CONTINUOUS MONITORING OF CLINICAL RESEARCH: THE REB's UNFULFILLED OBLIGATION

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Supervised by

Dr. Chris Kaposy

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ABSTRACT

The lack of specificity about the role of Research Ethics Boards concerning monitoring of clinical research in this new context of private sponsorship, and centrally depending on researchers to monitor clinical research is worrying—given the level of research misconduct and the recurrence of preventable scandals and unethical practices. This thesis is about the ethical necessity of ongoing REB monitoring, while clinical research is being conducted. An initial review, nominal annual reporting, and ad hoc notifications of problems after they occur are likely only to detect problems after harms have occurred. While acknowledging the recommendations of the various policy documents like Canada's TCPS2, US Common Rule, and ICH-GCP have been inadequate, I argue that adequate REB post-initial-review monitoring requires greater REB involvement, rather than trust and researchers' assurances. The REBs' monitoring should include continual onsite monitoring and paternalistic continuous review, to protect subjects who are contributing to scientific knowledge. Subject safety and overall research integrity are imperative to good science.

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AU	African Union
CIHR	Canadian Institutes of Health Research
CIOMS	Council for International Organizations of Medical Sciences
CFR	Code of Federal Regulations
DSMB	Data and Safety Monitoring Board
DoH	Declaration of Helsinki
DHHS	Department of Health and Human Services
EC	Ethics Committees
FDA	Food and Drug Administration
HAL	Hickling Arthurs Low
IRB	Institutional Review Boards
ICH-GCP	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
NBAC	National Bioethics Advisory Commission's
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
HREA	Health Research Ethics Authority

NSERC	Natural Sciences and Engineering Research Council
OHRP	Office for Human Research Protections
OTC	Ornithine transcarbamylase
REBs	Research Ethics Boards
RECs	Research Ethics Committees
SDMs	Substitute Decision-Makers
SSHRC	Social Sciences and Humanities Research Council
TCPS2	Tri-Council Policy Statement
UNAIDS	United Nations Programme on HIV and AIDS
UNECA	United Nations Economic Commission for Africa
UNESCO	United Nations Educational, Scientific and Cultural Organization
WHO	World Health Organization
WMA	World Medical Association

CHAPTER ONE: INTRODUCTION

1.1 General Introduction

Clinical research is continually being undertaken to test for the safety and effectiveness of new products and interventions (Parker, 2016). Clinical research is essential to understanding current treatment trends, providing better therapeutic options (Jain, Kuppili, Pattanayak, & Sagar, 2017), and improving overall human health (Grady, 2015). Research benefits society in several ways, including contributing to the understanding of how to reflect and act on medical issues (Romero, 2013; Steneck, 2007). These research begins with preclinical tests on animals to determine the level of toxicity of the intervention before it is tested on human subjects. However, the clinical research environment is plagued with several ethical issues relating to informed consent, conflicts of interest, the standard of care, therapeutic misconception, exploitation and many more. Clinical research also imposes or can impose unacceptable risks on human research subjects. Exposé from past research studies like the Tuskegee experiment by the US Public Health Service where the natural progression of syphilis with male African-Americans were studied (Wurtzurg, 2016), the Canadian nutritional experiments with aboriginal populations and residential schools (Mosby, 2013), the Willowbrook school experiment where mentally disabled persons were intentionally infected with hepatitis (Robinson & Unruh, 2008), and other recent instances of unethical research practices (which I discuss in subsequent chapters) highlights the need for institutions to continue to protect human research subjects who participate in research as a way of ensuring overall research integrity.

1.2 Formation of REBs

The history of research with human subjects in the 20th century is marred by scandals. These scandals were highly publicized, and dealt a blow to the reputation of both the research enterprise and the medical profession (Frohlich, 2006). Scandals, like the Tuskegee study, the Willowbrook school experiment and other infamous research scandals, left a huge legacy of distrust and a dent on the integrity of the research enterprise (Kohn, 1984; Nardini, 2014). Many clinical research projects ended up being disasters for which subjects would have been better off had they not been enrolled in those studies. The results of some of the scandals were terrible, costing the lives of many human research subjects who, for altruistic reasons, decided to volunteer as research subjects and for the many subjects who were coerced into such studies (Icenogle, 2003; Onixt & Sterling, 2009; Stephen, 2006; Willyard, 2007). The overall impact of the numerous past scandals and abuses is that, "unfortunately, the public's confidence in our work, our competence, and our ethics has been seriously shaken," as argued by Shalala (2000, p. 808), a former Secretary of the US Department of Health and Human Services. Scholars like Caplan (1989) have described these scandals as the turning point in research with human subjects and a reference point in modern bioethics (as cited in Rosner et al., 1991).

This history of research with human subjects has had a significant influence on how bioethicists, philosophers, policymakers and other scholars understand the concerns raised in clinical research and on how these players attempt to address research ethics issues (Wendler, 2017). That is, there have been several guidelines and reforms to human subject protection systems over the years as a direct response to several cases of abuse and scandals which led to public outcry about the 'unethical' nature of clinical research at the time. These policies, regulations and reforms were made to guide the ethical conduct of research with human subjects (Onixt & Sterling, 2009; Wendler, 2017). One of these such significant reforms was proposed by

a former National Institutes of Health (NIH) Director, James Shannon, who called for the independent evaluation of research involving human subjects in 1965 (Fleischman, 2005; Grady, 2015), subsequently leading to the formation of Institutional Review Boards/Research Ethics Boards (IRBs/REBs) in 1974 to adequately protect research subjects (Elliott, 2015; Fleischman, 2005; Godfrey, Payton, Tasker, Proestel, & Schouten, 2014; Rice, 2008; Weijer, 2001). Clinical research has since been regulated to ensure that risk-benefit analysis is favourable (i.e., risks and harms to research subjects do not outweigh the benefits) and also to ensure researchers are complying with all policies and regulations related to research subjects protection (Horner & Minifie, 2011; Steneck, 2007).

REBs serve as the primary institutional structure placed between researchers and human subjects being used for research (Icenogle, 2003) with a dual responsibility of guaranteeing research subjects' protection and ensuring researcher and institutional compliance (Greenwald, Ryan & Mulvihill, 1982). REBs review research on behalf of the institution, including approving, rejecting, proposing modifications to, or terminating any proposed or ongoing research involving humans within the jurisdiction of the institution (TCPS, 2014, p. 20). They also have an obligation to uphold the ethical integrity of research by continuously reviewing research protocols to ensure that research subjects are safe and are being ethically treated during the research (Shekelle, Ruelaz, Miake-Lye, Beroes, & Newberry, 2012). Currently, most universities, hospitals and research institutions in various countries have at least one REB and, in those jurisdictions, research cannot be conducted without the initial review and approval from a REB. Depending on one's jurisdiction, the Research Ethics Boards (REBs) may be known as Research Ethics Committees (RECs), Institutional Review Boards (IRBs), Ethics Committees (ECs), or by other similar names.

In recent times, the responsibilities and authority of REBs have been heavily debated and subjected to scrutiny creating an ongoing under-protection-over-protection argument (Pullman, 2002). Civil libertarians and human rights advocates have argued that research subjects are under-protected (Kohn, 1984)—in that the institution charged with the primary responsibility of protecting human research subjects (REBs) does not adequately protect research subjects when a study is ongoing. For instance, Caplan (1982) points out that:

> "the primary problem with the system of IRB review, in both its old and new guises, is that it devotes too much time to the production of paper promises and almost no time to the enforcement, investigation, or general assurance that the promises will be kept" (p. 8).

While the initial review of research by REBs is important and proper, REBs offer very little protection to research subjects after initial review (Elliott, 2015).

Researchers, on the other hand, have argued that REBs over-protect research subjects, and this over-protection slows the pace of research (Kohn, 1984). Thus, the REB system stifles the progress of scientific inquiry. In some instances, the activities of REBs have also been described as a threat to academic freedom (Thomson, Elgin, Hyman, Rubin & Knight, 2006).

Unfortunately, REBs have been subjected to such pressures regarding the over-protection and under-protection debate from various stakeholders. However, REBs have a moral imperative to continue to protect human subjects after the initial review of protocols.

It is worth noting that, REBs were created decades ago in a research environment that was not as complex as it is now. This research environment has expanded in many regards (Pullman, 2002). For instance, researchers are now under intense and increasing pressure to secure funding from private industry sponsors as government funding for clinical research continues to decrease in countries like the US and Canada (Taylor, 2010). These financial pressures on researchers to attract grants and the pressures to make new discoveries could be

partly responsible for the many cases of misconduct and unethical practices that have occurred in clinical research in recent decades. Examples of such misconduct and unethical cases include Paolo Macchiarini's synthetic trachea experimentation which resulted in 7 deaths out of the 9 patients who had the transplantation between 2011 and 2014. Macchiarini did not even seek the approval of his university's ethical review board, nor were his patients/subjects fully informed of the potential risks (Kremer, 2016; Rasko & Power, 2017). In a San Diego study which recruited veterans between 2014 and 2016, the research team removed extra pieces of liver from at least 9 veterans without informing them of this procedure or that the procedure could increase their risk of bleeding (Racino & Castello, 2019). Also, Pfizer's 1996 Trovan study in Nigeria resulted in the death of 11 children, and several other participants had severe consequences like blindness, deafness, and lameness (Stephen, 2006; Willyard, 2007). Later in chapter 3, I discuss a few other examples of cases that stained the integrity of the research enterprise.

The new research environment is also profit-driven, and therefore, we cannot have a lax system that is susceptible to misconduct. The danger of this lax oversight system is that altruistic research subjects will be at risk of ending up as victims, just like Macchiarini's subjects (Kremer, 2016; Rasko & Power, 2017), the San Diego veterans (Racino & Castello, 2019) and the vulnerable children who took part in the Trovan study (Stephen, 2006; Willyard, 2007). In the end, the already eroding trust the public has in clinical research would be blown away. Much more crucial, it is at this point where there are pressures coming from the stakeholders, where cases of misconduct are increasing, and public trust in the research enterprise is eroding that "IRB members will either raise themselves up to meet the challenge or, if they do not, the IRB system will be properly swept away" (Icenogle, 2003, p. 63).

1.3 Thesis Position

This thesis is about the ethical necessity of ongoing REB monitoring while research is being conducted, after the phase of initial review of protocols. This thesis focuses on REBs and how they should increase and maintain the quality and morality of an ongoing study. I address how REBs should best protect human subjects who are contributing to scientific knowledge as a way of ensuring integrity in research. The REB's initial review of research is a widely accepted practice, but what happens after the protocol approval? Do subjects enroll in clinical research at their own risk without adequate protection while the study is ongoing?

My overall position is that the continual monitoring function or oversight responsibility of REBs, as it is currently understood in many jurisdictions, is inadequate given the level of research misconduct and the recurrence of preventable scandals and unethical practices. I draw on empirical evidence and normative analysis/claims to make a normative argument against the current oversight mechanisms and provide guidance on how REBs should continually monitor clinical research. The mechanisms for monitoring research have not much changed since the 1980s. These mechanisms for ensuring research integrity and the safety of subjects are inadequate not only in the North American context but in many other jurisdictions like Ghana, South Africa, Zimbabwe and Nigeria. REBs as institutions responsible for the protection and welfare of human research subjects should ensure that subjects who are contributing to scientific knowledge are being adequately protected to ensure their safety, the overall integrity of the research project, and prevent the likelihood of research misconduct.

I define research misconduct as "behavior by a researcher, intentional or not, that falls short of good ethical and scientific standard" (Scott-Lichter, 2006). Research misconduct can include the violation of standard research practices and the failure to comply with regulatory

requirements. Among research ethics violations are the failure to obtain informed consent, the failure to obtain initial approval, the failure to obtain approval for amendments to protocols, the failure to report conflicts of interests, and the failure to report adverse events. Falsifying data or documents and maltreatment of research subjects are also research ethics violations (Baucher, Fontanarosa, Flanagin, & Thornton, 2018; Sheehan, 2007; Swartz, 2012). These forms of misconduct could be based on ignorance, sloppiness, or malice (Woollen, n.d.). However, the recurrence of some of the unethical practices is a cause for concern and a reason to strengthen our monitoring systems. As Shalala (2000) puts it, "if we are to keep testing new medicines and approaches to curing diseases, we cannot compromise the trust and willingness of patients to participate in clinical trials. Any deterioration in the protective foundation causes direct harm to human research subjects and indirect harm to the reputations of the investigators, their academic institutions, and the entire research community" (p. 809).

As I have already stated, the challenge with the current REB oversight system, which was created several decades ago, is that the clinical research space has changed and expanded in many regards (Pullman, 2002). However, the oversight system has not received the corresponding reforms, leaving an imbalance between the rate at which the research enterprise is expanding and the current oversight system. In practice, the oversight system has been ineffective to some extent and, therefore, inadequate. Interestingly, there have been calls for even lesser oversight, suggesting the current oversight is paternalistic. In the end, we may be failing our altruistic subjects. We must, therefore, identify ways of protecting subjects when research is ongoing and ensuring overall integrity as a way of restoring public confidence and trust in clinical research.

I focus on clinical research primarily because much of research funding from all sources (public and private) goes into clinical research compared to other research fields like anthropology and sociology. For instance, in the 2018 Canadian budget, the Federal government allocated more research funds to the Canadian Institutes of Health Research ($354.7 million)[1] as compared to the Social Sciences and Humanities Research Council ($215.5 million) (Owen, 2018). Also, unlike the other areas of research, the clinical research enterprise receives a higher percentage of its funds from private sponsors (Lexchin, Bero, Djulbegovic, & Clark, 2003). These private sponsors have other interests (mostly commercial), which may pose a significant threat to the enterprise's integrity (Wendler, 2017). That is, there are economic forces within the clinical research enterprise creating incentives for misconduct and other unethical practices.

In this thesis, I do not intend to further overburden REBs, neither do I suggest sponsors and researchers are unethical individuals who intend to harm research subjects. However, the coming chapters will demonstrate that while government agencies and private sponsors are spending billions of dollars on clinical research around the world, the lives of millions of people, including human research subjects, are put at risk (Icenogle, 2003). Therefore, research subjects should be adequately protected while a study is being conducted, that is, from initiation until completion. There is a need for REBs to balance the need for scientific knowledge against the moral duty to protect research subjects adequately.

