style-type: none"> <li>- Base decisions on disease prevalence &amp; unmet needs of the population</li> </ul>	<ul style="list-style-type: none"> <li>- Identifying prevalence &amp; unmet needs</li> </ul>
SU1: Who bears the cost of subject participation?	<ul style="list-style-type: none"> <li>- Follow local regulations</li> <li>- Industry-wide initiatives</li> </ul>	<ul style="list-style-type: none"> <li>- Debate about whether paying for standard of care is coercive</li> </ul>
SU2: Who bears the cost of treatment for injury?	<ul style="list-style-type: none"> <li>- Sponsor covers cost</li> </ul>	<ul style="list-style-type: none"> <li>- None</li> </ul>
SU3: Should there be compensation for injury?	<ul style="list-style-type: none"> <li>- Follow local requirements</li> </ul>	<ul style="list-style-type: none"> <li>- None</li> </ul>
SU4: Should end of trial care be provided and to whom?	<ul style="list-style-type: none"> <li>- Extension trials, compassionate use, accelerated access – all based on available regulatory options</li> </ul>	<ul style="list-style-type: none"> <li>- Manufacture just for a few who benefit?</li> <li>- Early stage trials – some may benefit, but may have unexpected side effects</li> <li>- Markets where governments don't have mechanisms in place</li> </ul>
SU5: Who will cover the cost of end of trial care?	<ul style="list-style-type: none"> <li>- Sponsors generally cover</li> </ul>	<ul style="list-style-type: none"> <li>- None</li> </ul>

### 3.3. Protection of Clinical Trial Subjects in Emerging Countries

Respondents were next asked to identify the challenges they face in ensuring ethical conduct of clinical trials in emerging countries. Two challenges were identified as posing the greatest challenges: i) local regulatory environment; and ii) differences in clinical training, including the knowledge and culture surrounding the conduct of clinical trials. A third of the respondents identified the state of local healthcare and local practice of medicine as another challenge. Respondents discussed how they try to overcome these challenges:

*Many issues can be prevented or addressed by working very closely with the sites. It requires people working on the grounds. The trend is toward remote monitoring and using technology and Internet. But in emerging markets, we have to have relationships with the sites. We can't do that sitting in an office remotely... We have to be there.*

*We have hubs - offices - around the world. These are staff with physicians, scientists, and operations people who are local. Because we have the right people staffed - they know the language, local culture, the regulations - the expectation is that the right things are being done.*

*We depend heavily on CROs and PIs. We look at information in real time that is generated by the sites. We can't go locally in all the countries to see how the site is doing. There is also the issue of how well do we know the practice of medicine in the country - is (it) practical to do the trial there give(n) the practice of medicine. It is important for us to get feedback and hope that the CRO understands the patient populations, but this needs to be considered. Through monitoring and looking at protocol deviations, we can tell, but this is still a challenge. Are we getting what we expect? Are there barriers in getting the data? There will always be unexpected country effects.*

Majority of the respondents indicated that the CROs face the same challenges as the pharmaceutical companies. However, a third of the pharmaceutical company respondents questioned the level of commitment by the CROs. They expressed concern that the CROs “may cut corners, as their profit is earned in the short term based on recruitment and completion of case report forms.” Addressing this concern would require effective oversight of the CRO by the pharmaceutical sponsor. The Access to Medicines Foundation observed in its 2012 Index: “evidence of oversight of CROs is weak” and “accountability for CRO behaviour is where one of the widest gaps exists between current industry performance and Index expectations...” (Access to Medicine Foundation, 2012a) More recently, however, improvements in the oversight of the CROs were observed: “In 2012, the Index reported that only four companies provided evidence of having procedures for enforcing compliance in outsourced trials. In 2014, ten companies provided strong evidence of enforcing compliance through monitoring and auditing procedures for their trials...” (Access to Medicine Foundation, 2014a).

### **3.4. Tradeoffs and Mutually Benefitting Balance**

Finally, the respondents were asked to provide their opinion regarding the possible tradeoffs of maximizing subject protection while promoting innovation, and the mutually benefitting balance. The CRO respondents concurred that the tradeoffs and the balance are associated with the regulatory requirements and compliance versus innovation. Majority of the pharmaceutical company respondents, on the other hand, identified the tradeoff and the balance to be associated with business versus charity for subjects.

Two of the pharmaceutical company respondents noted a difference in tradeoffs when the clinical trial involves experimental products for terminally ill patients:

*Evaluating tradeoffs is the hardest things at each decision point; at early discovery, you are at the cusp of first in human studies; you are looking at the data and there is a huge tradeoff for the patients; we have a luxury in terminal cancer patients in that there is no alternative, they have failed all treatment; so the tradeoff is worth it to push for an investigational drug.*

*The balance is sometimes difficult to obtain around benefits to individuals versus benefits to society. We can't always have benefits to individuals... in early stage cancer trials, some patients are very generous and they participate because they want to benefit others. They should get something out of it. Largely, there can be win win. It's ok to pay for standard of care because we are grateful to those who participate but we have to balance that with not being coercive by paying for it. Patients who take part in clinical trials generally have better outcomes.*

Two other pharmaceutical company respondents emphasized that through relationships with advocacy groups and subjects, and by investing in educating these entities, the companies are able to design better trials and retain more subjects. Thus, there is an initial investment of time and money in education and relationship building; however, there may be a payoff through better trial design and subject retention.

*Tradeoff for us is to decrease or reduce or stop thinking that we are the experts in every aspect of designing and executing trials. We have to make the subjects and the advocacy groups a bigger part of the process and start trusting. We will then find the right subjects quicker and they will stay longer because we have their buy in to what they helped design.*

*There is a balance - make more information available in lay language - educating more - if the patient is more involved in the development process, we can partner with the patient-centric organizations and advocacy groups. Small communities communicate with each other - they are networked together even with their doctors - they guide us and it makes an impact; they educate us on illness and we educate them on drugs. Hearing and seeing them makes a difference. As patients become more educated, there is willingness to participate, there is payoff - some may participate in multiple trials over time, some may*



*recommend people in the same space for trial participation and some may become advocates. Key opinion leaders are great as scientists, but not trialists that make the study design align with the patient interests. Go more toward patient sites, more interest from patients. So the tradeoff is we spend more time and effort in education.*

#### **4. Conclusions**

In the beginning of this chapter, I asked four very specific questions. I addressed these questions by taking my conceptual framework, consisting of endogenous and systemic uncertainties, and validating it through two methods: i) analysis of the two major international standards; and ii) interviews with industry experts. I now answer these in terms of the major findings of my research.

##### **4.1. To what extent do international standards establish industry players' responsibility toward protection of human subjects of clinical trials?**

The two major international standards used in literature to evaluate the ethical conduct of clinical trials by the industry players are Declaration of Helsinki and the ICH GCP. However, when I analyzed these standards using my conceptual framework, it became clear that neither of these standards clearly establishes the industry players' responsibility toward human subject protection. As noted in table 15 above, there are many gaps in both the Declaration and the GCP in terms of establishing the industry players' responsibilities toward protection of human subjects of clinical trials. Nevertheless, industry players are repeatedly evaluated based on the principles outlined in these two documents. It is interesting to note that, during the 9 interviews, none of the respondents made a reference to either the Declaration of Helsinki or the ICH GCP. Thus, I conclude that either the international standards must be enhanced to address the industry players' responsibilities, or the industry players must be evaluated using a different framework, such as the one offered in this thesis, or in terms of corporate social responsibility.

#### **4.2. How and to what extent do the industry players address the endogenous and systemic uncertainties identified in chapter 3?**

Section 3 above discusses in detail the mechanisms used by industry players in addressing each of the uncertainties. Most of the mechanisms identified by the industry experts can be grouped together into one overarching mechanism, that of building firm relationships amongst the players. Productive relationships will address these mechanisms as follows:

- Writing good quality protocols (EU1, EU4), in collaboration with all players
- Investing in education and training (EU1, EU3, EU5), in collaboration with and across all players
- Building relationships and having open communications amongst players (EU1, EU5)
- Sharing of information amongst players (EU2, EU4)
- Developing effective informed consent forms and materials (EU3), through sharing of knowledge as it relates to the local context
- Selecting right CROs / CRO monitoring (EU4), through long-term relationship and investment in identified CROs
- Effective government guidance (EU6, SU1, SU3, SU4), through partnership with the local government

Thus, the study presented in section 3 makes it clear that productive relationships amongst all the players involved in the implementation of clinical trials and effective strategies developed and implemented collaboratively by the players is the best way to convert many of these uncertainties into measurable risks.

#### **4.3. What challenges do the industry players face in the protection of clinical trial subjects?**

The challenges faced by industry players fall primarily in one of two categories: i) obtaining sufficient knowledge about the local context; and ii) lack of control over the CROs. Just as the mechanisms for converting each of the uncertainties into measurable risks can be addressed through productive relationships, so can both of these challenges. Strong relationships of the pharmaceutical company with the local government, subject advocates/communities, local CROs and local ethics committees will result in open communication with these players, and these players are essential in

providing information related to the local context. Additionally, trusting long-term relationships with the CROs will bring the two industry players closer to accomplishing agreed upon goals. I thus conclude that such relationship building will allow all players to develop integrated strategies toward effective protection of clinical trial subjects.

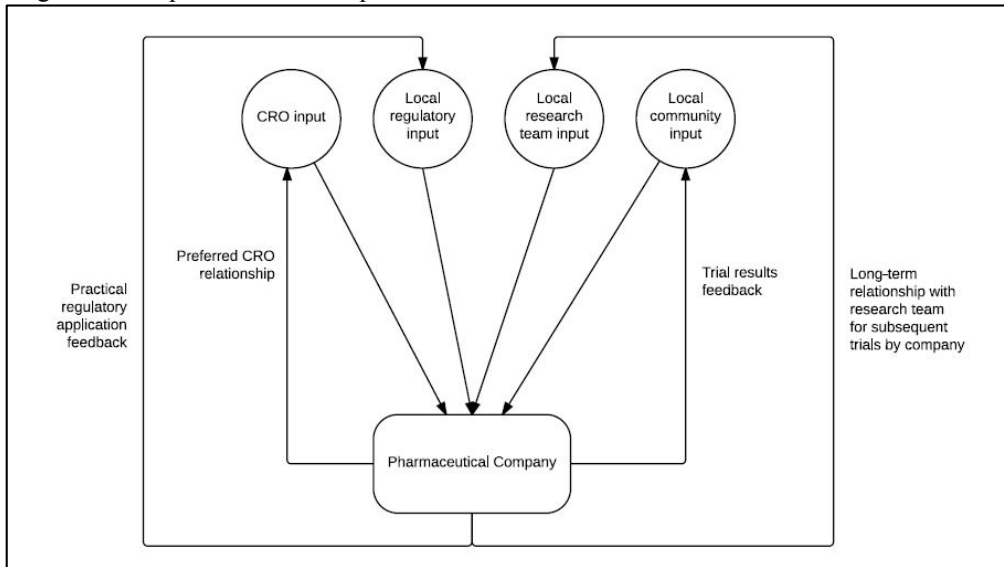
#### **4.4. What are the possible tradeoffs for maximizing subject welfare while promoting innovation, and where is the mutually benefitting balance?**

The industry players consider investment in the education of the CROs and the subjects, as well as investment in building long-term relationships with the various players, to be the tradeoffs for: i) gaining input regarding protocol design from CROs and subject groups, which then results in better protocol design and vested interest from the CROs and the potential subjects; ii) identification and recruitment of qualified subjects who will not withdraw; and iii) possible recruitment of subjects who will return for future trials and/or refer their family or friends to participate as subjects. At first glance, these investments may appear obvious. However, these are two areas that require significant investment. Therefore, the long-term benefits of investing in education and relationship building may be overlooked by the short-term goals of making a profit, recruiting subjects for the immediate trial or completing a phase of a trial.

### **5. Recommendation**

Overall, the answers to each of the questions addressed in 4.2, 4.3 and 4.4 all point to the importance of information exchange amongst the players through education and relationship building. Thus, in conclusion to this chapter, I propose a relationship structure that would allow for these two important methods of prospective and retrospective information sharing in figure 12 below. Given the conclusion that many of the methods for balancing welfare and innovation amount to the issue of strong relationship and partnership building amongst the various players (pharmaceutical company, the CRO, the local government and the community and advocacy groups (civil society)), the proposed relationship structure that would allow for prospective and retrospective information sharing.

Figure 12: Proposed Relationship Structure



\* Author's creation

## **CHAPTER 7: RISK CONTAINMENT**

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As identified at the beginning of this thesis and confirmed in chapters 4 and 5, within a country context, the governance of clinical trials takes place at the government level by the regulatory agencies and at the institutional level by the pharmaceutical company, the CRO and the ethics committee. Thus far, the focus of this thesis has been to identify and understand the nature of the uncertainties involved in the implementation of clinical trials. This chapter focuses on risk containment. As may be recalled from the introduction to this thesis, by risk, I refer to the probability of any event that may render harm to the clinical trial subject. By risk containment, I refer to any government policy or government or institutional strategy that reduces the probability of an event that could cause harm to a clinical trial subject.

The premise of this thesis is that the need for protecting the clinical trial subject's welfare must be balanced with the need for novel drug innovation through clinical trials. To achieve an effective balance of subject welfare and innovation, we must contain or minimize the associated risks. In this chapter, I will thus present possible government policies and institutional strategies for risk containment, and evaluate these in terms of their ability to balance subject welfare and innovation. I consider government policy in terms of investment in government programs and initiatives, as well as regulations. The strategies are derived from a culmination of results of the studies in all previous chapters. The proposed policies, initiatives and strategies would be used in combination, where applicable, and may not be as effective when implemented alone. I first cover endogenous uncertainties and then the systemic ones, and, for each, I identify if there are trade-offs between promotion of innovation and protection of clinical trial subject.

### **1. Addressing Endogenous Uncertainties Through Government Policies and Initiatives and Institutional Strategies**

Before I propose policies, initiative and strategies for addressing endogenous uncertainties, I note that effective implementation of each of these policies and strategies would require cooperation between the pharmaceutical company and the CRO, and input from the ethics committee and the local community.

## EU1 – Adverse Selection: Are one or more of the players causing a therapeutic misconception?

To address this type of adverse selection problem, first and foremost, a possible government initiative would be to leverage civil society organizations to raise public awareness of the role of clinical trials and participating subjects, and the rights of the subjects. Other stakeholders then have three options.

- i) **Awareness driven by pharmaceutical company and CRO:** As identified through the interviews of industry players in chapter 6, the pharmaceutical company and the CRO can join the government in implementing educational initiatives to educate and inform the public about the purpose and importance of clinical trials, as well as the rights of clinical trial subjects. This strategy clearly promotes subject welfare, and it does not introduce any procedures that would become a barrier to innovation. It may be argued that fewer individuals would enroll in a clinical trial if they fully understand the risks of participation. However, a clear understanding of the purpose of clinical trials in general as well as the experimental components of the clinical trial in question would allow the subjects to have a better understanding of the importance of their participation and therefore the need for them to comply with what is being asked of them. Subject non-compliance with research procedures may otherwise negatively impact innovation. Thus, this strategy would allow for a greater balance of welfare and innovation.
- ii) **Risk forecasts by pharmaceutical company and CRO:** Also identified through the interview study presented in chapter 6, both the pharmaceutical company and the CRO may assess the probability of causing a therapeutic misconception based on demographic information about the targeted subject population and their relationships with the research team members, if any, and then use this assessment to inform their recruitment and consent strategies. This strategy clearly promotes subject welfare, and it does not introduce any procedures that would become a barrier to innovation. Thus, this strategy would allow for a greater balance of welfare and innovation.

- iii) **Protocol development by pharmaceutical company:** Similarly identified through interviews with industry players, pharmaceutical company may provide well-defined acceptable protocols for recruitment and consent processes for each clinical trial, including the category of individuals who may obtain informed consent. This strategy clearly promotes subject welfare. It is possible for a pharmaceutical company developed protocol to introduce requirements that the CRO cannot effectively meet during the recruitment and consent processes due to local infrastructure or culture, which would then become a barrier to innovation. With cooperation, this strategy would allow for a greater balance of welfare and innovation.
- iv) **Clarification of roles and responsibilities by both pharmaceutical company and CRO:** As observed in literature presented in chapter 2, a possible strategy for containing this risk is to separate the roles of a treating physician from a non-treating physician within the recruitment, screening and consent processes. Again this strategy clearly promotes subject welfare. However, depending on local infrastructure and culture, involvement of non-treating physician or limiting the role of the treating physician may not be feasible. Therefore, implementation of this strategy, without adequate consideration of the local context, would become a barrier to innovation. With cooperation, this strategy would allow for a greater balance of welfare and innovation.

EU2 – Adverse Selection: Are one or more of the players not considering available alternatives adequately?

Five institutional strategies are possible for containment of risks associated with this uncertainty. Ways to address this uncertainty were not identified through literature review, and minimally addressed in documents reviewed for studies presented in chapters 2, 4, 5 and 6. The industry players interviewed for the study presented in chapter 6 were concerned about their need to rely on the other players in order to contain the risk associated with this uncertainty. Therefore, the strategies presented here are based on the industry players' need to rely on other players. The first four strategies presented below are interrelated. However, any one player may choose not to implement the strategy, while the others may decide to do so. Therefore,

these are being presented separately as actions that may or may not be taken by specific players.

- i) **Information sharing between pharmaceutical company and CRO:** Pharmaceutical company provides as complete a picture of available alternatives as possible to the CRO. This strategy clearly promotes subject welfare, and it does not introduce any procedures that would become a barrier to innovation. Thus, this strategy would allow for a greater balance of welfare and innovation.
- ii) **Survey of available alternatives by the CRO:** CRO takes locally available alternatives into consideration, and develops a comprehensive list of available alternatives for consideration by the ethics committee. This strategy clearly promotes subject welfare, and it does not introduce any procedures that would become a barrier to innovation. Thus, this strategy would allow for a greater balance of welfare and innovation.
- iii) **Evaluation of available alternatives in light of subject population by the ethics committee:** Ethics committee considers the comprehensive list provided by the CRO in light of what is accessible to the subject population based on the subject population's socio-economic demographics, and develops the final list of available alternatives. This strategy clearly promotes subject welfare, and it does not introduce any procedures that would become a barrier to innovation. Thus, this strategy would allow for a greater balance of welfare and innovation.
- iv) **Ethics committee and CRO negotiate final consent document:** The ethics committee and the CRO review the ethics committee's final list, negotiate any disagreements and agree upon a final list for incorporation into the consent document, in an effort to ensure that the subject is clearly informed of all available alternatives during the informed consent process by the research team. This strategy clearly promotes subject welfare, and it does not introduce any procedures that would become a barrier to innovation. Thus, this strategy would allow for a greater balance of welfare and innovation.



- v) **Institution of subject advocate by ethics committee and CRO:** The ethics committee and the CRO may consider having an independent subject advocate available during the informed consent process who may help the subject in understanding complex alternatives when appropriate. Again, this strategy clearly promotes subject welfare. However, the requirement for an independent advocate can become a barrier to innovation when an independent advocate is biased or is not available during all informed consent processes. Therefore, implementation of this strategy without consideration of the possible availability of a qualified unbiased advocate would become a barrier to innovation. With cooperation, this strategy would allow for a greater balance of welfare and innovation.

EU3 – Adverse Selection: Are the recruitment and informed consent processes adequately informing the subjects about their participation in research?

To address this type of adverse selection problem, a regulatory agency has to establish recruitment and informed consent standards. Such regulation will clearly promote subject welfare. Unlike the pharmaceutical company, which can develop a protocol on a case-by-case basis, the government standards must be sufficiently general, such that they can be applied to all clinical trials. This generalizability of the regulations makes the development of effective regulations in this area difficult. This is because the regulatory requirements for recruitment and informed consent must be practical and based on feasibility of their implementation by the pharmaceutical company or the CRO. If it were not feasible to meet these requirements, the regulations would become a barrier to innovation. On the other hand, they must be sufficiently specific so as to address local cultural differences. As a result, governments may consider implementing this policy through a combination of general regulatory requirements and more specific guidelines. With cooperation, this policy would allow for a greater balance of welfare and innovation as proposed below.