1.4 Chapter Summaries

[1] The term 'clinical research' is broadly used here to include biomedical research.

In this chapter, I have introduced the thesis with a highlight of the importance of clinical research and its current ethical challenges. I have argued that REBs, as institutions responsible for the welfare of human research subjects, should ensure that subjects are adequately protected until the completion of the research.

In chapter two, I present the recommendations of various influential research ethics guidelines regarding REB monitoring of research activities. The objective of this chapter is to help the research community rethink the systems of human research subject protection by presenting the various guidelines and policy statements and the relevant literature on the ethics and procedures of REB post-review monitoring. I make references in particular to the Canadian Tri-Council Policy Statement (TCPS2), the US Common Rule (45 CFR 46), the Council for International Organizations of Medical Sciences (CIOMS) guideline, the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH-GCP) guideline, the World Health Organization (WHO) guideline, the Nuremberg Code and the Declaration of Helsinki.

Monitoring of research after initial review is not outside the mandate of REBs, as various commentators like deLanda (2011) have argued. I summarize the REBs continuous oversight mechanisms using Cooper's (1984) description of how REBs monitor research.

In chapter three, by drawing on the information presented in the previous chapter, my objective is to point out the inadequacy of current methods of REB monitoring. I provide an understanding of why the current oversight systems and REBs' continual monitoring responsibilities have been inadequate, despite policies and regulations like the Common Rule, the TCPS2, the ICH-GCP, and many others. This chapter provides an argument focusing on the prevalence of research misconduct, recent instances of gross research misconduct, and the

centrality of researcher self-reporting for REB oversight, to defend the idea that adequate REB post-initial-review monitoring requires greater REB involvement.

The objective of the final chapter is to provide a framework for active research monitoring and to provide an ethical justification for a more proactive model of continual monitoring of research. In chapter four, I also outline what the increased monitoring that I am proposing should consist of, and the practical constraints associated with executing these monitoring functions. Here, I encourage a constructive reform that will enhance the oversight system, which is currently inadequate in several ways. The argument I make in this chapter is exclusively for the clinical research enterprise.

CHAPTER TWO: RESEARCH ETHICS GUIDELINES ON REB MONITORING

2.1 Influential Research Ethics Guidelines

Towards the second half of the twentieth century, the amount of research with human subjects increased significantly due to the growth of universities and the potential application of discoveries, prompting the proposal of ethics codes to protect research subjects (Schneider, 2005). At that same time, there were many ethical issues concerning human subject research, which called for government intervention through the development of regulations, guidelines and policy documents (Breault, 2006; Schneider, 2005).

Many of the guidelines, regulations, and policy statements produced during this period were in response to disastrous historical research events (Horner & Minifie, 2011). Indeed, such disastrous events mark the reference point in modern Bioethics. As Caplan (1989) puts it, "the whole discipline of biomedical ethics arises from the ashes of the Holocaust" (as cited in Rosner et al., 1991, p. 54). For instance, the Nuremberg Code was developed as a result of the trial of Nazi physicians for crimes committed against prisoners of war and those in concentration camps who were used as research subjects. Similarly, the Common Rule, which is an influential US government regulation on research ethics, came out in the aftermath of the Tuskegee syphilis experiment. The Tuskegee study is one of the biggest scandals in the history of research involving human subjects. The Tuskegee scandal led to US Congressional hearings, which led to demands for greater research oversight and eventually to new legislation and regulations on research with human subjects (Brown, 2017; Rice, 2008).

Over the years, several international and national commissions and agencies like National Institutes of Health (NIH), World Health Organization (WHO), Council for International

Organizations of Medical Sciences (CIOMS), United Nations Educational, Scientific and Cultural Organization (UNESCO), United Nations Economic Commission for Africa (UNECA), United Nations Programme on HIV and AIDS (UNAIDS), and several others within the biomedical scientific community have contributed valuable concepts and approaches to the protection of human research subjects. The formation of institutional REBs is one of these concepts— to assure the protection of human research subjects as a direct result of the history of terrible and unfortunate research abuses (Breault, 2006). REBs usually consist of at least five members including a community representative and other individuals with diverse expertise in relevant research disciplines, ethics, and law (45 CFR 46.107; CIOMS, 2016, guideline 23, p. 86; TCPS2, 2014, Article 6.4; WHO, 2000, p. 3). The REB is mandated to review the "ethical acceptability of studies on behalf of the institutions, including approving, rejecting, proposing modifications, or terminating any ongoing research involving human subjects within the jurisdiction of the institution" (TCPS, 2014, Article 6.3, p. 69). Currently, in many jurisdictions, research cannot proceed without REB approval.

The oversight and monitoring of research after initial REB review is unequivocally within the mandate of REBs (Weijer, Shapiro, Fuks, Glass, & Skrutkowska, 1995**)**. Almost all ethical and regulatory guidelines, policy statements and standards grant REBs the authority to approve, require modifications or disapprove research, to observe (or monitor) or have a third party observe (or monitor) the consent process and the research and to suspend or terminate approval of research (Cooper & McNair, 2014; Department of Health and Human Services [DHHS], 2018; TCPS2, 2014). REBs are to act in the interest of potential research subjects by taking into account relevant international regulatory guidelines and applicable national or local laws (CIOMS, 2016). These authorities focus the REB on both proposed and ongoing research.

These authorities also suggest that REBs protect research subjects and oversee research and, therefore, when researchers are non-compliant, the REBs can suspend or terminate the ongoing research.

There are several policy statements and guidelines regulating the conduct of research with human subjects. These include the Nuremberg Code, the TCPS2, the Common Rule, the CIOMS guidelines, WHO guidelines, the ICH-GCP guideline, and the Helsinki declaration. The TCPS2 and the Common Rule are applicable in Canada and the US respectively. The CIOMS guideline, the WHO guideline, the ICH-GCP guideline and the Declaration of Helsinki are, however, not country-specific. These influential research ethics guidelines provide some recommendations regarding REB monitoring of research activities. Below I will outline the recommendations and requirements regarding post-initial-review monitoring found in each of these documents.

2.1.1 Nuremberg Code

The principles and guidelines for conducting human research were first developed as the Nuremberg Code after the trial of the Nazi war criminals in 1947 (Rice, 2008). German physicians, among others, were prosecuted for conducting unethical, painful, and deadly experiments on thousands of war prisoners during World War II (Weindling, von Villiez, Loewenau, & Farron, 2016). The Nuremberg Code is an expression of the basic requirements for conducting research in a manner that respects the fundamental rights of human research subjects. The basic elements of the Nuremberg Code, including voluntary informed consent, favourable

risk/benefit analysis, and the right to withdraw without any repercussions, became the foundation for subsequent research ethics codes and regulations (Rice, 2008). The Nuremberg Code has ten articles, and articles 1 to 8 can be described to fit the initial review processes. Article 9 emphasizes on research subject's right to withdraw from an ongoing study without any penalty or repercussions. Also, article 10 states that researchers should be prepared to terminate their study if there is enough reason to believe that continuation of the study will likely have greater negative impact on subjects (Rice, 2008; The Nuremberg Code, 1949; United States Adjutant General's Department, 1947). At the time of the Nuremberg Code, REBs were nonexistent; therefore, researchers were required to self-monitor.

2.1.2 Declaration of Helsinki

The Declaration of Helsinki was developed in 1964 by the World Medical Association (WMA) as a policy statement of ethical principles for medical research with human subjects, including research on identifiable human material and data. The Declaration has since undergone several revisions. It was built on the principles of the Nuremberg Code (Rice, 2008). The Declaration is addressed primarily to physician-researchers, however, the WMA (2018) encourages other researchers who are involved in medical research involving human subjects to adopt these principles.

The Helsinki declaration states that research proposals must be submitted to REBs for consideration, comment, guidance, and approval prior to the commencement of a study (WMA, 2018, point 23). Risks and burdens of all medical research involving human subjects must be assessed and compared with anticipated benefits. Again, the Declaration highlights that there

should be measures to minimize the risks associated with the research and that the researcher must continuously monitor the risks to subjects (WMA, 2018, point 17).

The declaration emphasizes that REBs must have the right to monitor ongoing studies (WMA, 2018, point 23). However, the onus is on researchers to monitor their research. That is, researchers must provide monitoring information to REBs, especially information about serious adverse events, and when changes are made to the study protocol, REBs must be notified and must get the board's approval (WMA, 2018, point 23). The Declaration also suggests that research must take into consideration the laws and regulations of the country or countries in which research is being conducted as well as applicable international norms and standards, but these must not reduce or eliminate any of the protections for research subjects outlined in the declaration (point 10).

2.1.3 Operational Guidelines for Ethics Committees That Review Biomedical Research

The World Health Organization (WHO), in 2000, developed the Operational Guidelines for Ethics Committees That Review Biomedical Research. According to this guideline, Ethics Committees (ECs, in the language of the document) are responsible for reviewing proposed studies before the start of research (WHO, 2000, p. 1). After initial approval, ECs are to ensure regular review of the ethics of ongoing research. ECs must also communicate clearly the schedule or plan of an ongoing review to the researcher (WHO, 2000, p. 16.). The guideline recommends that,

> ECs should establish a follow-up procedure for following the progress of all studies for which a positive decision has been reached, from the time the decision was taken until the termination of the research. The ongoing lines of communication between the EC and the

applicant should be clearly specified. The follow-up procedure should take the following into consideration:

the follow-up review intervals should be determined by the nature and the events of research projects, though each protocol should undergo a follow-up review at least once a year;

the following instances or events require the follow-up review of a study:

a. any protocol amendment likely to affect the rights, safety, and/or well-being of the research participants or the conduct of the study;
b. serious and unexpected adverse events related to the conduct of the study or study product, and the response taken by investigators, sponsors, and regulatory agencies;
c. any event or new information that may affect the benefit/risk ratio of the study (p. 16-17).

2.1.4 Tri-Council Policy Statement (TCPS2)

The Tri-Council Policy Statement (TCPS2, 2014) is a joint policy by three federal research agencies, that is, the Canadian Institutes of Health Research (CIHR), the Natural Sciences and Engineering Research Council (NSERC) of Canada and the Social Sciences and Humanities Research Council (SSHRC) of Canada. Initially developed as the TCPS (TCPS1) in 1998, the TCPS has been revised many times, leading to the development of the 2014 TCPS2. The TCPS2 states that these Agencies have a continuing obligation to the people of Canada by promoting the ethical conduct of research with human subjects and also serve as a guide to researchers conducting research in Canada (TCPS2, 2014). The TCPS2 (2014) is a standard for the ethical conduct of research in Canada. Therefore, researchers and institutions in Canada, including REBs, are required to be guided by the TCPS2. For this thesis, I focus on sections of the 2014 TCPS2 related to health research.

The TCPS2 sets out “operational guidelines for REBs and research ethics review, both initially and throughout the course of the research project” (p. 67). The TCPS2 makes a clear

distinction between continuous monitoring and continuous review, describing continuous monitoring as a responsibility of the researcher and continuous review as that of the REB (Article 6.14).

Article 6.14 of the TCPS2 states that it is the researchers' responsibility to monitor their research to ensure that it is conducted ethically and to ensure compliance. Researchers are also required to report unanticipated issues (minor or serious) or events (short or long-term), changes to the protocol, and also to ensure that the research team has good knowledge in the ethical conduct of research. In addition, Article 11.7 of the TCPS2 states that researchers shall provide the REB with a plan for monitoring the safety of subjects to assess safety concerns and to protect the ongoing safety of subjects.

Again, Article 6.14 states that research is subject to continuing research ethics review from the date of initial REB approval until the study is completed. REBs have the authority to determine the term of approval, and the level at which continuing ethics review will occur, and as with initial review, continuous ethics review can be full REB review or review by delegated members. However, the minimum requirement is that, continuous research ethics review shall consist of an annual report (for a study more than one year) and an end of study report (for a study lasting a year or less). For studies whose start or end dates are difficult to establish, the REB shall work with researchers to determine "a reasonable timeline for continuing ethics review, and for determining the completion date dependent on the discipline and method of research" (Article 6.14, TCPS2, 2014). This schedule for continuing ethics review may be adjusted throughout the life of the project.

The TCPS2 sums up continuous monitoring as such;

> In accordance with the core principle of Concern for Welfare, it is a key responsibility of researchers and REBs to ensure that, as clinical trials proceed, the risks to participants

> remain in the acceptable range, and the safety of participants is monitored. Articles 11.7 and 11.8 address researchers' responsibility to include a safety monitoring plan in their proposal submitted for REB review, and their responsibility to ensure that any new information that may affect participant welfare or consent is shared with the REB and participants (see also Articles 6.15 and 6.16). Article 11.9 addresses the REB's responsibility to have procedures in place to receive and respond to reports of new information, including, but not limited to, safety data, unanticipated issues and newly discovered risks (see the Application of Article 11.8 for an expanded definition) (p. 159).

In summary, the researcher must monitor the research and submit a monitoring report for the REB to review.

2.1.5 International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Humans Use

The ICH- GCP guideline was adopted in 1996, taking into account good clinical practice standards in Canada, the US, Australia, Japan, the Nordic countries and the WHO (ICH-GCP, 2016). The latest version of this document is the 2016 version. Health Canada adopted the ICH-GCP guideline, and therefore, Canada adheres to the ICH-GCP guideline together with its TCPS2 (McCarthy, 2008).

Like the other influential ethics guidelines, this guideline spells out the responsibilities of REBs/RECs/IRBs/ECs. The ICH-GCP provides a guide on continuous review and monitoring of clinical research. According to this guideline, REBs shall "safeguard the rights, safety and well-being of all trial subjects," but special attention should be paid to vulnerable research subjects in the form of providing additional protection (ICH-GCP, 2016, p. 10). Also, aside from the initial review and subsequent decision on the review, REBs shall conduct a continuous review of

ongoing studies at appropriate timelines according to the study's degree of risks but not less than once per year (ICH-GCP, 1996). REBs rely on researchers to continuously review their studies.

However, when it comes to continuous monitoring, the ICH-GCP guideline states that it is the responsibility of research sponsors to monitor studies. Practically, the sponsor appoints an independent monitor, the Data and Safety Monitoring Board (DSMB), who must have adequate scientific knowledge required to monitor the study. The monitor who is independent of the study acts as the main line of communication between sponsors and the investigator. If monitoring should reveal issues related to non-compliance and unacceptable risks, the sponsor is notified by the monitor, and the former then terminates the study and notifies regulatory authorities like REBs (ICH-GCP, 2016).

In summary, REBs, whose primary responsibility is to ensure the safety of research subjects, may not have any direct interactions with trial monitors (i.e., DSMBs) when the study is ongoing (Romero, 2013).

2.1.6 International Ethical Guidelines for Health-related Research Involving Humans

The International Ethical Guidelines for Health-related Research Involving Humans was prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO) in 1982 (with its latest version adopted in 2016). CIOMS represents a "substantial proportion of the biomedical scientific community through its member organizations, which include many of the biomedical disciplines, national academies of sciences and medical research councils" (CIOMS, 2016, "Our Mission").

CIOMS (2016) seeks to "advance public health through guidance on health research including ethics, medical product development, and safety" ("Our Mission"). The CIOMS guideline was designed to be of use, particularly in developing countries.

According to the International Ethical Guidelines for Health-related Research Involving Humans, REBs must be authorized to monitor ongoing studies (CIOMS, 2016, p. 90). Researchers are to provide relevant information, especially information about any serious adverse events, to REBs to permit monitoring of research. Again, as part of monitoring ongoing studies, deviations and violations must be reported to REBs (CIOMS, 2016). For instance, the researcher must report to the REB all changes in the protocol, including changes in the inclusion and exclusion criteria or changes in the sample size. These must be reported or the researcher must submit an amendment for review in the case of protocol deviations. Protocol violations can significantly affect the wellbeing and interests of research subjects and also impact the scientific validity and integrity of the data. Concerning protocol violations, CIOMS (2016) states that REBs must ensure that subjects are informed, and provisions must be made for the protection of subjects' safety and welfare. Again, if a researcher fails to submit a protocol to an REB for subsequent review, then this type of omission or failure is a serious violation of ethical standards unless it falls within conditions for exemptions from continuous review (CIOMS, 2016).

2.1.7 The Common Rule (45 CFR 46)

The infamous Tuskegee syphilis experiment (1932-1972) which enrolled poor African-Americans is the most important single promoter of the development of human research ethics guidelines in the United States of America (Mandal, Acharya & Parija, 2011). Participants of the

Tuskegee study were unethically observed to assess the progression of syphilis without any therapeutic intervention, even at a time when there was a proven cure (Wurtzurg, 2016). Post-Tuskegee, there was a revolution leading to the United States Congress passing the National Research Act, which established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in 1978 (DHHS, 2018). The Commission, in its recommendations, outlined the basic ethical principles in research involving human subjects, known as The Belmont Report.

The Common Rule (45 CFR 46, Subpart A of the Federal Policy for the Protection of Human Subjects), which is the current U.S. system of protection for human research subjects, is heavily influenced by the 1979 Belmont Report (DHHS, 2018). The Common Rule represents the result of more than 40 years of development and discussions of the underlying ethical principles and guidelines for the conduct of research using human subjects, starting with the Nuremberg Code in 1947. It was first published in 1991 and has undergone several revisions with the latest version published in 2018 (Code of Federal Regulations, 2018).

The Common Rule mandates that IRBs (REBs) provide a continued review of studies at least once per year (Code of Federal Regulations, 2018). The IRB shall track and schedule continuous review of approved research to prevent lapses in IRB (REB) approval. The researcher is mandated to submit a yearly report to the IRB outlining the progress of the study, including changes to the protocol and reports on other adverse events (however, serious adverse events are reported immediately). The Common Rule similarly states that an IRB (REB) shall conduct a continuing review of research at appropriate intervals according to the degree of risk, but this should not be less than once per year. Again, IRBs (REBs) shall have the authority to observe or

have a third party observe the consent process and the research at large (Code of Federal Regulations, 2018).

2.2 How do REBs currently monitor research?

REBs have a critical role in maintaining the ethical integrity of a study's post-initial-review —by monitoring to ensure that research participants receive safe and ethical treatment during research, provide fully informed consent, minimize conflict of interest (Shekelle et al., 2012), and also ensure overall study compliance. However, in practice, the processes and procedures that are in place to satisfy the requirements for monitoring have been inadequate. Cooper (1984) describes ways REBs monitor research after the research has been initially approved. Cooper's (1984) description represents a summary of the various policy statements, regulations and guidelines on continuous monitoring of clinical research.

First, REBs often have a complaint procedure where research subjects can directly report to REBs about some unexpected risks or if they have been unfairly treated or unnecessarily exposed to risks (Cooper, 1984). This procedure is usually stated in the consent forms, indicating that research subjects should directly contact REBs if they have any complaints or questions.

REBs typically monitor research to conduct 'for-cause investigations' whenever there is a complaint of mistreatment by a subject. However, Elliott (2017b) critiques this monitoring process by arguing that very often, the oversight body (REBs) fails to interview the research subject who filed the complaint of mistreatment. Elliott (2017b) further argues that REBs often rely on written documents or records which are always written by research teams or staff

members, to investigate subject complaints. However, research teams may not document all research-related harms or unfair treatments to subjects (Elliott, 2017b). Elliot criticizes this monitoring mechanism and suggests the only reasonable way is to interview subjects who file complaints as part of the 'for-cause investigations.'

Secondly, there is a mechanism in place for researchers to report unexpected events or accidents to REBs when the study is ongoing (Cooper, 1984). This mechanism includes reporting newly identified risk information or harms (such as adverse events), reporting information suggesting clinical equipoise does not exist and reporting unanticipated problems involving therapeutic efficacy to the REB. These reports are designed to be sent regularly to REBs, or immediately after the adverse events occur. REBs can then decide on the implications for the study, including suspending or shutting down research that leads to unexpected and serious harm to subjects.

Lastly, REBs conduct annual or continuing reviews to determine whether there have been changes in procedures. These changes include changes in sample size, recruitment challenges (not meeting recruitment targets) and changes in exclusion or inclusion criteria. REBs conduct the continuing review of already approved research projects at appropriate intervals determined by the REB (not less than once annually). REBs use such reports to determine whether changes in the approval of an ongoing research project are reasonable and acceptable (Saver, 2004). Continual review is conducted at least once a year, or for studies lasting less than one year, it is conducted at the end of the study. REBs have the authority to suspend or terminate research projects that fail to adhere to the requirements for initial approval.

The various guidelines and policy statements, such as the TCPS2, Common Rule and CIOMS, and the existing literature on REB monitoring, match Cooper's description. That is, Cooper's (1984) description of how REBs monitor research is synonymous with the current oversight mechanisms stated in the various guidelines. These policies and guidelines focus mainly on an aspect of continuous monitoring, such as continuous review by REBs. Commentators like DeLande (2011) argue that it is the responsibility of the researcher to monitor a study and submit the monitoring report to the REB for continuous review. Thus, study-related events, including newly identified risks and adverse events, are reported to the REB for them to decide on the continuation of the study. However, there are many documented cases in which researchers failed to report protocol changes and newly identified risks and harms to REBs. Such cases were only exposed through whistleblowing (Fang et al., 2012; Kornfeld, 2012) — underscoring that these monitoring mechanisms may be inadequate.

Overall, these current monitoring mechanisms, policy statements, guidelines, and regulations are inadequate in ensuring subject safety when research is ongoing and in ensuring the overall integrity of research. Many commentators, including Elliott (2015), have described the REB's oversight system as a complete failure because of the inadequacy of these systems and mechanisms in protecting research subjects when a study is ongoing. These monitoring mechanisms also make research very vulnerable to misconduct and scientific fraud.

In the next chapter, I present an in-depth argument and evidence that these monitoring mechanisms are inadequate.

CHAPTER THREE: THE INADEQUACY OF CURRENT METHODS OF REB MONITORING

The REB system of human research subject protection came into existence in the 1970s (Elliott, 2015; Fleischman, 2005; Rice, 2008). During that time, there were increased pressures on universities, teaching hospitals and individual researchers to seek pharma-corporate sponsorship for their research projects as federal research funds had started to decrease (Kohn, 1984). Many of those with interests in the research enterprise at that time had argued that the most significant threat to subjects and the research enterprise came from particularly 'overambitious' university researchers, who were likely to pay less attention to ethical standards and the safety of research subjects (Elliott, 2015). Consequently, mechanisms like the REB system were established to protect research subjects (Godfrey et al., 2014; Rice, 2008; Weijer, 2001).

Primarily, the challenge with the REB oversight system is that the research enterprise have not been cognizant of the inadequacy of policy infrastructures for protecting research subjects, public interest, and overall industry integrity in this new era and environment of dominant corporate and pharma-industry sponsorship of clinical research (Fleischman, 2005). The existing international and national policies, guidelines, and practices have not sufficiently changed to consider these new circumstances. REBs oversight systems are believed to be particularly inadequate in this new era (Emanuel et al., 2004). Research with human subjects is, therefore, often described to be vulnerable to misconduct and fraud due to the overall inadequacy of mechanisms in place for oversight and monitoring responsibilities.

In this chapter, I provide evidence that REBs are failing at their ongoing monitoring responsibilities. I draw on the prevalence of research misconduct, instances of gross research misconduct, and the centrality of researcher self-reporting for REB oversight to defend the idea that adequate REB post-initial-review monitoring requires greater REB involvement, rather than relying solely on trust or the researcher's assurances.

3.1 How extensive is the problem of misconduct in medical research?

There has been a staggering increase in the amount of research with human subjects in the last two decades (Bajpai, 2013; Ghersi, 2004**)**. Similarly, although there has always been misconduct, fraud, and corruption in the research enterprise (Bissey, 2009), the rate of research misconduct and scientific fraud has been staggering (Gupta, 2013) and has increased in recent times (Roberts & John, 2014) despite the existence of policies and regulations on human research subject protection like the CIOMS guideline, the ICH-GCP guideline, the Common Rule (45 CRF 46) and the TCPS2. Below, I present evidence of the increasing rate of research misconduct.

3.1.1 Incidence of retractions

Retraction of published research articles has always been a disturbing trend in clinical research. Also, its surge in recent times (Steen, Casadevall, & Fang, 2013; Steen, 2011) has been a great course for concern. For instance, the overall rate of retraction increased from around 40 per year in 2000, to about 1500 per year in recent years (as cited in Worthington, 2019). Also, between 1997 and 2001, PubMed retracted fewer than 100 published articles for reasons related

to fraud and misconduct, as compared to over 400 retractions between 2007 and 2011 (Fang, Steen, & Casadevall, 2012). To add another example, the rate of retraction of published psychiatric articles because of ethical breaches and research misconduct increased from 3.56 per 10,000 in 2005 to 49.25 per 10,000 in 2012 (Balhara & Mishra, 2015). This increase occurred despite additional protections and requirements within research ethics guidelines meant to protect mentally ill subjects (Balhara & Mishra, 2015; Jain et al., 2017), like the various regulations requiring researchers to provide enough justification for using mentally ill persons as subjects, and the need for a substitute decision-maker to provide consent for subjects with diminished autonomy because of the likelihood of deception and maltreatment.

The rate of retractions of research articles per year increased significantly in the last decades (Steen et al., 2013; Steen, 2011). This increasing rate of retractions has been subjected to different interpretations. For instance, Fanelli (2013) attributes the increase in the rate of retractions of published articles to the efficiency of the system, and not to an increase in misconduct. Fanelli's argument could be partly true, in that some aspects of oversight may have improved, leading to more poorly designed, conducted, or otherwise unethical research being caught. This improved oversight might have resulted in increased retractions of published articles, even though most of these retractions are a result of whistleblowers, and in some cases, attentive reviewers (Fang et al., 2012; Kornfeld, 2012).

However, the fact is, the increasing rate of retraction of published articles is an indication of a weak system that fails to identify some of these unethical practices when the research is ongoing. The retraction of published articles explicitly indicates that the study or research has been completed and results have been disseminated. The retraction of published articles results from the inability of the current oversight system to detect unethical practices and misconduct

when a study is ongoing. That is, these unethical practices are not being noticed or caught while the study is ongoing or being conducted. Ultimately, published articles based on poorly designed, conducted, and otherwise unethical research practices may later be detected and retracted (even though most unethical practices are undetected), but that does not have any correlation with improved oversight when research is ongoing.

Also, assuming Fanelli's (2013) argument is wholly correct, that is, the increase in known cases of misconduct (resulting in an increase in retractions) is due to the current passive oversight system, then a more proactive oversight will do the research enterprise greater good. That is, misconduct and unethical practices will be noticed early and addressed, preventing the overall consequences of misconduct and subsequent retractions.

In the long run, instances of research misconduct (whether it leads to retractions or not) "harm patients, distort the evidence base, misdirect research effort, waste funds, and damage public trust in science" (Godlee, & Wager, 2012, p. 1). For instance, a US study showed that every retraction as a result of research misconduct costs the US taxpayer almost $400,000 (Stern, Grant, & Fang, 2014), and more worrying is the fact that the damage these retractions continues to have on public trust in clinical research is incalculable. Also, the average time for a published article to be retracted is approximately 33 months (Steen et al., 2013). Between the time of publication and retraction, these articles are continually being cited in other studies (one article which the *Lancet* retracted has had 758 citations) (Fang et al., 2012). Before retraction, they might even serve as evidence or the basis for clinical interventions in some cases (Kornfeld, 2012)—as happened in the UK, where an influential guideline on intravenous fluid therapy had referenced a poorly conducted/unethical study (Marcus, 2018).

3.1.2 Field evidence (Monitored cases)

There is evidence that research misconduct is common in Canada. A report on research integrity by the consulting firm Hickling Arthurs Low (HAL) showed that the 29 Canadian institutions (including universities and colleges, medical research organizations and government science-based departments and agencies) that responded to questions on research misconduct collectively dealt with 39 cases of misconduct every year (HAL Report, 2009).