- i) **Protocol standards by pharmaceutical companies:** As identified through the interviews presented in chapter 6, the pharmaceutical company can set standards that would be acceptable to them on a protocol-by-protocol basis. This strategy clearly promotes subject welfare. It is possible that a pharmaceutical company develops a

protocol to introduce requirements that the CRO cannot effectively meet during the recruitment and consent processes due to local infrastructure or culture, which would then become a barrier to innovation. With cooperation, this strategy would allow for a greater balance of welfare and innovation.

- ii) **Validation of research team qualifications by ethics committee:** As learned through the regulatory and guidance documents reviewed in chapters 2, 4, 5 and 6, the ethics committee assesses whether the research team is not only scientifically, but also culturally and linguistically, qualified to recruit subjects and obtain their consent consistently with the subject's language, literacy level and cultural context. This strategy clearly promotes subject welfare, and it does not introduce any procedures that would become a barrier to innovation. One may argue that this requirement may limit the individuals who may become part of the research team, and therefore, it may become a barrier to innovation. However, familiarity with the local culture and language is also essential for promoting innovation, as subjects must have a good understanding of what is expected of them in order to comply with the research protocol. Subject non-compliance with research procedures may otherwise negatively impact innovation. Thus, this strategy would allow for a greater balance of welfare and innovation.
- iii) **Institution of consent monitor or subject advocate by ethics committee:** As identified through literature review presented in chapter 2, community based subject advocates may play an important role in containing this risk. Thus, an optional strategy is that the ethics committee requires a consent monitor or subject advocate to participate in the informed consent process so as to ensure that the subject comprehends what is being explained. This strategy clearly promotes subject welfare. However, the requirement for an independent advocate can become a barrier to innovation when an independent advocate is biased or is not available during all informed consent processes. Therefore, unconsidered implementation of this strategy would become a barrier to innovation. With cooperation, this strategy would allow for a greater balance of welfare and innovation.

#### EU4 – Adverse Selection: Are any of the players exerting undue influence?

Any policy designed to address this challenge must clearly specify the requirements vis-à-vis acceptable methods of recruitment, informed consent, payment for participation and subject withdrawal by the regulatory agency. The requirement must again be consistent with the local cultural context. Thus, similar to the standard for informed consent and recruitment discussed above, implementation of this policy would require a combination of regulations and guidelines.

This policy clearly promotes subject welfare. As previously noted, government standards must be sufficiently general, such that they can be applied to all clinical trials. Thus, government standards must be practical and based on feasibility of their implementation to a variety of clinical trials. Standards set by the government that either the pharmaceutical company or the CRO cannot effectively meet during the recruitment and consent processes would then become a barrier to innovation. With cooperation, this policy would allow for a greater balance of welfare and innovation.

In addition to government policy, educational initiatives by the government, in collaboration with the civil society, regarding the experimental nature of clinical trials and the rights of clinical trial subjects would promote welfare without lowering incentives for innovation.

Other stakeholders then have 3 options:

- i) **Sponsor ensures clarity in recruitment and informed consent processes:** As identified through interviews presented in chapter 6, sponsor can define acceptable procedures for recruitment, informed consent, subject payment and withdrawal within its protocol. This strategy clearly promotes subject welfare. It is possible that a pharmaceutical company develops a protocol to introduce requirements that the CRO cannot effectively meet during the recruitment and consent processes due to local infrastructure or culture, which would then become a barrier to innovation. With cooperation, however, this strategy would allow for a greater balance of welfare and innovation.

- ii) **Ethics committee ensures cultural compatibility and compliance:** Ethics committee approved protocol clearly defines acceptable methods of recruitment and informed consent processes, which are customized to the local cultural context while being compliant with the government policy and sponsor's protocol. This strategy is derived from many of the regulatory and guidance documents reviewed and presented in chapters 2, 4, 5 and 6. This strategy would allow for a greater balance of welfare and innovation.
- iii) **CRO complies with ethics committee approved protocol:** CRO has procedures in place to ensure that the research team is complying with the ethics committee approved protocol. The need for this strategy was highlighted through literature review in chapter 2, empirical study presented in chapter 4 and interview study presented in chapter 6. This strategy clearly promotes subject welfare. It does, however, require monitoring and guiding of the CRO by the pharmaceutical company. With cooperation, this strategy would allow for a greater balance of welfare and innovation.

EU5 – Moral Hazard: How will the trial be monitored such that adverse events and unanticipated problems can be managed effectively?

To tackle this form of moral hazard, the government must put in place well-defined regulations for adverse event and unanticipated problems reporting and analysis by the regulatory agency. This policy clearly promotes subject welfare, and it does not introduce any procedures that would become a barrier to innovation. Thus, this policy would allow for a greater balance of welfare and innovation. The government's policy as well as institutional strategies presented here are a compilation of monitoring strategies identified through studies presented in chapters 2, 4, 5 and 6.

Other stakeholders can then implement the following strategies:

- i) **Sponsor develops monitoring procedures:** Sponsor provides clearly defined monitoring procedures for adverse event and unanticipated problems within the sponsor's protocol. This strategy clearly promotes subject welfare. Further, though it may be perceived as introducing extra costs to the sponsor, and therefore barrier to innovation, it is in fact necessary for innovation since, absent

monitoring, the clinical trial would yield invalid data regarding the safety of the experimental drug. Thus, this strategy would allow for a greater balance of welfare and innovation.

- ii) **Ethics committee approved protocol incorporates monitoring procedures:** Ethics committee establishes clearly defined monitoring procedures for adverse event and unanticipated problems within the ethics committee approved protocol, including the customization of the procedures to the local subject population's cultural and traditional context. This strategy clearly promotes subject welfare, and it does not introduce any procedures that would become a barrier to innovation. Thus, this strategy would allow for a greater balance of welfare and innovation.
- iii) **CRO invests efforts in monitoring:** CRO ensures adequate implementation of the monitoring procedures by the research team. This strategy clearly promotes subject welfare. However, it also requires that the CRO invest in monitoring procedures, the cost of which may be a disincentive for the CRO and therefore become a barrier to innovation. This also requires monitoring and guiding of the CRO by the pharmaceutical company. Thus, this effort by the CRO would only be as effective as its interest in investing in the efforts, which can be balanced by the sponsor through additional monetary and non-monetary (education and technological) support. With cooperation between the pharmaceutical company and the CRO, this strategy would allow for a greater balance of welfare and innovation.
- iv) **Ethics committee establishes process for monitoring:** Ethics committee has a clearly defined process for review of reported adverse events and unanticipated problems, and its communication of resulting analysis and actions required to the CRO. This strategy clearly promotes subject welfare, and it does not introduce any procedures that would become a barrier to innovation. Thus, this strategy would allow for a greater balance of welfare and innovation.
- v) **Requirement of a data safety monitoring board:** The sponsor or the ethics committee may require that a data safety monitoring board with clearly defined monitoring procedures be established. This strategy promotes subject welfare. However, it may be necessary for some but

not all clinical trials, depending on the phase of the trial, the number of subjects enrolled, and other scientific design considerations. Thus, cooperation amongst the pharmaceutical company, CRO and ethics committee is required to determine when it would be appropriate to implement this strategy. Where appropriate, this strategy would allow for a greater balance of welfare and innovation.

- vi) **Sponsor defined process for analysis and dissemination of information:** Sponsor has a well-established process for analyzing and disseminating resulting information and needs for action to all CROs. Again, though this may be perceived as introducing extra costs to the sponsor, and therefore barrier to innovation, it is in fact necessary for innovation, since sponsor's analysis may result in the sponsor's need to modify the clinical trial protocol, and without effective procedures to analyze and disseminate results of its analysis, this would not be possible. Therefore, this strategy would allow for a greater balance of welfare and innovation.

EU6 – Corruption: Is one or more player acting under the influence of an existing conflict of interest?

There are 2 possible government policies and 3 possible institutional strategies for containment of risks associated with this uncertainty:

- i) **Government Publications:** The government publishes national healthcare priorities, which are then used to allow clinical trials that fall within the national priorities and therefore reduce the chance of trials that may not ultimately benefit the local population. This policy clearly promotes subject welfare, and it does not introduce any procedures that would become a barrier to innovation relevant to the local population. Thus, this policy would allow for a greater balance of welfare and innovation. This policy option was developed based on literature related to exploitation of subjects in emerging markets that is presented in chapter 5. According to this literature, there is a need for clinical trials to be based on the local disease burden and national healthcare priorities.
- ii) **Regulatory requirements:** Originating from documentary analysis presented in chapters 2 and 4, one policy option is that the

government issues regulations for disclosure and management of conflicts of interest of reviewers within the regulatory agency. This policy clearly promotes subject welfare, and it does not introduce any procedures that would become a barrier to innovation. Thus, this policy would allow for a greater balance of welfare and innovation.

- iii) **Well-defined protocols of the sponsor:** Again from documentary analysis presented in chapters 2 and 4, a policy option is for the sponsor to have clearly defined and well-implemented requirements for disclosure and management of conflicts of interest of each member of the research team within the CROs. This strategy clearly promotes subject welfare, and it does not introduce any procedures that would become a barrier to innovation. Thus, this strategy would allow for a greater balance of welfare and innovation.
- iv) **Well-defined protocols of the ethics committee:** Ethics committee has clearly defined rules for disclosure and management of conflicts of interest of reviewers within the ethics committee. This strategy clearly promotes subject welfare, and it does not introduce any procedures that would become a barrier to innovation. Thus, this strategy would allow for a greater balance of welfare and innovation. This policy option is derived through documentary analysis presented in chapters 2, 4 and 6.
- v) **Monitoring of CROs:** A policy option emerging from the outcomes of the empirical study presented in chapter 4 is that the sponsor implement mechanisms for monitoring of the CROs to ensure that the CROs are following the approved protocol. This strategy clearly promotes subject welfare. Again, this may be perceived as introducing extra costs to the sponsor, and therefore a barrier to innovation. However, if the CRO does not follow the sponsor's protocol, the sponsor will receive inaccurate data, which then will not be valid for its innovation. Thus, this strategy would allow for a greater balance of welfare and innovation.

The above results can be summarized as in tables 17 and 18.