Misconduct also occurs commonly in other jurisdictions. For instance, Ochieng, Ecuru, Nakwagala, and Kutyabami (2013) did a secondary review of site monitoring reports covering a period of four years from research studies in Uganda. This secondary review of monitoring reports (i.e., the retrospective study) revealed a range of misconduct that were initially identified by site monitors. For instance, violations of regulatory requirements for valid ethical approval (including researchers implementing changes to the protocol without REB review and subsequent approval of amendments) accounted for 25% of the misconduct. Instances of informed consent violations (including no informed consent form or no documentation to prove it) accounted for 36% of the misconduct. Violation of the rights and welfare of research subjects accounted for 28%, and not reporting serious adverse events to regulatory authorities accounted for 38% of misconduct. Even though Ochieng et al. (2013) reported that most of the monitored sites had the capacity to conduct these studies, ethical breaches and misconducts still occurred.

3.1.3 Surveys

Evidence from several studies shows that more than 40% of surveyed researchers or people involved in research knew of or engaged in some form of research misconduct (Geggie,

2001; Okonta & Rossouw, 2012; Ranstam et al., 2000). For instance, a survey involving 442 biostatisticians (members of the International Society for Clinical Biostatistics, mostly from Europe and America) assessed the characteristics of fraud in medical research. In the survey, 51% of the 163 biostatisticians that responded acknowledged knowing about fraudulent projects or knew about at least one fraudulent research project in the past ten years (Ranstam et al., 2000). Also, Geggie's (2001) study in the UK to determine the prevalence of, and attitudes towards, observed and personal research misconduct among newly appointed medical consultants reported that 55.7% of these new medical consultants admitted to observing some form of research misconduct. In that same study, 5.7% of the new consultants admitted to previous research misconduct alluding to the fact that medical careers are competitive, and there are pressures to publish scientific works to enhance career prospects (Geggie, 2001).

Okonta and Rossouw (2012) did a study on the prevalence of scientific misconduct among a group of researchers in Nigeria. The study was a survey of researchers who attended a scientific conference in 2010 in Nigeria. Out of a total of 150 administered questionnaires, 133 were returned, giving a response rate of 88.7% (Okonta & Rossouw, 2012). They found that 68.9% of the 133 respondents admitted to having committed at least one form of scientific misconduct. Among the various forms of scientific misconduct are the intentional protocol violations related to subject enrolment, intentional protocol violations pertaining to procedures, pressure from study sponsors to engage in unethical practices, plagiarism, falsification of data, selective dropping of 'outlier' cases, disagreement over authorship and falsification of biosketch/resume.

Again, in Fanelli's (2009) study, up to 33.7% of the scientists/researchers admitted to questionable research practices. When these scientists/researchers were also asked about the

behaviour of colleagues other than themselves, the rate for questionable research practices was up to 72%. This systematic review and meta-analysis on scientific misconduct involved 21 and 18 studies, respectively, published between 1987 and 2008 in which researchers were asked about experiences of misconduct, that is if these researchers had committed or observed their colleagues commit scientific misconduct in the past (Fanelli, 2009). Sadly, most of these cases of misconduct go unreported. (Gupta, 2013).

The increasing number of retracted publications, the evidence of research misconduct and fraud from surveys, meta-analysis, systematic review, and site monitoring reports are indicators of the state of the research enterprise and can be attributed to the overall inadequacy of monitoring systems. The research enterprise can imagine the number of research subjects whose lives were put at risk in the name of scientific inquiry based on the above estimates of research misconduct.

Indeed, not all practices could be monitored by REBs. However, REBs (when adequately resourced) can monitor the violation of standard research practices such as failure to obtain informed consent, failure to obtain initial approval, failure to obtain approval for amendments to protocols, failure to report conflicts of interests, failure to report adverse events, failure to publish negative finding, failure to comply with regulatory requirements, falsifying data or documents and maltreatment of research subjects (Baucher et al., 2018; Sheehan, 2007; Swartz, 2012). Thus, REBs' active continual monitoring of ongoing research will prevent or detect early unethical research practices, thereby preventing the overall impact of misconduct and subsequent retractions (i.e., harm to patients, distortion of the evidence base, wasting of limited and competitive research funds, and damage to public trust in clinical research) (Godlee, & Wager, 2012; Stern et al., 2014). I will provide further arguments for this position in chapter 4.

3.2 The size of the problem may be greater

Despite the above evidence, the extent of the problem of research misconduct may be much worse than these estimates. Commentators like Fanelli (2009) have described these known cases of research misconduct as the 'tip-of-the-iceberg' (Fanelli, 2009), since it is obviously difficult to get answers from researchers/scientists for questions on deeds and practices that are "embarrassing, illegal and otherwise liable,"—such questions will most likely result in evasive and dodgy responses (George, 2016, p. 18; HAL report, 2009). Again, most cases of research misconduct are unreported by researchers (Gupta, 2013; Titus, Wells, & Rhoades, 2008) due "to an unwillingness to risk one's reputation or sour relationships with colleagues , or simply an unwillingness to engage a process that can lead to frustration and additional work stress" (HAL Report, 2009, p. 57).

The HAL report (2009) also raised concerns that research misconduct allegations are likely to be "swept under the carpet" by institutions (p. 57). Research institutions have incentives for sweeping research misconduct allegations under the carpet. There is potential harm to institutions (i.e., damage to the reputation of institutions) should unethical and fraudulent research lead to the commercialization of unsafe interventions, or should the public become aware of it. Some institutions are equally, if not more, interested in protecting their reputations than are individual researchers. Aside from the embarrassment research misconduct could bring to research institutions, sponsors may withdraw their grants, and these institutions may likely lose future research funding should these unethical practices and misconduct be made public (NSERC, 2012).

Quite clearly, even though it is challenging to measure misconduct, there is still enough evidence to suggest that the problem of research misconduct exists. These instances of misconduct and ethical breaches potentially put subjects at risk and damage the reputation of the research enterprise.

3.3 Why are REBs not monitoring?

Research misconduct is a reality the research enterprise cannot overlook (Gupta, 2013). REBs are charged with monitoring responsibilities with the goal of protecting research participants (Klitzman, 2011). Therefore, REBs are required to be more active when research is ongoing rather than "simply seeking a researcher's assurances" (Medical Research Council of Canada, 1987, p. 50). Unfortunately, the majority of REBs do not monitor studies to see how research procedures are being conducted. Thus, REBs very often fail at maintaining ongoing contact with research teams (Christakis, 1988; Elliot, 2015) since majority of institutions rely on volunteers and very limited funds. For instance, a study of Canadian REBs by the National Council on Ethics in Human Research (NCEHR) in 1995, found out that only 18% of surveyed REBs conducted some form of ongoing monitoring aside from annual review of studies (as cited in Weijer, 2001).

Many Canadian REBs and IRBs in other jurisdictions like Ghana and Nigeria, similarly, do not fulfill the ongoing monitoring requirement because they employ only an annual review (Boateng, Ndebele, & Mwesiga-Kayongo, 2014; Weijer, 2001; Weijer et al., 1995) which should be only one aspect of continuous monitoring. In most developing countries, particularly, the oversight or monitoring system is even non-existent (Kilama, 2005). Researchers do what they

want to do —a probable reason why most pharma-sponsored clinical trials are now being conducted in the developing world (Robbins, 2017; Kilama, 2005).

A significant challenge with the various policy statements and guidelines like the TCPS2, the CIOMS, and the Common Rule is that these guidelines outline responsibilities without much specificity. The goal of continual monitoring which is to ensure the ongoing safety and well-being of subjects, the integrity of the data, and compliance with regulatory standards (Ansmann, Hecht, Henn, Leptien, & Stelzer, 2013), cannot be achieved if these regulatory requirements lack specificity or clarity. Even policies and guidelines (like the Common Rule and the Declaration of Helsinki) which state that continual monitoring is a responsibility of the REB lack the kind of specificity required of a guideline document that is supposed to provide direction or guidance. These policy statements and guidelines, therefore, do not provide optimal guidance.

One of the observations by the Working Committee of the Interagency Advisory Panel on Research Ethics after the Oliveri scandal[2] was that "some aspects of the TCPS lack explicit standards and specificity … and lack the precision and details found in other leading national and international documents" (Interagency Advisory Panel on Research Ethics, 2008, p. 3). The committee recommended that there is a need to clarify the researcher's duty of sharing updated information. This recommendation could be fulfilled by "clarifying the investigator's continuing consent duties, by specifying the REB's role in reviewing contracts that unduly restrict the sharing of information, and by clarifying one of the REB's basic functions in initial and ongoing ethics review of clinical trials (that is, to make more precise the REB's purpose and its duties to

[2] https://www.caut.ca/docs/academic-freedom/summary-of-the-olivieri-report.pdf?sfvrsn=0

manage new information as part of ethics review, and to make these duties an explicit part of ongoing REB review)" (Interagency Advisory Panel on Research Ethics, 2008, p. 3-4). The lack of specificity regarding the responsibilities of REBs when a study is ongoing is worrying and potentially dangerous for research subjects and a threat to the integrity of the research enterprise.

The primary role of the REB, which is to protect the rights and welfare of human research subjects (Christakis, 1988; Garrard & Dawson, 2005; Godfrey et al., 2014; Morse, Califf, & Sugarman, 2001; Pullman, 2001; TCPS2, 2014; Weijer, 2001), has been shifted to the researcher. The various regulations and policies on monitoring, and the different forms of monitoring research as outlined by Cooper (1984) shift greater monitoring responsibility to the researcher. The researcher has a responsibility of subject protection and ensuring research integrity, but the overall responsibility of monitoring should not be shifted to the researcher, nor should REBs rely solely on researchers' reports to continuously monitor research.

All the guidelines and policies talk about the REB's oversight responsibility in protecting research subjects throughout the study. However, the REB's oversight responsibility (i.e., continuous review) is again highly dependent on self-reporting of researchers (CIOMS, pp.88-90; TCPS2, Article 6.14; WMA, point 23). That is, those who are likely to engage in misconduct (i.e., researchers) are given the responsibility to centrally monitor ongoing studies (as per TPCS2 Articles 11.7, 11.8, and 11.9) and report to REBs, to enable continuous review.

Also, in some clinical trials, REBs require research teams to have a data monitoring plan, which leads to sponsors appointing or setting up a DSMB for the trial. However, these DSMBs are accountable to the trial sponsor who appointed them. Thus, the DSMB submits its monitoring report to the sponsor (and the researcher) who is required to submit to the REB.

The appointment of DSMBs should not alter the monitoring responsibility of REBs or preclude REBs from their continual monitoring responsibilities. Therefore, if the protection of research subjects when a study is ongoing is all about continuously getting reports from researchers and reviewing those reports, then that clearly cannot be adequate protection, especially when there are obvious disincentives in researchers reporting on their misconduct.

The Canadian research oversight system is a passive system. The monitoring mechanisms, as stated by the various guidelines, are not proactive ways of protecting subjects, ensuring research protocol compliance, and dealing with potential research misconduct. Researchers may not always report adverse events or report changes to their protocol, and participants may not be aware when they have been unnecessarily exposed to risks. Canada's oversight system has been over-reliant on whistle-blowers and also focused on responding to misconduct rather than having ways of identifying and addressing potential research misconducts when a project is ongoing (HAL report, 2009). That is, for REBs to become aware that something has gone wrong in the research, they must be told, hence the reliance on whistleblowers who might not be the researchers and might have an incentive of not reporting.

The inadequacy of the oversight system is not limited to the developed world. Currently, many African countries do have regulatory documents that guide the ethical conduct of research, just like Canada's TCPS2 and the US Common Rule. In theory, the oversight system in most African countries is not so different from the developed world. For instance, in 1974, Zimbabwe established a medical research council under the Research Act of 1959 to provide research oversight. Around the same time, South Africa also established a medical research council to provide research oversight (Ndebele et al., 2014). The US National Research Act that gave birth to the Belmont Report and subsequently the Common Rule was established in 1974, 15 years

after Zimbabwe's Research Act of 1959. Also, institutions like the African Union (AU) and the United Nations Economic Commission for Africa (UNECA) have played a significant role in promoting and strengthening research oversight in Africa (Ndebele et al., 2014).

However, research oversight in Africa has some lapses, just like in the developed world. In practice, oversight in the African context has been described to be very weak and sometimes non-existent (Boateng et al., 2014; Kilama, 2005; Kombe et al., 2014), even though minimal scholarly work has been done on the nature and extent of research oversight in Africa (Kombe et al., 2014). The weak oversight system has been the reason for the recent increase in the amount of research conducted in Africa and other developing countries (Jeong et al., 2017). Some commentators have suggested the consequences of the 'lax oversight system' is ethics dumping (that is, many unethical research practices are being exported to Africa and other developing countries) (Schroeder, Cook Lucas, Hirsch, Fenet, & Muthuswamy, 2018). Surprisingly, there have been fewer documented cases of research misconduct (Kombe et al., 2014; Okonta & Rossouw, 2014), unlike the developed world, and that does not in any way suggest the absence of challenges. The absence of scholarly work on research oversight and misconduct is, in itself, a considerable concern. Indeed, the developing world is challenged in several ways.

3.4 Why trust alone is an inadequate regulatory mechanism

The REBs regulatory systems or monitoring mechanisms rely heavily on reports from researchers (Klitzman, 2011) and function largely on trust (Korenman, 2006). REBs rely on the good faith of researchers to assure compliance with an approved study (Sheehan, 2007). That is, REBs trust that researchers will carry out studies according to approved protocols, that the data

will be collected carefully, that the interests of the subjects will be primary and will supersede that of the researcher or any research interests. REBs trust that researchers' potential conflicts of interest will also not interfere with or bias the study. Elliott (2015) therefore describes the REB's regulatory systems or monitoring mechanisms as an "honour code".

However, many reformers including Elliott have been wondering why a potentially dangerous enterprise like the research enterprise would rely on an "honour code or a trust code" to protect research subjects and to ensure research integrity. Elliott (2015) draws an analogy likening research oversight by REBs to the work of food inspectors. Elliot (2015) quizzes; "imagine if food inspectors never actually set foot in meatpacking plants, but gave approval based entirely on paperwork filled out by the owners" (para. 9). Something analogous is happening with REB oversight.

The claim that 'there is a need for active monitoring of research' is often perceived to imply that researchers are dishonest and unethical individuals who cannot be trusted or are not interested in the safety of research subjects (Cooper, 1984; Levine, 1980). For instance, Levine (1980) argues that active monitoring would likely back the presumption that researchers may be "operating from presumptions of mistrust"(p. 100). He further argues that active monitoring erodes one of the basic assumptions that form the foundation of life within a university community— "that members of the institution are to be trusted until contrary evidence is brought forward" (Levine, 1980, p. 99-100).

Interestingly, there is enough evidence to suggest that a substantial number of researchers engage in unethical behaviour (Cohen & Lynch, 2014). Research scandals like 'Tuskegee' (Wurtzurg, 2016), 'Dan Markingson' (Apau Bediako, 2018; Elliott, 2010; 2015), 'Ranjit

Chandra's study' (Webb, 2017), 'Jesse Gelsinger' (Meyer, 2000; Steinbrook, 2008; Stolberg, 1999) and other similar ones have left behind a huge legacy of distrust in the field of research with human subjects. These studies were conducted and often completed, and subjects were exposed to greater risks -resulting in deaths in some cases- without the knowledge of REBs. These scandals would not have been exposed if not for whistleblowers or for the deaths that occurred. These research scandals have led us to the conclusion that trust is not enough (Korenman, 2006), and therefore Levine's argument against monitoring - and in favor of trust-lacks force. Even though trust is necessary, it is woefully inadequate in ensuring ethically appropriate conduct in the conduct of research.

Also, the reputation of clinical researchers as truth-seekers is continually being threatened by the discovery of scandals and research abuses (Fanelli, 2009). Therefore, the research enterprise should not "unjustifiably assume that investigators with good faith will entirely implement the recommendations of REBs" (Christakis, 1988, p. 9). Clinical research, traditionally a scholarly affair, is now a multi-billion-dollar profit-driven industry (Elliott, 2015). The causes and pressures leading to misconduct are more powerful, pervasive, and much more complicated. Again, increasingly, the research enterprise is shifting from being publicly-funded towards pharma and private sponsorship (Tierney et al., 2016**)**. These current trends are a potential threat to subject safety and have many implications for the integrity of the research enterprise. In this new context of private funding, the lack of specificity about the role of REBs concerning continuous monitoring of research and centrally depending on researchers to monitor research is worrying. It is puzzling as to why a researcher with a financial conflict of interest is the same individual who monitors his or her research to ensure that the financial conflict of interest does not compromise subject safety. The dynamics of research in practice can be very

different from what is presented in protocols and proposals even though there may be no deliberate intention to deceive REBs or put subjects at serious risk (Sieber et al., 2002; Woollen, n.d.). Researchers sometimes fail at implementing REB recommendations not through intentional means, but through administrative error (Christakis, 1988; Woollen, n.d.), which equally places subjects at serious risk (Adkinson et al., 1983).

3.5 What "trust" has led to (Infamous research scandals)

The current REB monitoring mechanism has been inadequate. If there were any lessons learned from the Tuskegee syphilis study, the nutrition study in residential schools, and the Willowbrook school experiment, these recent similar scandals would not have happened. These instances of research misconduct have stained the integrity of the research enterprise and lend credence to the fact that trusting researchers is not enough to protect research subjects and to ensure the integrity of the research industry. These instances of misconduct are reflections of weakness in oversight and highlight the overall inadequacy of current continuous monitoring mechanisms. I present below what the current regulatory/monitoring system (i.e. the trust code) had led to, that is, infamous research scandals.

The Dan Markingson Scandal

In 2004, Dan Markingson violently killed himself while enrolled in a pharmaceutical company-sponsored multi-site study (the CAFÉ study) at the University of Minnesota's teaching hospital (Elliott, 2017a, 2015, 2010). The study compared 3 second-generation antipsychotics

among persons experiencing psychosis for the first time. Dr. Olson, the site investigator, was also Markingson's psychiatrist, and $15,648 was generated for the University of Minnesota's psychiatry department for each subject who completed the CAFE study (Elliott, 2010). These conflicts of interest were enough reasons for the study to be actively monitored to avoid coercive enrolment of vulnerable patients as subjects and to also ensure subject safety.

The study's informed consent process was flawed (Apau Bediako, 2018). Markingson while on a court-granted involuntary commitment to treatment order, was enrolled in the CAFÉ study. The court order was deemed necessary as Markingson was assessed to be dangerous, and disorganized in thinking, and therefore, could not make treatment decisions (Apau Bediako, 2018; Elliott, 2017a, 2015, 2010). Despite his inability to make treatment decisions, he surprisingly consented to participate in the CAFÉ study. Again, Markingson was threatened to sign a document that if he failed to both show up for his research appointments and take his research medications, he would be returned to involuntary confinement. Even when Markingson's mental health was retrogressing and was at risk of suicide, he was still kept in the study until his death (Elliott, 2017a, 2015, 2010). These events were not reported to the IRB.

Without active monitoring of research, subjects and overall safety standards can be taken for granted. The CAFÉ study was furthered at the expense of Markingson's clinical needs. REBs should, in practice, have mechanisms for monitoring the standard of care subjects receive in a research setting.

Dr. Mani Pavuluri's research

Dr. Mani Pavuluri was a child psychiatrist at the University of Illinois at Chicago. Her study, which ran from 2009 until 2013, investigated the functioning of the brains of adolescents with bipolar affective disorder during the manic state and after eight weeks of lithium treatment, using imaging. Dr. Pavuluri was non-compliant with approved study guidelines and abandoned the study's safety precautions. She violated protocol and put the lives of these children at serious risk. The violations in Pavuluri's research included the fact that 89 of the 103 subjects (86%) did not meet eligibility criteria. Pavuluri recruited children younger than ten years even though the approved inclusion criteria by the National Institute of Mental Health (NIMH) required boys and girls of ages 13 to 16 years. She also failed to give some girls pregnancy tests before administering them lithium, and knowingly made false statements about the subjects' medication histories which 'seriously compromised' the integrity of her work (Cohen, 2018).

The University of Illinois's IRB gave approval for the eligibility age to be lowered to 10 years despite the grantor's (NIMH) prohibition. The University's IRB failed to demand an explanation as to why the recruitment age was being lowered to 10 years after the initial review of the study (the NIMH letter to the University's Vice Chancellor for Research cited by Cohen, 2018). A letter from the NIMH that followed an investigation of the misconduct also stated that there was "insufficient initial review by the IRB and inadequate documentation to support subsequent expedited review" (Cohen, 2018, p. 2 of NIMH letter).

Even though her research was reviewed by an IRB and passively monitored, this did not prevent research misconduct. Pavuluri was subsequently barred from conducting research, and published articles from three studies were retracted. The University of Illinois paid back the NIMH's $3 million that was granted Pavuluri for the research.

Ranjit Chandra's research

Dr. Ranjit Chandra was a professor at Memorial University, and also practiced pediatrics at the Janeway Child Health Center, St. John's. He was one of the world's leading experts on the relationship between nutrition and immunity, and was referred to as the "father of nutritional immunology" (Webb, 2017).

Marilyn Harvey, a nurse who was employed by Chandra to recruit new parents to take part in his infant formula trials, 'blew the whistle' and reported that Chandra had published the results before all subjects were even recruited for the study, leading to Memorial University's 1994 enquiry (Webb, 2017). Chandra had data on only 46 subjects out of the 86 he had reported. Also, in a different study, Chandra did not mention anything about psychological testing in his proposal or protocol. Nonetheless, Chandra continued to conduct psychological testing on research subjects without any amendment to his protocol or approval from the REB (Pryse-Phillips Report, 2009). Even though Chandra's research was reviewed and passively monitored by an REB, these misconducts still occurred.

Jesse Gelsinger and the genetic study

In 1999, eighteen-year-old Jesse Gelsinger died while enrolled in a genetic study at the University of Pennsylvania. Gelsinger suffered from ornithine transcarbamylase (OTC) deficiency but was relatively healthy as his condition was controlled with a strict non-protein diet and drugs. Gelsinger had offered to enroll in the genetic study to test the safety of an intervention

for babies with a fatal form of his disorder, even though he was not going to benefit directly from the study (Stolberg, 1999).

Dr. J. Wilson (the researcher) did not stop the study after learning of 'serious toxicities or Grade III liver toxicity' caused by the therapy (Steinbrook, 2008; Stolberg, 1999) and also failed to disclose these risks to participants. Though the study passed through initial approval by an IRB, the informed consent Gelsinger signed was different from what was reviewed, with some essential information on risks missing (Meyers, 2000). The conflict of interest in the Gelsinger scandal included significant financial interests in the outcome of the study (Stolberg, 1999). The researcher failed to halt the study even after some volunteers reached a "Grade III" liver toxicity (Steinbrook, 2008), probably because of an eagerness to be the first to achieve success in the gene-therapy of a rare condition. Novel or breakthrough studies such as this genetic study should have been monitored more closely to ensure compliance and safety of subjects.

In all these scandals, researchers were able to carry on with their research because they knew their projects were being only passively monitored based on what they as researchers sent to REBs. The researchers in the Markingson study did not report Markingson's health risks to their IRB or remove him from the study when he became at greater risk. Dr. Puvaluri made unapproved protocol changes and lied to her IRB. Dr. Chandra engaged in fraud undetected by his REB. Jesse Gelsinger was enrolled in a high risk study without being adequately informed of the risks as they appeared on the IRB-approved consent form. Research oversight bodies cannot assume that researchers will always implement their recommendations. These scandals are a dent on the integrity of the research enterprise and lend credence to the fact that there are lapses in the monitoring and oversight systems. If the enterprise sticks with the current monitoring mechanisms, these scandals will likely repeat themselves.

Continual monitoring of research is designed to ensure subject safety, research compliance, and integrity after post-initial-review of research (Ochieng et al., 2013). Even though REBs have a responsibility to monitor approved studies for ethical conduct as well as adherence to the approved protocol (WMA, 2018), continual monitoring seems to be a challenge (Ochieng et al., 2013). However, it is a step forward in re-establishing public confidence and trust in medical research (de Jong, van Zwieten, & Willems, 2013).

I have argued that research with human subjects is vulnerable to misconduct and fraud due to the overall inadequacy of mechanisms in place for oversight and continual monitoring responsibilities. I also provided evidence of the prevalence of research misconduct, instances of gross research misconduct, and the centrality of researcher self-reporting for REB oversight, to defend the idea that adequate REB post-initial-review monitoring requires greater REB involvement, other than relying on trust and the researcher's assurances. There is a need for a more proactive approach to these problems if the ethical conduct of research is to be achieved. REBs should be more active and have a more robust system that can guarantee the safety of research subjects and overall research integrity.

CHAPTER FOUR: HOW REBs SHOULD MONITOR RESEARCH

In previous chapters, I outlined the recommendations and requirements regarding REBs post-initial-review monitoring found in various influential research ethics guidelines like the TCPS2, the Common Rule, the CIOMS guideline, the WHO guideline, the ICH-GCP and the Declaration of Helsinki. I have also argued that research with human subjects is vulnerable to misconduct due to the overall inadequacy of mechanisms in place for oversight and monitoring responsibilities. Drawing on the prevalence of research misconduct, instances of gross research misconduct, and the centrality of researcher self-reporting for REB oversight, I defended the idea that adequate REB post-initial-review monitoring requires greater REB involvement, rather than trust and researcher's assurances. In this final chapter, I outline what the increased monitoring I propose should consist of, and the practical constraints and challenges associated with executing these continuous monitoring responsibilities. I will also provide ethical justification for active ongoing monitoring mechanisms by REBs. This chapter focuses on a proactive monitoring process.

4.1 The REB's Active Continual Monitoring

REBs evaluate proposed research for its ethical acceptability, evaluate researchers' potential conflicts of interests, and evaluate the proposed study's compliance with local and international regulations, laws, and policy statements designed to protect human subjects (Grady, 2015). Primarily, REBs are institutions mandated to protect the rights and welfare of human research subjects and to ensure that a study is being conducted as per the approved protocol.

Undoubtedly, the continual monitoring responsibility remains within the purview of REBs (Heath, 1979; Weijer et al., 1995). Continual monitoring after initial review and subsequent approval of research is meant to protect the rights and welfare of research subjects throughout the study and ensure compliance (Christakis, 1988; de Jong et al., 2013; Garrard & Dawson, 2005). Thus, the protection of human research subjects does not end after the initial review and approval (Saver, 2004; Silverman, 2007). However, it seems that the constitution of the monitoring responsibilities of REBs is somewhat indeterminate (Korenman, 2006). For instance, consent forms direct research subjects with complaints to REBs, and not to any other institution or office, such as Data and Safety Monitoring Boards (DSMBs) (Klitzman, 2011).

Interestingly, in many jurisdictions, REBs do not fulfill the continuous monitoring responsibilities even though research non-compliance can compromise the safety and well-being of subjects and overall research integrity (Ochieng et al., 2013; Weijer et al., 1995). Relying on nominal annual review/reporting and ad hoc notifications of problems after they occur risk detecting problems only after harms have occurred. Bodies like DSMBs provide some form of oversight by monitoring collected data to ensure trial safety. Like the REB's oversight mechanism, the DSMB's monitoring of research is highly dependent on researchers, which I have argued against. Also, DSMBs are often appointed by research sponsors, raising ethical concerns (potential conflicts of interest) related to their continual monitoring responsibility.

Klitzman (2011) suggested that how REBs learn about research misconduct includes whistle-blowing and occasional complaints by research staff and sometimes research subjects. In some other cases, REBs may not know about misconduct until a study is completed, and journals notice some misconduct during review (Kornfeld, 2012). These ways of learning about research misconduct are not proactive ways of ensuring subject safety and research integrity. Also, as I

have detailed previously, the kind of oversight typically provided by REBs when a study is ongoing is the continuous study review, where REBs rely primarily on the reports submitted by researchers, rather than on other possible means of oversight. Continuous research review may seem to mitigate research-related risks and harms when research is ongoing. However, the review of reports submitted by researchers does not optimally protect subjects, even though REBs are fulfilling their bare minimum requirement. Essentially, REBs are not adequately protecting research subjects but are being used by institutions to somewhat manage risks (Stark, 2012), and to also protect these institutions from liabilities. There is a need for REBs to continually monitor research from post-initial-review until the dissemination of results (Romero, 2013) to adequately protect while fulflling the interests of institutions. The integrity of clinical research and the safety of research subjects should not be traded off or taken for granted (Silverman, 2007).