Table 17: Government policies or initiatives for containment of risks associated with endogenous uncertainties, their tradeoffs and costs

<b>Endogenous uncertainty</b>	<b>Government policy or initiative</b>	<b>Possible impact on subject welfare and/or innovation</b>	<b>Tradeoffs</b>	<b>Cost considerations as additional tradeoffs</b>
EU1 – Adverse Selection: Are one or more of the players causing a therapeutic misconception?	Educational initiatives	Promote welfare	None	Public bears cost for such initiatives
EU2 – Adverse Selection: Are one or more of the players not considering available alternatives adequately?	None	None	None	None
EU3 – Adverse Selection: Are the recruitment and informed consent processes adequately informing the subjects about their participation in research?	Establish recruitment & informed consent standards within regulations & guidelines	- Promote welfare - Negative impact on innovation if unfeasible standards	None	Requires adequate budget for regulatory agency to implement



EU4 – Adverse Selection: Are any of the players exerting undue influence?	Establish requirements for subject recruitment, consent, payment & withdrawal within regulations & guidelines	- Promote welfare - Negative impact on innovation if unfeasible standards	None	Requires adequate budget for regulatory agency to implement
	Educational initiatives	Promote welfare	None	Public bears cost for such initiatives
EU5 – Moral Hazard: How will the trial be monitored such that adverse events and unanticipated problems can be managed effectively?	Regulations for adverse event & unanticipated problem reporting and analysis	Promote welfare	None	Requires adequate budget for regulatory agency to implement
EU6 – Corruption: Is one or more player acting under the influence of an existing conflict of interest?	Government publication of national healthcare priorities & subsequent use in clinical trial approval process	Promote welfare	None	Public bears cost of such government efforts
	Regulatory requirements for disclosure & management of conflicts of interest	Promote welfare	None	Requires adequate budget for regulatory agency to implement

Table 18: Institutional strategies for containment of risks associated with endogenous uncertainties, their tradeoffs and costs

<b>Endogenous uncertainty</b>	<b>Institutional strategy</b>	<b>Possible impact on subject welfare and/or innovation</b>	<b>Tradeoffs</b>	<b>Cost considerations as additional tradeoffs</b>
EU1 – Adverse Selection: Are one or more of the players causing a therapeutic misconception?	Educational initiatives by pharmaceutical company or CRO	Promote welfare	Sponsor tradeoff	Sponsor bears cost for such initiatives
	Risk forecasting by pharmaceutical company & CRO	Promote welfare	Sponsor tradeoff	Sponsor bears cost of forecasting
	Protocol development by pharmaceutical company	- Promote welfare - Negative impact on subject welfare and/or innovation if company unfamiliar with local context	None	Negligible – sponsor must develop its clinical trial protocol regardless of this consideration
	Clarification of roles & responsibilities by pharmaceutical company & CRO	Promote welfare	None	None

EU2 – Adverse Selection: Are one or more of the players not considering available alternatives adequately?	Information sharing between pharmaceutical company & CRO	Promote welfare	None	None
	Survey of available alternatives by the CRO	Promote welfare	Sponsor tradeoff	Sponsor pays for CRO efforts
	Evaluation of available alternatives in light of subject population by ethics committee	Promote welfare	None	Requires adequate budget for ethics committee to implement
	Ethics committee & CRO negotiated consent form development	Promote welfare	None	Negligible
	Subject advocate instituted by ethics committee (typically volunteers)	Promote welfare	May result in minimal sponsor tradeoff	Sponsor bears cost, if any
EU3 – Adverse Selection: Are the recruitment and informed consent processes adequately informing the subjects about their participation in research?	Protocol standards by pharmaceutical company	- Promote welfare - Negative impact on subject welfare and/or innovation if company unfamiliar with local context	None	Negligible – sponsor must develop its clinical trial protocol regardless of this consideration
	Validation of research team qualifications by ethics committee	Promote welfare	None	Negligible – part of ethics committee's charge

	Consent monitor or subject advocate instituted by ethics committee (typically ethics committee member or volunteer)	Promote welfare	May result in minimal sponsor tradeoff	Sponsor bears cost, if any
EU4 – Adverse Selection: Are any of the players exerting undue influence?	Pharmaceutical company defines acceptable subject recruitment, consent, payment & withdrawal within its protocol	- Promote welfare - Negative impact on subject welfare and/or innovation if company unfamiliar with local context	None	Negligible – sponsor must develop its clinical trial protocol regardless of this consideration
	Ethics committee ensures cultural compatibility and compliance	Promote welfare	None	Negligible – part of ethics committee’s charge
	CRO ensures compliance with ethics committee approved protocol	Promote welfare	Sponsor tradeoff	Pharmaceutical company may need to invest in monitoring CRO compliance
EU5 – Moral Hazard: How will the trial be monitored such that adverse events and unanticipated problems can be managed effectively?	Sponsor develops monitoring procedures	Promote welfare	Sponsor tradeoff	Sponsor must invest in monitoring procedures
	Ethics committee approved protocol incorporates	Promote welfare	None	Negligible – part of ethics committee’s charge

	monitoring procedures			
	CRO invests efforts in monitoring	Promote welfare	Sponsor tradeoff	Sponsor charged for cost
	Ethics committee establishes process for monitoring	Promote welfare	None	Requires adequate budget for ethics committee to implement
	Sponsor or ethics committee require a Data Safety Monitoring Board (members are typically volunteers)	Promote welfare	May result in minimal sponsor tradeoff	Sponsor charged for cost, if any
	Sponsor has process for analysis and dissemination of information	Promote welfare	Sponsor tradeoff	Sponsor must invest in analysis and information dissemination procedures
EU6 – Corruption: Is one or more player acting under the influence of an existing conflict of interest?	Well-defined requirements for disclosure and management of conflicts by the sponsor	Promote welfare	Sponsor tradeoff	Sponsor bears cost
	Well-defined requirement for disclosure and management of conflicts by ethics committee	Promote welfare	None	Negligible – part of ethics committee's charge
	Monitoring of CROs by sponsor	Promote welfare and innovation	Sponsor tradeoff	Sponsor must invest in monitoring of CROs

## 2. Addressing Systemic Uncertainties Through Government Policies and Initiatives and Institutional Strategies

The policy and strategy options for containment of risks associated with the systemic uncertainties were identified by combining the information identified through literature review, policy options present in US and India as well as through interviews with industry players.

### SU1: Who bears the cost of subject participation?

There are 4 possible government policies for containment of risks associated with this uncertainty:

- i) **Cost sharing with subjects:** Government policy allows some costs associated with clinical trials to be passed to subjects. Depending on the cost of participation being passed to the subjects and the socio-economic demographics of the subject population, allowing the cost to be passed to the subject may tip the balance away from subject welfare. On the other hand, requiring the sponsor to bear all costs, including those that may be part of providing standard clinical care during the course of the trial, may result in sponsors not bringing clinical trials to the given market, and therefore become a barrier to innovation. Careful consideration of the local environment by the government is required to determine the extent to which this policy would balance welfare and innovation.
- ii) **Sponsor as cost-bearer:** Government policy requires that sponsor cover all costs associated with clinical trials. Requiring sponsors to cover all costs associated with the conduct of clinical trials, including the cost of standard treatment provided to trial subjects, is likely to result in sponsors leaving the country, and therefore, become a barrier to innovation.
- iii) **Sponsor or third party as cost bearers:** Government policy requires that costs must be covered either by the sponsor or the third party payer, but not the subject. Allowing the costs to be passed to third party payers in a country where third party payers are unlikely to approve such costs on a subject-by-subject basis would result in the sponsor bearing all costs, in which case we return to government policy 2 above with a likelihood of the policy becoming a barrier to

innovation. On the other hand, if the government is able to introduce regulatory requirements or enter into negotiated agreements with third party payers by which certain clinical trial costs may be covered by the third party payer, then welfare and innovation may be better balanced.

- iv) **Ethics committee determines which costs can be passed to subjects:** When government policy allows costs to be passed to the subjects or their third party payer, government policy gives the ethics committee the authority to determine whether the sponsor's cost sharing proposal is appropriate based on an assessment of the socioeconomic status of the subject population. The pharmaceutical company and the ethics committee would have to negotiate an agreement on how best to balance subject welfare and innovation.

#### SU2: Who bears the cost of treatment for injury?

There are 3 possible government policies and 1 possible institutional strategy for containment of risks associated with this uncertainty:

- i) **Cost sharing based on pharmaceutical company and CRO's assessments of injury:** Government policy allows cost of treatment for injury not related to the trial to be passed to the subject or third party payer. However, government policy requires that the sponsor cover costs of treatment for injury related to the trial. Pharmaceutical company and CRO together assess whether injury is related to the clinical trial. This policy would rely heavily on the assessment of the pharmaceutical company and the CRO. Assuming that the risks associated with conflicts of interest (EU6) have been contained adequately, this policy may allow for a balance of innovation and welfare. This is because subjects would not be required to pay for trial related costs, and sponsor would not be required to pay for costs not related to the trial.
- ii) **Sponsor as cost-bearer:** Government policy requires that all costs associated with injury, whether related to the clinical trial or not, must be covered by the sponsor. Requiring sponsors to cover all costs associated with an injury, whether related to the clinical trial or not, is

likely to result in sponsors leaving the country, and therefore, become a barrier to innovation.

- iii) **Sponsor or third party as cost bearers:** Government policy requires that costs of any treatment for injury must be covered either by the sponsor or the third party payer, but not the subject. Again, allowing the costs to be passed to third party payers in a country where third party payers are unlikely to approve such costs on a subject-by-subject basis would result in one of two situations: either the sponsors will have to bear all costs, in which case we return to government policy 2 above with a likelihood of the policy becoming a barrier to innovation; or the subjects will have to bear the costs, which would adversely affect subject welfare. On the other hand, if the government is able to introduce mechanisms by which certain costs of treatment for clinical trial related injuries may be covered by the third party payer, then welfare and innovation may be better balanced.
- iv) **Sponsor's procedures for assessment of injury relatedness:** Where government policy allows costs associated with treatment for injury that is not related to the trial to be passed to the subjects and/or their third party payer, sponsor has well-defined procedures in place to make assessments of the relatedness of an injury to the clinical trial, and passing only those costs not related to the trial to the subjects and/or their third party payer. This strategy would allow for a balance between welfare and innovation.