The active continual monitoring of research by REBs should constitute active onsite visits (Ochieng et al., 2013; Pickworth, 2000) and paternalistic continuous review, to examine research data and other study documents, observe and assess the informed consent process and documents, and also interview subjects and research staff. In this model of monitoring, REBs should look for the standard of care, informed consent, and conflict of interest and how these affect or are likely to affect the safety of research subjects. The active continual monitoring of research is a means to such ends. Optimal continual monitoring would not only strengthen protections research subjects, but likely support researchers in ensuring the highest quality research.

4.1.1 Active Onsite Monitoring

The overall goal of this active onsite monitoring is to ensure compliance (protect subjects), to ensure quality improvement (by educating researchers), and to restore public confidence in the research enterprise (Ansmann et al., 2013; Gunsalus, 1993; London, 2012; Weijer et al., 1995). Active onsite monitoring goes beyond policing research with the sole intention of catching research misconduct. Active monitoring seeks to ensure that the study is being conducted ethically as per the terms of approval (Christakis, 1988; de Jong et al., 2013; Weijer, 2001) and aims to help researchers improve on research quality.

The continual onsite monitoring of research can be done through routine visits, random spot-checks or both, to study sites to observe research procedures, review study documentation, and in some cases have interviews with subjects and relevant research staff (Ochieng et al., 2013; Shetty, Jadhav, Saiyed, & Desai, 2014). The continual monitoring process should include monitoring informed consent procedures to ensure they are consistent with the principle of respect for persons, and that the moral and legal requirements of informed consent are also fulfilled (Pullman, 1999). Also, the continual monitoring process should include monitoring conflict of interests to ensure such conflicts do not affect a subject's well-being and safety, and the overall integrity of a study. The process should include monitoring the standard and quality of care in a research setting. Similarly, inclusion eligibility and exclusion requirements, timely safety monitoring (including reporting of adverse events), "adherence to protocol-mandated investigations and follow-up" (Godfrey et al., 2014, p. 2) should be monitored (Food and Drug Administration, 2013).

4.1.2 What should REBs lookout for during continual monitoring?

Ideally, REBs should have an arrangement before the start of studies (i.e., clinical research) on the terms of active continuous monitoring. REBs should go on-site to have a first-hand feel of how the study is going —rather than relying on the current passive monitoring system where REBs review reports submitted by researchers as a continual monitoring mechanism, or do an audit of suspected misconduct in a study, or of real misconduct after it has occurred (de Jong et al., 2013; Shetty et al., 2014).

First, there is a need for REBs to ensure that proper research subject protection mechanisms are firmly in place by ensuring that all research subjects or SDMs are fully informed before giving their consent (Meyers, 2000). One of the ways researchers fail research subjects is by failing to enable informed consent, even though the REB might have initially approved the consent documents. Informed consent is a key element of the ethical conduct of research (Lorell, Mikita, Anderson, Hallinan, & Forrest 2015; Resnik, 2009) which incorporates a dual moral obligation, that is, respecting the autonomy of subjects and protecting vulnerable subjects (TCPS2, 2014). REBs should, therefore, monitor the informed consent process to ensure either of the dual moral obligations is fulfilled.

Also, it is important for REBs to monitor to ensure that the cornerstone of research ethics (informed consent process) (Lorell et al., 2015) meets both the legal and moral requirements (Pullman, 1999). Fulfilling the moral requirement advertently and inadvertently leads to fulfilling the legal requirements (Pullman, 1999). This means a research subject should not only be made to sign consent forms to meet legal requirement but that the informed consent is given by a competent individual who has received the needed information, adequately understood the information and who, after careful consideration of the received information, has made a choice without being coerced, unduly influenced or induced, or intimidated. REBs must check the

consent process to ensure that subjects are aware of study-related risks and are also notified of changes about risks, benefits, and other study procedures (for example, the current version of consent forms are being used). The REB's focus on monitoring informed consent should involve simple processes such as observing the recruitment and informed consent documentation process (Robertson, 1982), checking signed forms, and interviewing subjects to know they understood what they are consenting to.

Secondly, whether or not researchers declare a conflict of interest at the initial review, it is crucial for REBs to continually monitor to ensure that the researcher's conflict of interest (either dual physician-researcher role or financial conflict of interest) or even institutional conflict of interest do not affect the interests or safety of research subjects in any way. REBs can fail subjects if they do not address potential or actual conflicts of interest when a study is ongoing (Sheehan, 2007).

The major concern with conflict of interest is that it has the potential to unduly influence professional medical judgments, which affect a subject's interests and defeats the goals of medicine (Lo & Field, 2009). For instance, the physician's new role as a researcher can unduly influence a patient (a potential subject) because of the already existing physician-patient relationship. The relationship can make patients (i.e., potential subjects) vulnerable, which hinders autonomous decision-making. Also, financial conflicts of interest in the form of receiving financial incentives for the number of subjects who are able to complete a trial, or the promise of some shares should the trial be successful, or when the investigational product is commercialized, are ethically problematic. A financial conflict of interest might compel researchers to recruit potential subjects who may not meet inclusion criteria, or to require that subjects who ideally should be withdrawn from a study stay until the end of the research, as

exemplified in scandals like that of Dan Markingson (Elliott, 2010, 2015, 2017), Jesse Gelsinger (Meyer, 2000; Stolberg, 1999), and Dr. Pavuluri's psychiatric research (Cohen, 2018). Sadly, research subjects become the ultimate victims whenever there are conflicts of interest.

Also, the relationship between pharmaceutical companies or corporate sponsors, on the one hand, and researchers and their institutions, on the other hand, comes along with some ethical challenges even though this relationship is a boost for the research enterprise (Kaitin, 2012; Komesaroff & Kerridge, 2002). The likelihood of researchers and their institutions becoming handmaidens of sponsors, acceding to sponsor's demands, which may include engaging in unethical practices considering how powerful and pervasive the sponsor's influence can be, should not be underestimated in this new research environment (Kohn, 1984). This relationship calls for REBs to be ethically vigilant by way of continuous monitoring when a study is ongoing. Merely declaring a conflict of interest is not enough, but continually monitoring conflict of interest is key to ensuring subject safety and overall research integrity. Research contracts should be thoroughly reviewed, and research procedures should be closely monitored to ensure ethical standards are not compromised.

Lastly, it is important for subjects to receive the standard of care or its equivalent in a situation of clinical equipoise. That is, subjects who volunteer to ensure the progress of science should receive the standard of care that was approved by the reviewing REB. Anything less than the REB-approved standard or level of care can jeopardize the well-being and safety of these subjects and the trust of these subjects in research, should anything go wrong.

REBs should monitor ongoing research by examining study documents and going to study sites to know the quality or standard of care research subjects receive in the research setting; this is what the ongoing protection of subjects and ensuring the well-being of research

subjects should be about. The onsite visits and review of study documents will ensure that the research is not being furthered at the expense of the clinical needs of subjects who may also be patients as well (Schooler & Baker, 1999). For instance, in the Dan Markingson and Jesse Gelsinger cases, research was furthered at the expense of the clinical needs of these subjects. Markingson was kept on the experimental drug until he died, even though he was not doing well on that medication (Apau Bediako, 2018; Elliott, 2010, 2015). As we have seen, he was threatened with involuntary confinement by the researchers if he stopped taking the experimental drug. Also, the decision to give Gelsinger the highest dose of the vector infusion even though his liver was not functioning at the minimal level required for infusion raises a concern about the quality of care in a research environment (Steinbrook, 2008; Wilson, 2009). Subjects before Gelsinger reached a "Grade III" liver toxicity even when they received lower dosages of the vector than what Gelsinger received (Steinbrook, 2008; Wilson, 2009). The "Grade III" liver damage or toxicity is a serious adverse event that required the study should be temporarily stopped, and regulators notified. However, researchers neither halted the study nor notified REBs (Weiss & Nelson, 1999).

REBs have a role in protecting research subjects both by fostering meaningful informed consent and by protecting from bias due to conflicts of interest. In the absence of ongoing monitoring, deficits in informed consent or untoward effects of conflicts of interest might otherwise be missed. The standard and quality of care subjects receive when the actual project is being done should be of importance to REBs.

4.1.3 Paternalistic continuous review

There is a moral duty to protect (and rescue) altruistic research subjects. Therefore, in the course of the study, REBs continuously review research reports to assess the study's progress. During this review, REBs may suspend or terminate an ongoing study for non-compliance or safety concerns (Godfrey et al., 2014). This continuous review process to protect research subjects' interests, while the study is ongoing, after initial approval and after subjects or substitute decision-makers (SDMs) have consented to participate, has been described as "paternalistic" (Edwards, Kirchin, & Huxtable, 2004). Though considered paternalistic, REB review of research reports is a bare minimum requirement for the protection of research subjects (Weijer et al., 1995). This paternalistic continuous review (as I have already argued) is insufficient.

Interestingly, some commentators have advanced arguments against even this minimum level of "paternalistic" review. For instance, Greener (2009) argues that paternalistic continuous review likely stunts research progress. The arguments against paternalistic continuous review are designed to justify a situation in which there will be less research oversight or even no oversight. Another argument is that paternalistic continuous review defies the subject's autonomous decision-making (Wendler, 2017), even though such a review is an exercise of moral and legal authority. According to this line of argument, once a subject consents to participate in a study after "full disclosure," any subsequent decision that overrules that of the competent-autonomous subject is paternalistic, and this form of paternalism is stifling. The autonomy-based argument suggests that informed consent adequately justifies exposing subjects to risks and harms.

Indeed, the paternalistic continuous review of research is not *pro tanto* wrong. While still insufficient, continuous paternalistic review helps ensure the safety of subjects by terminating studies whose risks seem to be increasing or for reasons related to protocol non-compliance.

REBs must ensure the safety of these “altruistic” research subjects who have volunteered to contribute to scientific knowledge while ensuring that researchers also comply with all local, federal, international and institutional research ethics regulations to protect institutions from liabilities (Fleischman, 2005; Greenwald et al., 1982). It is only right for REBs to exercise their moral and legal authority by shutting down studies whose risks or harms seem no longer reasonable or for ethical non-compliance even though subjects or the public are likely to benefit (Savulescu, 2001). If anything, REBs should be doing this paternalistic continuous review together with active onsite visits as part of the continual research monitoring process of an ongoing study.

Currently, REBs are poorly armed to deal with the realities and uncertainties of research with human subjects (Cohen & Lynch, 2014). Therefore, the calls for less or even no oversight when a study is ongoing are absurd and worrying, given that research misconduct is common (Gupta, 2013), and that research subjects would be unnecessarily exposed to unreasonable levels of risk without some level of oversight. The active continual research monitoring is justified on both utilitarian and deontological grounds to adequately protect subjects, ensure researchers' compliance and also ensure the overall integrity of the research enterprise. That is, continuous paternalistic research review along with my recommended active onsite visits would help researchers to comply with terms of approval, leading to improvement in the quality of research, thereby “preventing disastrous social outcomes” that the research enterprise and all of its stakeholders wish to avoid and also act as a moral safeguard against the abuse of social authority (London, 2012, p. 931). This process would also provide a “credible social assurance” that research subjects are not being abused and that the risks to which they are being exposed are reasonable and relatively proportional to the potential social value of the scientific knowledge

likely to be generated from the study (London, 2012, p. 942). It would also ensure that overall balance of benefits against risks and harms are maximized (Resnik, 2015).

I will now turn to examine the challenges and proposing a justification for this new model of REB oversight that incorporates active monitoring.

4.2 Challenges with continual monitoring

Active continual monitoring comes with several challenges. Central to this challenge is the already heavy workloads of the boards (Burman et al., 2001; Fost & Levine, 2007), the huge cost continual monitoring comes with (Hyman, 2007; Levine, 1988; Page & Nyeboer, 2017; Sugarman et al., 2005) and the institutional REB's inherent conflict of interest (Pullman, 2002). Many of the recommendations for change to research subject protection mechanisms have subsequently suggested the need for support in reviewing and monitoring studies involving human subjects (De Vries & Forsberg, 2002; Page & Nyeboer, 2017). For instance, the National Bioethics Advisory Commission's (NBAC) report in 2001 recommended adequate resources be provided for research oversight systems. Despite these recommendations, the system has still not received sufficient support.

Currently, the composition of many REBs suggests there are very few members of the various boards to continually monitor the many studies REBs review (De Vries & Forsberg, 2002; Fost & Levine, 2007). For instance, in 2001, the US Office for Human Research Protections (OHRP) shut down some REBs (IRBs) because of very limited resources and fewer staff dedicated to the heavy workloads of these boards (De Vries and Forsberg 2002). An example of such closures was that of John Hopkins University School of Medicine REB (IRB), where the OHRP stated that oversight has been insufficient and that could be due to the

REB's/IRB's increasing workload and growing responsibilities *vis-à-vis* its limited resources (McNeilly, 2001). Also, De Vries and Forsberg (2002) cited how 86 REBs (IRBs) in the US had oversight of a total of 35,071 studies. This increasing workload suggests the volunteer-driven REB model ought to be realigned. There should be employees who would perform these monitoring functions, as in the case of Uganda (Ochieng et al., 2013).

Fulfilling the active continual monitoring of research would be even more costly (Shetty et al., 2014). For instance, the estimated median amount spent by 63 academic medical centers in the US in 2002 for human research subject protection, which involved between 350 and 700 protocols, was nearly $750,000 per year (Sugarman et al., 2005). The research oversight related costs would likely increase with active continual monitoring because REBs would have to employ many more experts as monitors in addition to their volunteers.