### SU3: Should there be compensation for injury?

There are 2 possible government policies for containment of risks associated with this uncertainty:

- i) **Sponsor bears cost:** Government policy requires sponsors to provide compensation for injury related to the trial. Requiring sponsors to provide compensation for injury is likely to result in sponsors leaving the country, and therefore, become a barrier to innovation.
- ii) **Joint decision on compensation:** Government policy requires that the sponsor, CRO and ethics committee together decide whether to compensate for injury related to the trial. This policy would require



negotiation amongst the sponsor, CRO and the ethics committee on how best to balance subject welfare and innovation based on their assessment of the injury, its relatedness and the cultural context.

#### SU4: Should end of trial care be provided and to whom?

There are 4 possible government policies and 1 possible institutional strategy for containment of risks associated with this uncertainty:

- i) **Sponsor bears burden:** Government policy requires that sponsor provide end of trial care when care is proven to be beneficial to the subject. This policy would promote subject welfare. However, requiring sponsors to provide end of trial care may result in sponsors leaving the country, and therefore, become a barrier to innovation, particularly if the government's processes for approval and monitoring of expanded access or compassionate use protocols introduces unnecessary burdens to the sponsor. Since the sponsor may benefit from data collected during expanded access or compassionate use trials, this policy may still be able to provide a balance between welfare and innovation so long as the process for regulatory approval and monitoring of expanded access or compassionate use trials is effective and efficient.
- ii) **Sponsor has decision-making authority:** Government policy allows sponsor to decide whether to provide end of trial care and to whom. This policy promotes innovation, and has the potential to promote subject welfare. However, in cases where the sponsor does not have anything to gain, it may negatively impact subject welfare.
- iii) **Regulatory process for oversight of end of trial care protocols:** Regulatory agency has procedures in place for approving and monitoring end of trial care protocols, and the procedures do not create unnecessary bureaucratic burdens or delays. Government policies 1 and 2 are both dependent on this strategy. If a process for approval and monitoring is not established by the government, it would not be possible for sponsors to bring expanded access or compassionate use trials to the country.

iv) **Government and pharmaceutical company negotiated agreement:**

The government and the pharmaceutical company enter into a negotiated agreement that defines the strategy for transition from expanded access or compassionate use to commercial availability of drug should it prove beneficial at the end of all phases of clinical experimentation. This strategy allows for a balance of welfare and innovation, whereby the parties have made considered decisions about long-term access to drugs that have proven to be beneficial. To be effective, this strategy requires extensive cooperation between the pharmaceutical company and the government.

SU5: Who will cover the cost of end of trial care?

There are 3 possible government policies and 1 possible institutional strategy for containment of risks associated with this uncertainty:

- i) **Cost sharing with subjects or third party payers:** Government policy allows costs associated with end of trial care to be passed to subjects or their third party payer. Depending on the cost of participation being passed to the subjects or their third party payer, and the socio-economic demographics of the subject population, allowing the cost to be passed to the subject or their third party payer may tip the balance away from subject welfare. However, given the minimal benefit to the pharmaceutical company in providing end of trial care, this policy may be necessary. Thus, careful consideration of the local environment and the pharmaceutical company's needs by the government is required to determine the extent to which this policy would balance welfare and innovation.
- ii) **Sponsor bears costs:** Government policy requires the sponsor to cover all costs associated with end of trial care. Requiring the sponsor to bear all costs may result in sponsors not implementing end of trial care protocols, which would tip the balance away from subject welfare. The only incentive for the pharmaceutical company to provide end of trial care would be if it could benefit from data resulting from such protocol, and thus tangentially support innovation. Thus, careful consideration of the local environment and the pharmaceutical company's needs by the government is required to determine the extent to which this policy would balance welfare and innovation.

- iii) **Sponsor or third party as cost bearers:** Government policy requires that costs must be covered either by the sponsor or the third party payer, but not the subject. Allowing the costs to be passed to third party payers in a country where third party payers are unlikely to approve such costs on a subject-by-subject basis would result in one of two situations: either the sponsors will have to bear all costs, in which case we return to government policy 2 above; or the subjects will have to bear the costs, which would adversely affect subject welfare. On the other hand, if the government is able to introduce regulatory requirements or enter into negotiated agreements with third party payers by which the third party payer must cover certain end of trial costs, then welfare and innovation may be better balanced.
- iv) **Ethics committee determines which costs can be passed to subjects:** When government policy allows costs to be passed to the subjects or their third party payer, government policy gives ethics committee the authority to determine whether the sponsor's cost sharing proposal is appropriate based on an assessment of the socioeconomic status of the subject population. This strategy would promote subject welfare. However, it would require the pharmaceutical company and the ethics committee to negotiate an agreement on how best to balance subject welfare and innovation.

The above results can be summarized as in tables 19 and 20.

Table 19: Government policies for containment of risks associated with systemic uncertainties, their tradeoffs and costs

<b>Systemic uncertainty</b>	<b>Government policy</b>	<b>Possible impact on subject welfare and/or innovation</b>	<b>Tradeoffs</b>	<b>Cost considerations as additional tradeoffs</b>
SU1: Who bears the cost of subject participation?	Cost sharing with subjects	Possible negative impact on subject welfare depending on socioeconomic status	- Subject tradeoff - Sponsor tradeoff	Sponsor and subject both bear cost
	Sponsor as cost-bearer	Negative impact on innovation & welfare	Sponsor tradeoff	Sponsor bears cost
	Sponsor or third party as cost bearers	- Promote welfare - Promote innovation - Negative impact on innovation & welfare	Sponsor tradeoff	Sponsor or third party payer bear cost
	Ethics committee determines which costs can be passed to subjects	- Promote welfare - Possible negative impact on innovation	- Subject tradeoff - Sponsor tradeoff	Sponsor and subjects may both bear costs
SU2: Who bears the cost of treatment for injury?	Cost sharing based on pharmaceutical company and CRO's assessment of injury	- Promote welfare - Promote innovation	- Subject tradeoff - Sponsor tradeoff	Sponsor bears trial related costs

	Sponsor as cost bearer	- Promote welfare - Negative impact on innovation	Sponsor tradeoff	Sponsor bears cost
	Sponsor or third party as cost bearers	- Promote welfare - Promote innovation - Negative impact on innovation & welfare	Sponsor tradeoff	Sponsor or third party payer bear cost
SU3: Should there be compensation for injury?	Sponsor bears cost	- Promote welfare - Negative impact on innovation	Sponsor tradeoff	Sponsor bears cost
	Joint decision on compensation	- Promote welfare - Promote innovation	Sponsor tradeoff	Sponsor bears cost, if any
SU4: Should end of trial care be provided and to whom?	Sponsor bears burden	- Promote welfare	Sponsor tradeoff	Sponsor bears cost
	Sponsor has decision-making authority	- Promote welfare - Promote innovation	Sponsor tradeoff	Sponsor bears cost, if any
	Regulatory process for oversight of end of trial care protocols	- Promote welfare	None	Requires adequate budget for regulatory agency to implement
	Government & sponsor negotiated agreement	- Promote welfare - Promote innovation	Sponsor tradeoff	Both sponsor and government bear cost

SU5: Who will cover the cost of end of trial care?	Cost sharing with subjects or third party payer	<ul style="list-style-type: none"> <li>- Promote welfare</li> <li>- Negative impact on welfare</li> <li>- Negative impact on innovation</li> </ul>	Subject tradeoff	Subject or third party bear cost
	Sponsor bears cost	<ul style="list-style-type: none"> <li>- Promote welfare</li> <li>- Negative impact on welfare</li> </ul>	Sponsor tradeoff	Sponsor bears cost
	Sponsor or third party as cost bearers	<ul style="list-style-type: none"> <li>- Promote welfare</li> <li>- Negative impact on welfare</li> </ul>	Sponsor tradeoff	Sponsor or third party payer bear cost
	Ethics committee determines which costs can be passed to subjects	<ul style="list-style-type: none"> <li>- Promote welfare</li> <li>- Negative impact on welfare</li> </ul>	<ul style="list-style-type: none"> <li>- Subject tradeoff</li> <li>- Sponsor tradeoff</li> </ul>	Sponsor and subjects may both bear costs

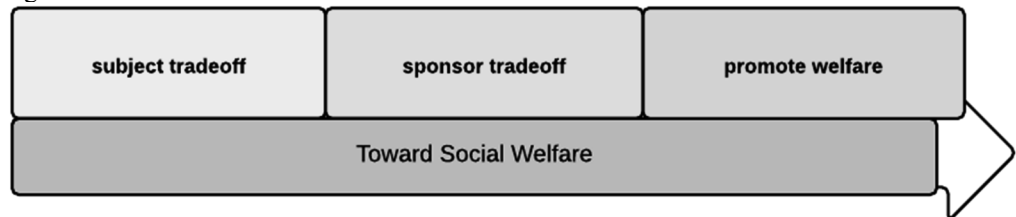
Table 20: Institutional strategies for containment of risks associated with systemic uncertainties, their tradeoffs and costs

<b>Systemic uncertainty</b>	<b>Institutional strategy</b>	<b>Possible impact on subject welfare and/or innovation</b>	<b>Tradeoffs</b>	<b>Cost considerations as additional tradeoffs</b>
SU1: Who bears the cost of subject participation?	None	None		None
SU2: Who bears the cost of treatment for injury?	Sponsor's procedures for assessment of injury relatedness	Promote welfare	Sponsor tradeoff	Sponsor bears cost
SU3: Should there be compensation for injury?	None	None		None
SU4: Should end of trial care be provided and to whom?	None	None		None
SU5: Who will cover the cost of end of trial care?	None	None		None

As noted at the beginning of this chapter, the proposed policies, initiatives and strategies would be used in combination, where applicable, and may not be as effective when implemented alone, thus creating a spectrum of decisions leading toward optimal subject welfare or toward a social dilemma. The steps toward optimal subject welfare would either simply promote welfare or involve subject tradeoff and sponsor tradeoff, whereas the steps toward a social dilemma would involve negative impact on innovation, welfare or both. Thus, I have labeled each policy or strategy in tables 17-20 with its possible step on the path toward welfare or social dilemma. I propose that the decisions leading to the optimal subject welfare take the path

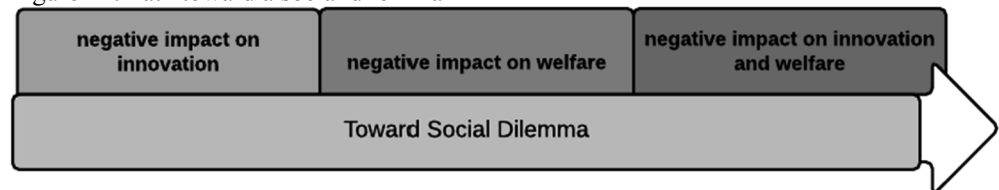
illustrated in figure 13 below, and the decisions leading to a social dilemma take the path illustrated in figure 14 below.