Many scholars have argued against the huge costs associated with active continual monitoring. For example, Levine (1988) proposed that "trust is much less costly, whether the costs are expressed in terms of dollars or human resources…" (p. 349). However, 'the trust system' (as I have argued) is currently inadequate as the clinical research environment has changed and continues to evolve. The research environment has become more complex and more profit-driven in the last two decades. The trust system led to many research scandals and abuses in the past, and some of these scandals are recurring. Essentially, 'the trust system' cannot be trusted. REBs should, therefore, be adequately resourced to undertake this continual monitoring responsibility (Kombe et al., 2014). More resources should be allocated to REBs than they currently are receiving (Kombe et al., 2014; Pullman, 2002). Institutions should increase budgets allocated to REBs (Boateng et al., 2014; Kombe et al., 2014), taking into consideration not only the costs of doing this active research monitoring (i.e., the financial cost of continual monitoring

and providing adequate human resources), but also the costs of not doing it (i.e., costs to research subject safety and research integrity). For instance, (as I have mentioned previously), a US study suggested that the dollar cost of retraction of a published article is almost $400,000 (Stern et al., 2014). However, the damaging effect of a single scandal or case of research misconduct to the trust in the research enterprise is immeasurable or incalculable (Schwarz, 1991). The cost of a loss of a trust is a bigger expense than the money not spent.

While some commentators (for example, London, 2012) have suggested that the active continual monitoring of research could lead to "discontent among researchers who are able to identify the costs and burdens" associated with continual monitoring easily but fail to identify its benefits (p. 931), this is not necessarily the case. In some jurisdictions, the need for active continual monitoring has been identified and has been supported by researchers (McCusker, Kruszewski, Lacey, & Schiff, 2001; McNeill., Berglund & Webster, 1992). For instance, in Australia, even though REBs/RECs rely on researcher self-reporting to continually monitor research, researchers expressed support for active monitoring by REBs/RECs, stating that monitoring would "prevent people from deviating from their research if they knew it was possible that they would be monitored. One researcher said monitoring was 'a big stick that makes you think" (McNeill et al., 1992, p. 321). Also, a Canadian study by McCusker et al. (2001), which reported on continual monitoring suggested that researchers were supportive of continual monitoring of research. Evidence from studies in Uganda and the UK on the REB's continual monitoring responsibilities also lend credence to the fact that this model is not only feasible but helps identify and prevent misconduct and also helps in educating researchers (McCusker et al., 2001; Ochieng et al., 2013; Pickworth, 2000) who may unintentionally be engaging in research misconduct or unethical practices (Woollen, n.d.). In a resource-challenged

setting like Uganda, Ochieng et al. (2013) acknowledge the success of an active monitoring program. The monitoring teams, made up of two experts and an assistant, used methods such as scheduled and unscheduled visits to study sites to review documents, to make observations, and also have verbal interviews with research staff and subjects. The site monitoring activities revealed unethical practices, including violations of subjects' rights and welfare, and violations of the informed consent process, among other things. Researchers were also educated during these site visits (Ochieng et al., 2013).

4.3 Is Self-monitoring an alternative to this "resource-intensive" model?

First of all, I attempt to address the institutional REB's conflict of interest before discussing whether or not there is an alternative to this "resource-intensive" model.

REBs serve the interests of various stakeholders, including that of research subjects and the institutions that established REBs, and are therefore inherently in conflict (Pullman, 2002). As Pullman (2002) argues, "the current tension between their legal and moral responsibilities can hinder them in their moral mandate" (p. 542). Likewise, REBs may fail research subjects in an attempt to also serve the interests of institutions that established them. To deal with the inherent institutional conflict of interest, which sometimes contributes to the REB's lax oversight when research is ongoing, the alternative is to have an independently funded regional oversight body just like Newfoundland Provincial Health Research Ethics Authority (HREA). Such an independent oversight body will provide an arm's length monitoring —where academic or research institutions would have no or less authority over the REBs (Pullman, 2002). This would partly address the inherent conflicts of interests and the pressures mounted on REB members by an institution in cases where the institution stands to significantly benefit from the research.

A proposed alternative to this resource-intensive model of oversight is a heavier reliance on self-monitoring by both research sponsors and research institutions. Some have argued that public research sponsors could be strengthened in their ability to penalize the research institutions in which misconduct occurs. In particular, institutions have a clear financial interest in the research enterprise (Pullman, 2002) such that their financial self-interest might be directed to ensure that researchers comply strictly with their research protocols and that they protect research subjects. The disincentive in engaging in misconduct is that there would be huge financial consequences or penalties and institutions may lose their right to conduct research. These penalties and sanctions may address institutional conflicts of interests, which sometimes contribute to the lax oversight or misconduct being 'swept under the carpet'.

However, the fear of being financially penalized may not adequately ensure the kind of oversight that is ideal for the current research enterprise, especially in this age of clinical research commercialization— thus, it may not prevent researchers from engaging in misconduct, nor will it likely detect unethical practices early. For instance, even when researchers know they risk being personally penalized, when they risk ending their enviable academic careers and all other successes they have built over the years, some researchers still engage in misconduct. Therefore, if institutions are to be penalized for unethical research or research misconduct, that may not prevent researchers from engaging in unethical practices.

The way institutions can prevent scandals and their likely consequences (i.e. the heavy financial penalties and losing the right to conduct research) is to be more proactive. That is, if institutions fear they might be penalized for unethical research, then the way for institutions to avoid such penalties is to empower and adequately resource REBs who will, in turn, ensure strict protocol compliance by being proactive. As Pullman (2002) argues, "if ongoing human research

is to be conducted in an ethically responsible manner, IRBs will need to be supplied with the resources necessary to fulfill their institutional and societal roles" (p. 527). Increased financial penalties can only result in greater protections against research misconduct if they incentivize proactive oversight that would prevent research misconduct.

Also, the idea of financial penalties enforced by public granting agencies would only work for clinical research funded through public grants. Unfortunately, many studies are exclusively funded by private sponsors. Thus, many research institutions may evade public sponsors' sanctions or penalties.

4.4 Justifying the need for continual monitoring of research by REBs

There are three underlying reasons why REBs do not actively monitor ongoing studies after the initial approval. These reasons include the cost of active continual monitoring in terms of both financial and human resources, a lack of a clear framework on what should constitute continual monitoring (Ochieng et al., 2013; Pickworth, 2000) and the institutional REB's inherent conflict of interest (Pullman, 2002). I have outlined what continual monitoring should constitute, addressed REBs' conflict of interests and will now provide justification for the need for active continual monitoring.

There is a need to continually monitor research through active on-site monitoring and continuous paternalistic review to minimize unethical tendencies. Research misconduct has very often occurred after REBs have given initial approval of studies. Given the evidence on increasing levels of research misconduct and the recurrence of preventable research scandals, the status quo (i.e., the current continuous monitoring mechanisms) is not adequately protecting research subjects and ensuring the integrity of the research enterprise. Most cases of known

misconduct and scandals could have been prevented if there were proper monitoring systems in place after the initial research approval. Also, the anti-paternalistic call for less research oversight or less stringent ongoing oversight would be disastrous for the research enterprise and unreasonably risky for these altruistic research subjects. The need to strengthen our continual monitoring system is urgent if the protection of research subjects and ensuring research integrity are key to the ethical conduct of research. Therefore, there are convincing reasons why REB continual monitoring mechanisms should be strengthened or revamped. I offer three arguments in support of this approach.

First, there is a moral interest in ensuring the ethical conduct of clinical research because it acts as evidence for the approval of new medications, therapies, interventions and health policies. Clinical research is an important aspect of clinical medicine and the development of healthcare policies (Fleischman, 2005). If the integrity of clinical research monitoring and oversight are based only on trust and researchers' self-reporting (Klitzman, 2011; Korenman, 2006), then medications, clinical practice guidelines, approved therapeutic intervention, and healthcare policies risk being based on compromised research. For instance, if we fail to continually monitor research to ensure its integrity, we may continue to have drugs like Vioxx and Trovan on the market. Even though these drugs were eventually withdrawn from markets, an FDA investigator, David Graham, estimated Vioxx alone could have resulted in about 60,000 deaths out of 140,000 associated heart attacks (Herper, 2005, 2004). The Vioxx adverse events were noted in a post-market trial that compared Vioxx and another medication. To give another example, an influential guideline on intravenous fluid therapy in the UK had referenced some tainted articles by German anesthesiologist Joachim Boldt, which were subsequently retracted (Marcus, 2018). There is a need to ensure the highest form of scientific evidence that is based on

sound ethical practices to understand the current trends in the management of diseases and disorders. The "trust code" is inadequate in ensuring overall research integrity. We cannot continue to allow unethical or compromised research to serve as the foundation of clinical medication or inform healthcare policies. Hence the need for a revamp to the current monitoring systems. The lives of millions of people, including research subjects and users of these medications and therapies, are at stake. We are all potential users of the pharmaceuticals and other end products of clinical research.

Secondly, even though misconduct may not always affect study results, it seriously undermines public trust in medical research. The revelation of clinical research scandals after World War II and subsequent notable cases created a fearful impression of medical research. The trust of the public in clinical research continues to erode. The reservoir of public trust and confidence is reduced whenever there is a revelation of a scandal or research abuse (London, 2012), risking pervasive public skepticism of research with human subjects. The trust and willingness of patients, subjects, and the general public to participate in research have been taken for granted in times past.

The current monitoring mechanisms which have led to scandals, abuses and unethical practices left a huge legacy of distrust (Kohn, 1984), most notably in the developed worlds. By sticking to current monitoring mechanisms, we implicitly assume that researchers are "fundamentally ethical individuals who will always put the best interest of participants in research first, and certainly before the needs of the research itself" (Jamrozik, 2000, p. 336). However, this assumption is not entirely right, as research misconduct is a reality. Extensive evidence also shows that many researchers engage in unethical practices (Cohen & Lynch, 2014). There is a need to ensure that the research process does not continue to damage the trust

and confidence of the public in scientific endeavours, as have previous scandals and abuses (HAL report, 2009; Kohn, 1984). The reform of current monitoring mechanisms could mitigate the damage that research misconduct, abuses, and scandals have done to public trust in clinical research, which is important for accepting the role of scientific evidence in clinical care and public health policy (HAL report, 2009).

Lastly, the research enterprise is a multi-billion dollar industry (Elliott, 2015). Over time, the percentage of research funding coming from the pharma-industry and other private agencies has increased (Bluestone et al., 2018**)**. For instance, pharma industry research spending increased from approximately $1 billion in 1970 to $30 billion in 2010, which far exceeds the National Institutes of Health (NIH) budget (NIH Office of Budget, 2010). Also, as of 2015, the US federal government's investment in research stood at 22%, whereas the industry's investment represented 64% of total spending on research (Bluestone et al., 2018). The decline in federal funds suggest that many medical institutions and research centers have been under pressure over the last few years to attract industry dollars to fund their research programs. Also, researchers are under pressure and compelled to seek industry funding due to decreasing success rates in applying for the already declining federal funds leading to an "interesting" new relationship between pharmaceutical companies and cooperate sponsors, on the one hand, and researchers and their institutions, on the other hand. This relationship is very much needed and a boost for the research enterprise.

However, the relationship comes with several ethical challenges (Komesaroff & Kerridge, 2002**)**. The commitment or interest of researchers and their institutions, and the commitment or interest of sponsors are not always aligned, and mostly in sharp contrast (Lewis et al., 2001; Wendler, 2017**)**. Whereas researchers and their institutions are interested in

scientific knowledge (non-profit interest), sponsors, especially pharma industries, have an interest in securing huge profits for shareholders (Wendler, 2017). The commercial sponsorship of research has heightened the potential for conflicts of interest which is a threat to the integrity of scientific investigations and also threatens the public's trust in medicine. Also, the powerful and pervasive influence of these sponsors create an environment where researchers and their institutions succumb to the demands of sponsors, which may include engaging in unethical practices (Kohn, 1984). It is, therefore, potentially dangerous not to monitor such a profit-driven industry with such huge investments for ethical compliance and quality improvement. The current monitoring system is not enough to ensure the integrity of research in this new environment of private sponsorship.

4.5 Conclusion

Clinical research represents the medical community's desires and hopes to acquire knowledge to help advance the health of individuals and societies. This attempt to fulfill the desires and hopes of the scientific community comes along with several risks to the human research subjects who are being used as a means to an end. As a result of these risks to the human subjects, there has been a keen focus on research subject protection over the years, leading to several regulations and reforms. Unfortunately, recent attempts at reforming the protection mechanisms are often met with stiff disagreements between those who see the REB system as inadequate and those who see the REB oversight as stifling and therefore, should not go beyond continuous review. Several commentators have also suggested there are not enough resources for REBs to go beyond continuous research review.

However, as I have demonstrated, the *status quo* is not working given the level of research misconduct and the recurrence of preventable scandals and unethical practices. There have been so many acts after the initial protocol review and approval that are inconsistent with research ethics practices. More important, the safety of research subjects and the integrity of clinical research are imperative to good science. Therefore, REBs should be more active than they currently are by continually monitoring research after initial approval.

As I have argued previously, REBs have the moral and legal authority to monitor clinical research until its completion. Their authority stems from the moral imperative to ensure that research subjects are safe and protected and to ensure the integrity of the research enterprise. Many REBs in Europe, North America, and other jurisdictions also draw their authority from federal regulations. Also, REBs have a significant role in preventing and dealing with research misconduct.

Even though there is substantial evidence of research misconduct and resulting harm and sometimes deaths, little empirical work has been done to probe what actually happens on the ground in terms of monitoring. That is, little has been done on ways REBs can prevent and minimize risk factors for misconduct, detect early and timely investigate and correct research misconduct. I have argued on the ethical necessity of ongoing REB monitoring while the clinical research is being conducted; however, more scholarly work needs to be done on the experiences of members of REBs and university or hospital research offices on how they identify and address research misconduct and ethical breaches when identified. These scholarly works (especially qualitative studies) are also necessary for the reforms many stakeholders are calling for.

Bibliography

Adkinson, N. F., Starklauf, B. L., & Blake, D. A. (1983). How can an IRB avoid the use of obsolete consent forms? *IRB Ethics and Human Research*, *5*(1), 10.

Ansmann, E. B., Hecht, A., Henn, D. K., Leptien, S., & Stelzer, H. G. (2013). The future of monitoring in clinical research - a holistic approach: linking risk-based monitoring with quality management principles. *German medical science: GMS e-journal*, *11*, Doc04.