Figure 13: Path toward social welfare



\* Author's creation

Figure 14: Path toward a social dilemma



\* Author's creation

### 3. Conclusion

I now return to the overarching question of this thesis, how to maximize clinical trial subject welfare while promoting novel drug innovation. As shown by tables 17, 18, 19 and 20, to achieve a balance between welfare and innovation in this context, the uncertainties associated with having an impact on subject welfare and/or innovation must be reduced such that considered policies and strategies to address measurable risks can be established at all levels of clinical trial governance. From a governance perspective, the combination of policies and strategies implemented can lead a country toward optimal social welfare or toward a social dilemma. Clearly, there is not one best combination of policies and decisions that can be made across all countries. Rather, a spectrum of decisions, when made in combination, can lead to either better social welfare or a greater social dilemma.

In the four tables, I categorized each of the possible policies and strategies according to their implications, which can then be correlated with the spectra, so as to clarify their impact on the overall balance of welfare and innovation. The two spectra and the tables together can give insights on the implications of choices. It is important to note, however, that many of the policies and



strategies would require cooperation amongst the various players. Therefore, depending on the level of cooperation, a given policy or strategy may lead to placement on the path toward optimal welfare or toward social dilemma. However, it is beyond the scope of the present thesis to explore these issues, as they would depend on the context being studied. This, however, can be a matter to be explored in future research. Thus, some of the policies or strategies have been assigned more than one possible placement on the spectrum. From the above, it is clear that containment of risks associated with endogenous and systemic uncertainties requires cooperation amongst many of the players. With cooperation, however, all uncertainties can be placed on a path toward optimal social welfare. This, thus, brings us back to the conclusions drawn from the studies in chapter 6, and the need for establishing an effective relationship structure amongst the various players.

## CHAPTER 8: CONCLUSIONS, CONTRIBUTIONS AND RECOMMENDATIONS

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Innovation in drug development is one component of improvements in public health. Drug development requires the conduct of clinical trials to test the novel drugs for safety and efficacy in humans. Clinical trials are also the most expensive aspect of the drug development process. “Conducting a trial costs \$25,000 or more per patient studied, and phase 3 trial programs consume more than 40% of a sponsoring company’s expenditures” (Kocher & Roberts, 2014). Clearly, the sponsoring company, most often the pharmaceutical company whose product is being tested, is interested in maximizing its return on such an investment. The sponsor’s competing agenda is one area of debate about the ethical conduct of clinical trials (Perlis et al., 2014).

Physician investigator is another actor in the clinical trial process whose actions are sometimes questioned:

*...investigators' primary obligation to care for the human subjects of their research is the strong temptation to subordinate the subjects' welfare to the objectives of the study. That is particularly likely when the research question is extremely important and the answer would probably improve the care of future patients substantially. In those circumstances, it is sometimes argued explicitly that obtaining a rapid, unambiguous answer to the research question is the primary ethical obligation. With the most altruistic of motives, then, researchers may find themselves slipping across a line that prohibits treating human subjects as means to an end (Angell, 1997).*

Contract Research Organizations (CRO) is another group of actors in the conduct of clinical trials, and there have been concerns raised with the rise of non-academic CROs in the recent years. “...trials conducted in the commercial sector are heavily tipped toward industry interests, since for-profit CROs... contracting with industry in a competitive market, will fail if they offend their funding sources” (Bodenheimer, 2000).

Finally, the government is responsible for regulatory oversight of clinical trials, not only from the perspective of ensuring that the drugs brought to market are safe and effective, but also that the clinical trials are conducted in a manner that protects the rights and welfare of human subjects. However, governments also have a conflicting agenda, namely one of economic growth. “Medical innovation also creates economic value. Biopharmaceutical advances support high-value jobs and help stimulate regional and national economic activity” (Eckstut, Chang, Blair, Apostolatos, & Burns, 2009).

How do all these actors balance their sometimes-conflicting agendas to provide overall effective governance of clinical trials? Do these conflicting agendas affect human subjects and their societies (Schüklenk, 2000)? Historically, there have been numerous examples of unethical conduct of clinical trials (Angell, 1997; Comfort, 2009; Schüklenk, 2000; Tuskegee University, 2011), and these have continued into the modern days (Attarwala, 2010; Weyzig & Schipper, 2008). However, one must believe that these ethical violations are the exceptions and not the norm. The questions of what causes these violations to occur and how these can be avoided were the early foundation for this thesis, and thus led to the current work.

Given the number of varied actors involved in the clinical trial process, with their respective agendas, and the complexity of the process itself, it was important to ask how these actors can integrate their strategies, i.e. cooperate, in an effort to maximize the welfare of the clinical trial subjects while promoting novel drug innovation. To do so, I first identified the various concerns regarding the protection of human subjects of clinical trials that have been raised in literature, and characterize these using concepts borrowed from game theory, in an effort to establish a framework for evaluating government and institutional policies and procedures. Concepts borrowed from game theory provided a construct by which the “relative merits of cooperation and self interest in an ensemble of strategic interactions can be investigated” (Cohen, 1998). The use of the framework to evaluate the US regulatory oversight system, the Indian regulatory oversight system, and industry participation in protection of clinical trial subjects resulted in the identification of policy and strategy options for addressing various uncertainties involved in the clinical trial process, such that the decision makers can strive to achieve a better balance between subject welfare and innovation.

## **1. Main Conclusions**

At an overarching level, this thesis contributes to literature by initiating a discussion on the need to balance subject welfare with innovation, rather than to focus separately on the protection of subjects and the need to promote innovation in drug development. More specifically, this thesis contributes in three major ways: i) it provides a framework for evaluating policies and procedures for ethical conduct of clinical trials in terms of their ability to reduce uncertainties; ii) it proposes a relationship structure for interdependent decision making amongst the various players involved in the implementation of clinical trials; and iii) it provides policy and strategy recommendations for use by each of the players involved in the governance of clinical trials.

In order to identify why risk containment is still a challenge in clinical trials, one must first understand the complexities involved in the conduct of clinical trials and in the protection of clinical trial subjects. Chapters 1-3 do just that by presenting the clinical trial process, providing an overview of the evolution of clinical trials, their oversight, and a brief history of ethical violations. In chapter 1, I break down the process of each clinical trial into three stages (pre-trial, events during a trial, and post-trial). This information is then combined with a literature and documentary review of ethical concerns associated with clinical trials in chapter 2. The concerns identified were: consideration of available alternatives, undue influence including coercion, conflicts of interest, compensation for injury, end of trial care, informed consent, monitoring of clinical trials, payment for participation, therapeutic misconception, treatment for injury, cost of participation, privacy of subjects and confidentiality of data. These concerns were then woven into a framework developed in chapter 3 to identify the risks to clinical trial subjects that arise from systemic uncertainty and endogenous uncertainty stemming from adoption of a non-ethical stance on the part of one or more players. Players involved include the government, which provides regulatory oversight; the sponsor, typically the pharmaceutical company; the CRO, including the research team and the PI; the ethics committee; and the human subjects. At the end of chapter 3, I present a case study, which reveals that inadequate individual decision making by each player in a clinical trial can result in ethical violations, and without an integrated approach, one violation can multiply exponentially through subsequent related actions by other players. Hence, the importance of integrated decision-making is established.

The framework developed in chapter 3 was used to evaluate the US regulatory oversight system in chapter 4. The systematic application of this framework helped identify ways in which the US regulatory approach to addressing the uncertainties associated with the implementation of clinical trials can be improved. Specifically, I recommend adding a new step within the US regulatory oversight system to address the weaknesses identified in chapter 4. The proposed modified regulatory oversight system is illustrated in figure 9. The framework was then used to evaluate the Indian regulatory oversight system in chapter 5, with similar results for improving the overall regulatory oversight system.

In addition to local regulatory requirements, there are international standards for conducting ethical clinical trials. Though lacking in enforcement power, these are often used as the basis for evaluating industry players and their ethical conduct. The two most commonly referenced international standards for ethical conduct of clinical trials are the Declaration of Helsinki and the International Conference on Harmonisation's Good Clinical Practices (Access to Medicine Foundation, 2012a; Cekola, 2007; Irene Schipper, 2009; Schüklenk, 2000). As such, it was important to evaluate, using the same framework, whether these establish an ethical responsibility of the industry players. A surprising conclusion of my evaluation was that neither of these documents truly establishes the industry players' responsibility toward ethical conduct of clinical trials. Gaps in these documents are outlined in table 15.

An interview study of the industry players using the same framework revealed that pharmaceutical sponsors rely heavily on the CRO and the ethics committee for implementation of clinical trials in an ethical manner. They also rely on the local government's requirements, and design their studies in accordance with local requirements. However, there are also challenges related to these two areas: i) the implementation by the CRO and the ethics committee is based on local context and subjective interpretation of the sponsor's policies and procedures; and ii) the local regulations may create barriers to conducting the clinical trial. The study concluded that the best mechanisms for addressing these challenges are for each of the players to cooperate in establishing their policies and procedures, and to develop long-term relationships with each of the other players. As a contributing conclusion, I present a proposed relationship structure in figure 12, which accounts for the players and the types of information to be shared for effective implementation of clinical trials.

The use of the framework to evaluate the US and Indian regulatory oversight systems and the industry perspective provided the basis for identification of possible policy and strategy options, which are provided chapter 7. I combine these policy and strategy options with a newly proposed spectrum of decisions that lead toward either optimal social welfare or toward a social dilemma. Combining these in this manner resulted in a clear delineation of ways in which the decision makers can achieve a balance between subject welfare and innovation. As a secondary result, this analysis also validated the need for a novel relationship structure such as the one proposed in figure 12.

## **2. Methodological Challenges Faced**

As noted in chapters 2 and 3, consideration for an overarching economic impact of the clinical trial process, especially in terms of cooperative decision making, and viable options for the welfare maximizing governance of the clinical trial process, its consequences, or possible tradeoffs between the different players is a fairly unexplored area of research. Research, thus far, has focused on identification of specific ethical violations (Srinivasan, 2009; Weyzig & Schipper, 2008), identification of the various ethical risks that may exist (van Huijstee & Schipper, 2011), recommendations to regulators for monitoring and oversight of clinical trials based on current international standards (Irene Schipper, 2009), and studies that focus on singular ethical considerations (Benatar, 2002; Bhutta, 2004; B. Brown, Kinsler, Folayan, Allen, & Cáceres, 2014; Califf et al., 2003; Largent, Grady, Miller, & Wertheimer, 2012; Schüklenk, 2000; Silverman, 2007). Studying the clinical trial process as a whole, from the perspective of each of the players and looking at the possible tradeoffs toward obtaining best social outcomes, requires access to data that is currently limited. This includes access to government's data on regulatory approvals, non-compliance rates, and audit results; industry data, including access to their policies and procedures, sample contracts and templates; and ethics committee data, including access to their policies and procedures, templates and post-approval monitoring. Thus, willingness of all players to share their respective data, whether publicly or through research agreements, is essential for this type of research to continue.

### **2.1. Challenges in Documentary Analysis**

The empirical study presented in chapter 4 relied on limited available data from OHRP and FDA. For the purpose of this study, I had to make some

assumptions regarding number of active clinical trial sites under FDA oversight, number of active IRBs under FDA oversight, number of PIs involved in active clinical trials and that agencies routinely audit sufficient numbers of institutions or trials so as to provide significant basis for conclusions. Additionally, to identify the occurrences of non-compliance, I had to convert qualitative data such as OHRP determination letters and FDA warning letters into quantitative data regarding number of citations. Finally, the denominator for the total number of active clinical trials was obtained through a third source, [clinicaltrials.gov](http://clinicaltrials.gov), as this is not available through OHRP or FDA. To add to these concerns, neither the FDA nor the OHRP clearly publish a formula for compliance monitoring, such as percentage of total trials, sites, PIs or sponsors they audit or investigate routinely. For the research presented in this thesis to be expanded and for similar research to continue, data presented by the regulatory agencies should not only be in the form of letters and notices sent to the individual players, but also include agency wide quantitative data and formulas. Despite these limitations, I do believe that the study presented in chapter 4 provides valuable information in terms of the types of violations that occurred and their relative frequency, which then allowed me to identify the issues that are not sufficiently addressed by the US regulations.

Similar data for India would have been helpful. India is beginning to accrue such data and starting to publish it. Over time, these challenges may be reduced with better data.

The industry study presented in chapter 6 could have also benefitted from documentary analysis of individual industry players' policies, procedures, sample contracts and templates. However, access to these documents is very limited due to their proprietary nature. It is noted that industry players themselves would benefit from making such documents more accessible to researchers, even if these are provided under non-disclosure agreements.

## **2.2. Challenges in Interview Studies**

The India study presented in chapter 5 focused on enforceable regulatory requirements. Several interviewees commented that there are soft practices that promote ethical conduct of clinical trials. This is not surprising in an emerging country, which is in the process of establishing a regulatory oversight system, and is in constant flux due to its necessity to learn lessons regarding the effectiveness of each decision made and to react accordingly.

However, these soft practices were not further discussed or evaluated for the purpose of this study due to their lack of enforceability and the limitations on being able to reliably identify all of these. This is a challenge for studying the real oversight versus the documented oversight of clinical trials in emerging countries. However, this thesis is valuable in providing a framework upon which the governments of emerging countries can base their regulatory requirements, and also in providing possible policy and strategy options, such that these governments can start converting some of the more effective soft practices into regulatory requirements, where appropriate.

The study on industry perspective presented in chapter 6 was entirely based on interviews with industry experts. Interviews, by their nature, allow for respondents to give socially desirable responses (Holbrook, Green, & Krosnick, 2003). However, I was able to overcome this concern by asking the respondents to discuss the challenges they face in conducting ethical trials and the tradeoffs for balancing industry and subject interests. These questions resulted in the respondents' acknowledgment that challenges exist, and they were then more willing to discuss their approach and tradeoffs.

### **3. Policy Implications and Recommendations**

The results of this thesis may be used to enhance governance of clinical trials in both traditional and emerging markets. More importantly, the results of this thesis bring to the forefront the need to balance welfare and innovation in the governance of clinical trials. This research yields a number of policy recommendations targeted toward three levels of policy-makers in the drug development process: i) organizations of global governance; ii) individual country governments; and iii) clinical trial institutions, including the sponsors, CROs and ethics committees.

#### **3.1. International Standards**

As discovered in chapter 6, the two most commonly referenced international ethical standards for the conduct of clinical trials, Declaration of Helsinki and ICH Good Clinical Practice, do not adequately define the responsibilities of the industry players. However, these two documents continue to serve as the basis for assigning ethical responsibility to all players, including the industry players (Access to Medicine Foundation, 2014b; Adobor, 2012; Cekola, 2007; Petryna, 2005; Schüklenk, 2000). Since the Declaration of Helsinki is addressed primarily to physicians, it has a limited scope and is expected to



focus on only the physician's responsibilities. The ICH "mission is to achieve greater harmonisation to ensure that safe, effective, and high quality medicines are developed and registered in the most resource-efficient manner<sup>66</sup>." Perhaps the gaps in international standards that are outlined in chapter 6 exist due to the international standards' focus on either the physicians (the Declaration) or the regulatory and technical harmonization in drug registration (ICH). Since ICH has evolved as the leading source for global guidelines in pharmaceutical product development, it seems to reason that it should also be the body that issues comprehensive ethical guidelines at the global level. How should it do this?

Given that the ICH GCP already divides the document into the roles and responsibilities of ethics committees, investigators and sponsors, it contains the structure to expand on these responsibilities. Additionally, the ICH includes participants from industry and government, thereby already having access to both government and industry perspectives. Thus, use of tools such as the framework and policy and strategy options developed in this thesis by the ICH participants could allow them to develop international guidelines for all players with the ultimate social good of balancing welfare and innovation as the preferred outcome.

### **3.2. Government Policies**

As noted in chapters 1-5, international ethical standards are not sufficient in and of themselves due to the impact of local socio-economic factors on ethical considerations. As such, local level regulations and guidelines play a critical role in both promoting the welfare of the local subject population, and in bringing innovative drugs to the local market. Regulatory bodies issue a combination of enforceable regulations and ethical guidelines for the conduct of clinical trials. "A regulatory system capable of delivery of publicly defensible assessments, which are uncompromisingly in the interests of public health, is needed" (Abraham, 2002). It is recommended that governments, and in particular the governments of emerging markets where local players are still learning the complexities of the trial processes, make every effort to clearly distinguish between enforceable regulations and ethical guidelines, and also clearly define the implications of non-compliance with each. Additionally, the regulatory agencies can use tools such as the

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<sup>66</sup> <http://www.ich.org/home.html>

framework and policy and strategy options presented in this thesis to determine the best combination of regulatory requirements and ethical guidelines to promote within their local context.

### **3.3. Institutional (Sponsor, CRO and Ethics Committee) Policies and Procedures**

Chapter 4 and 5 both highlight the importance of effective institutional policies and procedures in the oversight of clinical trials. These institutions include the pharmaceutical sponsor, the CRO and the ethics committee. A conclusion of this thesis is that the effective governance of clinical trials, where welfare and innovation are balanced, requires the implementation of integrated strategies for the governance of clinical trials. As concluded in chapter 4 and 5, there is a need for prospective rather than responsive method of institution level education and advice relevant to the development of effective policies and procedures. The conclusions of both the US and the India chapters result in a recommendation for the governments to identify an effective way to accomplish this within the local context without creating additional barriers toward innovation. Examples of such efforts include certification of institutional policies and procedures in advance of their implementation and requirements for baseline accreditation of each institution's human subject protection program.

Results of the analysis in chapter 6 emphasize the importance of long-term relationships amongst the players. Current literature is silent on the need for a well-established relationship structure amongst clinical trial players. As noted in section 1 above, relationship building is one of the mechanisms by which social good can be enforced. Thus, the results of this thesis emphasize the importance of each institution taking into consideration its respective role in the overall clinical trial process at a policy level, and thereby establishing effective relationships with other players.

## **4. Suggestions for Future Research**

This thesis could be used as a starting point for research focused on balancing the welfare of clinical trial subjects with the need for innovation. Additionally, the framework established in this thesis can be used to perform future research to evaluate the existing and evolving oversight systems of traditional and emerging markets within their local context and to identify any gaps in the oversight. Second, the policy and strategy options along with

their placement on the social welfare or social dilemma spectra can be used to recommend resolutions to any gaps identified. Third, researchers within the field of game theory can use this thesis as the basis for developing game models, which can explore how the rules of the game, for a given market or for the global clinical trial process, can be changed to reach a better balance between welfare and innovation at a specific market level or at a global level. Finally, the framework and the policy recommendations could be used by researchers to similarly analyze and evaluate the balance between welfare and innovation in the development of other pharmaceutical products, such as medical devices, diagnostics, etc.

To conclude, current literature regarding the ethical conduct of clinical trials focuses on one part of the equation, namely maximization of subject welfare. This thesis offers a broader perspective, which allows for maximization of subject welfare to be considered along with the consideration for a need for innovation in drug development. The analysis presented in this thesis provides insights for all decision-makers involved in the governance of clinical trials, the pharmaceutical sponsor, the CRO, the ethics committee, and the government to develop regulations, policies and procedures in a manner that maximizes subject protection, but that does not become a barrier to innovation. Finally, the thesis provides researchers with methods for evaluating the governance of clinical trials, and for practitioners to develop integrated strategies for maximizing subject welfare while promoting innovation.

## SUMMARY

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Clinical trials are an essential part of the new drug development process, as they are necessary in order to demonstrate the safety and efficacy of new drugs for humans. These trials cannot be conducted without the availability and participation of human volunteers willing to participate as research subjects. These trials are linked to multiple interests of many stakeholders. The governments are interested in the economic benefits that can be gained by bringing clinical trials to their markets, and they are also interested in making new drugs accessible to their people. The pharmaceutical companies are interested in successful clinical trials, which then result in a profit for the company. However, they are also interested in the safety and efficacy of the drugs, so as to avoid drug recalls after the drug is approved for marketing. The contract research organizations (CRO) responsible for carrying out one or more aspects of the trial are interested in their own profit, as well as in carrying out the trials with sufficient integrity so as to gain a positive reputation and win additional contracts. Subjects of clinical trials are hopeful for receiving care to which they may not otherwise have access, while also serving an altruistic cause. All these interests combine to make the clinical trial process a very complex process. Within the process, the various agendas of the different stakeholders leave room for various conflicts of interest. Therefore, it is not surprising to see both allegations of and proven cases of ethical violations related to the conduct of clinical trials in media. Such ethical violations have given rise to the field of protection of human subjects of clinical trials, which comprises of governance of clinical trials at three levels: i) international governance through the establishment of international standards; ii) national level governance through regulatory oversight; and iii) institutional governance through policies and procedures of the pharmaceutical company, the CROs and the ethics committees. The purpose of these regulatory and policy oversight systems is to protect the rights and welfare of human subjects during the clinical trial process.

Literature dealing with protection of human subjects of clinical trials focuses on the outcomes of the ethical violations, and then addresses the individual processes, such as informed consent process or monitoring process, to prevent such violations from recurring. There are, however, two major gaps in literature: i) consideration of the clinical trial process as whole, rather than the individual processes within; and ii) discussion of the fact that subject welfare requirements must be balanced with the need to allow clinical trials

to take place. This thesis, thus aims to address these gaps by answering the question of how to maximize clinical trial subject welfare while promoting novel drug innovation. I use qualitative research methods to address this question as described below.

A historical overview of the evolution of clinical trials, and the emergence of ethical standards for the conduct of clinical trials is provided in chapter 1. The first chapter then illustrates the clinical trial process based on the US regulations as a model. The process presented in this chapter is used throughout the thesis as the clinical trial process under study.

A literature and documentary review to identify the existing ethical concerns related to the implementation of clinical trials is presented in chapter 2. Three sources of information are used: current literature, regulatory and guidance documents, and reports by non-profit organizations. The information obtained is then combined to identify themes associated with ethical concerns about conduct of clinical trials, which are then used toward the development of a conceptual framework for evaluation of clinical trial governance. The resulting themes derived from this analysis include: consideration of available alternatives, undue influence including coercion, conflicts of interest, compensation for injury, end of trial care, informed consent, monitoring of clinical trials, payment for participation, therapeutic misconception, treatment for injury, and cost of participation.

Chapter 3 begins by characterizing the clinical trial process using concepts borrowed from game theory. Then, these characterizations are combined with the themes identified in chapter 2 to develop a framework by which to evaluate clinical trial governance at various levels. The resulting framework consists of 6 types of endogenous uncertainties, or uncertainties stemming from unethical stance of one or more players, and 5 types of systemic uncertainties, or uncertainties resulting from the absence of rules or the presence of multiple rules, that are involved in the clinical trial process. Examples of where these may arise during the clinical trial process are provided. The chapter concludes with a breakdown of the impact of each of these uncertainties on subject welfare and innovation.

Chapter 4 provides an overview of the US regulatory oversight system, and presents an evaluation of this system based on the framework developed in chapter 3. I then present an empirical study conducted using publicly

available data, combined with the framework, to determine the effectiveness of the US regulatory system in promoting subject welfare while allowing for novel drug innovation. The conclusion of the studies presented in this chapter is that there are many gaps and needs for improvement within the US oversight system, which must be addressed if subject welfare and innovation were to be balanced. These gaps are primarily associated with the absence of regulations or guidance related to some of the uncertainties and the US government's reliance on institutional policies and procedures to provide protection of human subjects of clinical trials. I propose that the gaps resulting from the government's reliance on institutional policies and procedures can be addressed through the addition of a proactive education and advice layer to the oversight system.

Chapter 5 begins with a presentation of the Indian regulatory oversight system for the governance of clinical trials. Through an empirical study involving interviews with experts in the field, the strengths and weaknesses of India as a clinical trial market are identified, along with any challenges faced by the Indian oversight system in the governance of clinical trials. The conceptual framework developed in chapter 3 is then used to evaluate the Indian regulatory oversight system in terms of its ability to balance subject welfare and novel drug innovation. A number of gaps and needs for improvements very similar to those within the US regulatory oversight system are identified.

The first goal of chapter 6 is to establish industry's responsibilities toward protection of human subjects of clinical trials. Through literature and documentary review, it is determined that the industry players are primarily evaluated based on the principles outlined in the international guidelines. Through an evaluation of the two primary international guidelines, the Declaration of Helsinki and the ICH Good Clinical Practices, using the conceptual framework developed in chapter 3, it is found that these documents do not adequately establish the industry's responsibility toward subject welfare. Finally, industry stakeholder's perceptions and efforts with respect to their role in maximizing subject welfare is established through interviews with industry representatives. The interview study identifies efforts made by industry players to address some of the uncertainties, and finds that relationship building amongst the various players involved in the implementation of clinical trials is the best method for addressing industry's

challenges and protecting human subjects. Thus, a possible relationship structure is proposed at the end of this chapter.

Chapters 4, 5, and 6, provide insights into how the uncertainties faced by the players involved in the clinical trial process can be converted into measurable risks. Chapter 7 thus focuses on identifying possible policies and strategies for containing these risks. The chapter ends with an evaluation of how each of the possible policies and strategies, and the possible tradeoffs of each, impact the balance between subject welfare and innovation. It is clear from this study that combination of strategies and policies implemented will determine if a given country is on the path toward better welfare or greater social dilemma. One conclusion of this exercise is that cooperation amongst the players is necessary in order to achieve a balance between welfare and innovation. Thus, supporting the need for a relationship structure, such as the one recommended at the end of chapter 6. Chapter 8 closes the thesis with a summary of conclusions, contributions and recommendations.

At an overarching level, this thesis contributes to literature by initiating a discussion on the need to balance subject welfare with innovation, rather than to focus on only one side of this equation. More specifically, this thesis contributes in three major ways: i) it provides a framework for evaluating policies and procedures for ethical conduct of clinical trials in terms of their ability to reduce uncertainties; ii) it proposes a relationship structure for interdependent decision making amongst the various players involved in the implementation of clinical trial; and iii) it provides policy and strategy recommendations for use by each of the players involved in the governance of clinical trials.

Outcomes of this thesis can be used to evaluate and enhance the governance of clinical trials at international, national and institutional levels. Practitioners can use the framework for evaluation of governance of clinical trials developed in this thesis to systemically evaluate the governance of clinical trials at each of the three levels. Additionally, the game theoretic concepts embedded within the framework will contribute to an understanding of how decision makers develop their policies and strategies in light of plausible outcomes for themselves and for the other players. In terms of economics literature on clinical trials, the novelty of the thesis is the incorporation of game theoretic approach to conceptualize the process of clinical trial governance. Thus, scholars can use the framework to compare various

oversight systems. Finally, the thesis establishes possible policy and strategy outcomes and their impact on the balance between subject welfare and novel drug innovation.



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## VALORIZATION ADDENDUM

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This addendum discusses the valorization potential of the research presented in this thesis. This research is driven by the need for overall advancement in the governance of clinical trials at the international level, the national level and at the institutional level. The research presents a novel perspective by recognizing, on the one hand, that subjects of clinical trials must be protected, and on the other hand, acknowledging that, without clinical trials, the need for novel drug development may not be fulfilled. In this thesis, I apply concepts borrowed from game theory to analyze and understand the priorities of the various players involved in the implementation of clinical trials, and based on these, to determine policy and strategy options for each of the decision makers. The application of game theory concepts to the study of governance of clinical trials is a novel concept introduced in this thesis.

To find this balance, I developed a framework for the evaluation of governance of clinical trials, which serves as the first innovative outcome of this thesis. The framework was developed using concepts borrowed from game theory, which allowed for a systematic analysis of the agenda of each of the stakeholders in the implementation of clinical trials, and to identify the areas of uncertainty in the governance of clinical trials. The framework can be used by policymakers at each of the three levels identified above for two purposes: i) to evaluate and modify their current policies in an effort to achieve a better balance between subject welfare and innovation; and ii) to establish new policies. The case studies presented within the thesis illustrate how the framework may be utilized by the various stakeholders. The case studies also demonstrate that cooperation amongst the various players is necessary in order to reach an optimum balance. I thus introduce a proposed relationship structure of the players involved in clinical trials as a second innovative outcome. This relationship structure can be initiated and implemented by any one or more of the stakeholders in order to achieve more effective overall governance of clinical trials.

Building on the literature reviews as well as case studies, and again using concepts borrowed from game theory to structure my analysis, I present a set of possible government policies and institutional strategies, and provide an evaluation of each proposed policy and strategy's possible impact on subject welfare and/or innovation. This can be used as a tool for decision-making by each of the stakeholders. The possible outcomes highlight the need for

cooperation amongst the players as well as the importance for consideration of local context in identifying the best set of policies and strategies. As such, the structured presentation of this analysis, in the form of tables, can be further used as a starting point for discussions pertaining to effective strategies amongst the stakeholders as they implement the relationship structure mentioned above.

Stepping out of the realm of drug development, the tools resulting from this research can be used toward the identification of effective policies and strategies for governance of clinical trials of medical devices and genomic medicine, or other forms of treatment.

I discussed some parts of this thesis at conferences pertaining to the governance of global clinical trials. Industry players, regulators and academics all participated in the discussion of topics raised, debated how to best address the issues relevant to them, and agreed that cooperation is necessary for all stakeholders to meet their respective goals. The fact that the research presented herein can initiate such dialogue demonstrates its societal value.

## **CURRICULUM VITAE**

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Farida Lada was born in Karachi, Pakistan, in 1974. Farida has worked in the field of research compliance for the past 15 years. She began her research compliance career in the area of human subject research, and later broadened her scope to provide leadership and management in responsible conduct of research, research misconduct investigations, human subject protection, animal welfare, biosafety, export controls and conflicts of interest in research. Farida is married to Peter Lada and has a daughter (Amaya, 5 years old).

### **Professional Record**

- University Director for Research Compliance, The City University of New York, 2011 – Present
- Director, Research Compliance, Weill Cornell Medical College in Qatar, 2007 – 2010
- Assistant Director, Human Subject Research, University of California Los Angeles, 2005 – 2007
- Institutional Review Board Administrator, University of California Los Angeles, 2004 – 2005
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- Master of Business Administration, University of Louisville, 2001
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