Apau Bediako, R., & Kaposy, C. (2020). How research ethics boards should monitor clinical research. *Accountability in Research, 27*(1), 49-56. doi: 10.1080/08989621.2019.1706048

Apau Bediako, R. (2018). Ensuring Integrity of Studies: Analysis of the Dan Markingson Case. [Blog] *Mad In America*. Available at: https://www.madinamerica.com/2018/07/ensuring-integrity-studies-analysis-dan-markingson-case/ [Accessed 18 Sep. 2018].

Bajpai, V. (2013). Rise of clinical trials industry in India: An analysis. *ISRN Public Health*, *2013*.

Balhara, Y. P., & Mishra, A. (2015). A study exploring attributes and nature of the retracted literature on mental disorders. *Indian J Med Ethics*, *12*(1), 30-7.

Bauchner, H., Fontanarosa, P. B., Flanagin, A., & Thornton, J. (2018). Scientific misconduct and medical journals. *Jama*, *320*(19), 1985-1987.

Bissey, B. S. (2009). CROs - Who is Doing Your Clinical Research ?? Health Care Compliance Association Research Compliance Conference. Retrieved from; https://www.hcca-

info.org/Portals/0/PDFs/Resources/Conference_Handouts/Research%20Compliance%20Conf/2009/603H1.pdf

Bluestone, J. A., Beier, D., & Glimcher, L. H. (2018). The NIH is in danger of losing its edge in creating biomedical innovations. *STAT News*. Retrieved from; https://www.statnews.com/2018/01/03/nih-biomedical-research-funding/

Boateng, O., Ndebele, P., & Mwesiga-Kayongo, D. (2014). On-going Monitoring of Research, Post REC Approval. In *Research ethics in Africa: a resource for research ethics committees*. Kruger, M., Ndebele, P., & Horn, L. (Eds.). African Sun Media. pp. 47-57.

Burman, W.J., Reves, R.R., Cohn, D.L. & Schooley, R.T. (2001). Breaking the Camel's Back: Multicenter Clinical Trials and Local Institutional Review Boards. Ann Intern Med. 134:152–157. doi: 10.7326/0003-4819-134-2-200101160-00016

Breault, J. L. (2006). Protecting Human Research Subjects: The Past Defines the Future. *The Ochsner Journal*, *6*(1), 15–20. http://doi.org/10.1043/1524-5012(2006)006[0015:PHRSTP]2.0.CO;2

Brown, D. L. (2017, May 16). You've got bad blood': the horror of the Tuskegee syphilis experiment. *Washington (DC): The Washington Post*. Retrieved from; https://www.washingtonpost.com/news/retropolis/wp/2017/05/16/youve-got-bad-blood-the-horror-of-the-tuskegee-syphilis-experiment/

Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, and Social Sciences and Humanities Research Council of Canada, Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans, December 2014. (TCPS2).

Canadian Research Integrity Committee. (2009). The State of Research Integrity and Misconduct Policies in Canada. Prepared by HAL consultants.

(Canadian Research Integrity Committee, Hickling Arthurs Low Corporation, & Canadian Electronic Library. (2009). *The state of research integrity and misconduct policies in Canada* (DesLibris. Documents collection). Ottawa, Ont.: Hickling Arthurs Low Corporation).

Christakis, N. A. (1988). Should IRBs monitor research more strictly?. *IRB: Ethics & Human Research, 10*(2), 8-10.

Cohen, J.S. (2018, April 26). The $3 Million Research Breakdown. Retrieved from; https://www.propublica.org/article/university-of-illinois-chicago-mani-pavuluri-3-million-research-breakdown

Cohen, I. G. & Lynch, H.F. (2014). Basic Bioethics: Human Subjects Research Regulation: Perspectives on the Future, MIT Press. ProQuest Ebook Central, http://ebookcentral.proquest.com/lib/mun/detail.action?docID=3339830

Common Rule. (2018). Basic HSS Policy for Protection of Human Research Subject. 45 CFR 46.101-124. Subpart A. Retrieved from; https://www.ecfr.gov/cgi-bin/retrieveECFR?gp=&SID=83cd09e1c0f5c6937cd9d7513160fc3f&pitd=20180719&n=pt45.1.46&r=PART&ty=HTML#se45.1.46_1107 (45 CFR 46, Subpart A, the Federal Policy for the Protection of Human Subjects).

Cooper, J.A. & McNair, L. (2014). IRB Authority**.** *Journal of Empirical Research on Human Research Ethics.* Vol. 9(4). pp 86–87.

Cooper, J. (1984). The Perceived and Actual Role of the IRB in Mandatory Research In *J.E Sieber (Ed.). NIH Readings and the Protection of Human Subjects in Social and Behavioural Research*. (pp, 114-116). Fredrick, Maryland; University Publication of America Inc.

Council for International Organizations of Medical Sciences (CIOMS). (2016). International ethical guidelines for biomedical research involving human subjects. *Bulletin of medical ethics*, (182), 17.

de Jong, J. P., van Zwieten, M. C., & Willems, D. L. (2013). Research monitoring by US medical institutions to protect human subjects: compliance or quality improvement?. *Journal of medical ethics*, *39*(4), 236-241.

deLanda, B. (2011). Data Safety Monitoring and the IRB. Retrieved from; https://humansubjects.stanford.edu/staff_member_edu/2011_02_data_safety_monitoring.pdf

Department of Health and Human Services (DHHS). (2014). The Belmont Report. Ethical principles and guidelines for the protection of human subjects of research. *The Journal of the American College of Dentists*, *81*(3), 4.

De Vries, R. G., & Forsberg, C. (2002). What do IRBs look like? What kind of support do they receive?. *Accountability in Research: Policies and Quality Assurance*, *9*(3-4), 199-216.

Edwards, S., Kirchin, S., & Huxtable, R. (2004). Research ethics committees and paternalism. *Journal of Medical Ethics*, 30(1), 88-91.

Elliott, C. (2017a). Institutional Pathology and the Death of Dan Markingson. *Accountability in Research*, *24*(2), 65-79. DOI:10.1080/08989621.2016.1246969

Elliott, C. (2017b). Why Research Oversight Bodies Should Interview Research Subjects. *IRB*, *39*(2), 8-13.

Elliott, C. (2015, May 26). The University of Minnesota's Medical Research Mess. *The New York Times*. Retrieved from; https://www.nytimes.com/2015/05/26/opinion/the-university-of-minnesotas-medical-research-mess.html

Elliott, C. (2010). The deadly corruption of clinical trials. *Mother Jones*, 55-63.

Emanuel, E. J., Wood, A., Fleischman, A., Bowen, A., Getz, K. A., Grady, C., ... Muse, C. T. (2004). Oversight of human participants research: identifying problems to evaluate reform proposals. *Annals of internal medicine*, *141*(4), 282-291.

Fanelli, D. (2013) Why Growing Retractions Are (Mostly) a Good Sign. *PLoS Med* 10(12): e1001563. https://doi.org/10.1371/journal.pmed.1001563

Fanelli, D. (2009). How Many Scientists Fabricate and Falsify Research? A Systematic Review and Meta-Analysis of Survey Data. *PLoS ONE* 4(5): e5738. https://doi.org/10.1371/journal.pone.0005738

Fang, F. C., Steen, R. G., & Casadevall, A. (2012). Misconduct accounts for the majority of retracted scientific publications. *Proceedings of the National Academy of Sciences of the United States of America*, *109*(42), 17028-33.

Fleischman, A. R. (2005). Regulating Research with Human Subjects—Is the System Broken?. *Transactions of the American Clinical and Climatological Association*, *116*, 91.

Food and Drug Administration. (2013). Guidance for industry: oversight of clinical investigations—a risk-based approach to monitoring. *Silver Spring, MD: FDA*.

Fost, N., & Levine, R. J. (2007). The dysregulation of human subjects research. *Jama*, *298*(18), 2196-2198.

Frohlich E. D. (2006). Current challenges in clinical research. *The Ochsner journal*, *6*(1), 10–11.

Garrard, E., & Dawson, A. (2005). What is the role of the research ethics committee? Paternalism, inducements, and harm in research ethics. *Journal of medical ethics*, *31*(7), 419-423.

Geggie, D. (2001). A survey of newly appointed consultants' attitudes towards research fraud. *Journal of Medical Ethics*, *27*(5), 344-346.

George, S. L. (2016). Research misconduct and data fraud in clinical trials: Prevalence and causal factors. *International Journal of Clinical Oncology*, *21*(1), 15-21. doi:http://dx.doi.org.qe2a-proxy.mun.ca/10.1007/s10147-015-0887-3

Ghersi, D. (2004). The future of institutional review boards. *The lancet oncology*, *5*(5), 325-329.

Godfrey, C., Payton, M., Tasker, S., Proestel, S., & Schouten, J. T. (2014). Ensuring Participant Safety and trial integrity with clinical trials oversight. *Journal of acquired immune deficiency syndromes (1999)*, *65*(0 1), S40.

Godlee, F., & Wager, E. (2012). Research misconduct in the UK. *BMJ*, 344(7838), D8357.

Grady, C. (2015). Institutional review boards: Purpose and challenges. *Chest*, *148*(5), 1148-1155.

Greener, M. (2009). The good, the bad and the ugly red tape of biomedical research. How could regulators lower bureaucratic hurdles in clinical research without compromising the safety of patients? EMBO Reports, 10(1), 17-20.

Greenwald, R., Ryan, M. and Mulvihill, J. (1982). *Human Subjects Research: A handbook for institutional review boards*. New York, NY: Plenum Press.

Gunsalus, C. K. (1993). Institutional structure to ensure research integrity. *Academic Medicine, 68*(9), S33-S38.http://dx.doi.org/10.1097/00001888-199309000-00032

Gupta, A. (2013). Fraud and misconduct in clinical research: A concern. Perspectives in Clinical Research, 4(2), 144–147. http://doi.org/10.4103/2229-3485.111800

Heath, E. J. (1979). The IRB's monitoring function: four concepts of monitoring. *IRB: Ethics & Human Research, 1*(5), 1-12.

Herper, M. (2004, December 13). Face Of The Year: David Graham. Retrieved from: https://www.forbes.com/2004/12/13/cx_mh_1213faceoftheyear.html#5580b21c6d57

Herper, M. (2005, August 19). David Graham On The Vioxx Verdict. Retrieved from: https://www.forbes.com/2005/08/19/merck-vioxx-graham_cx_mh_0819graham.html#cc6f0195698e

Horner, J., & Minifie, F. D. (2011). Research ethics I: Responsible conduct of research (RCR)—Historical and contemporary issues pertaining to human and animal experimentation. *Journal of Speech, Language, and Hearing Research, 54*(1), S303-S329.

Hyman, D. A. (2007). Institutional review boards: is this the least worst we can do. *Nw. UL Rev., 101*, 749.

Icenogle, D. L. (2003). IRBs, conflict and liability: will we see IRBs in court? Or is it when?. *Clinical medicine & research, 1*(1), 63-68.)

Interagency Advisory Panel on Research Ethics (PRE). (2008). Recommendations – Researchers' Continuing Duty to Share New Information in Clinical Trials; Confidentiality Clauses in Ethics Review; Continuing Consent Duties and REB Purpose and Functions. http://www.pre.ethics.gc.ca/policy-politique/initiatives/docs/CTI_Recommendations_-_EN.pdf

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH-GCP). (2016). Retrieved from; https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4_2016_1109.pdf

Jain, S., Kuppili, P.P., Pattanayak, R.D., & Sagar, R. (2017). Ethics in Psychiatric Research: Issues and Recommendations. *Indian Journal of Psychological Medicine,* 39(5), 558–565. Retrieved from; http://doi.org/10.4103/IJPSYM.IJPSYM_131_17

Jamrozik, K. (2000). The case for a new system for oversight of research on human subjects. *Journal of medical ethics*, *26*(5), 334-339.

Jeong, S., Sohn, M., Kim, J. H., Ko, M., Seo, H. W., Song, Y. K., … Lee, E. (2017). Current globalization of drug interventional clinical trials: characteristics and associated factors, 2011-2013. *Trials*, *18*(1), 288. doi:10.1186/s13063-017-2025-1

Kaitin, K. I. (2012). Translational research and the evolving landscape for biomedical innovation. *Journal of Investigative Medicine*, *60*(7), 995-998.

Kilama, W. L. (2005). Ethical perspective on malaria research for Africa. *Acta tropica*, *95*(3), 276-284.

Klitzman, R. (2011). Views and Experiences of IRBs Concerning Research *Integrity. The Journal of Law, Medicine & Ethics : A Journal of the American Society of Law, Medicine & Ethics*, 39(3), 513–528.

Kohn, E. S. (1984). Ethical Consideration in Protecting Human subjects in Social and Behavioural Research In J.E Sieber (Ed.), *NIH Readings and the Protection of Human Subjects in Social and Behavioural Research*. (pp. 159-165). Fredrick, Maryland; University Publication of America Inc.

Kombe, F., Anunobi, E. N., Tshifugula, N. P., Wassenaar, D., Njadingwe, D., Mwalukore, S., ... Ramiandrisoa, F. N. (2014). Promoting Research Integrity in A frica: An African Voice of Concern on Research Misconduct and the Way Forward. *Developing world bioethics*, *14*(3), 158-166.

Komesaroff, P. A., & Kerridge, I. H. (2002). Ethical issues concerning the relationships between medical practitioners and the pharmaceutical industry. *Medical Journal of Australia*, *176*(3), 118-121.

Korenman, S.G. (2006). Teaching the Responsible Conduct of Research in Humans. DHHS, Office of Research Integrity, Responsible Conduct of Research Resources Development Program. Washington, DC. Retrieved from; https://ori.hhs.gov/education/products/ucla/default.htm

Kornfeld, D. S. (2012). Perspective: Research misconduct: The search for a remedy. *Academic Medicine*, *87*(7), 877-882.

Kremer, W. (2016, September 10). Paolo Macchiarini: A surgeon's downfall. *BBC News*. Retrieved from; https://www.bbc.com/news/magazine-37311038

Levine, R. J. (1988). *Ethics and regulation of clinical research*. 2nd ed. Yale University Press. Pp. 348-350

Levine, R. (1980). The Impact of Institutional Review Boards on Clinical Research. *Perspectives in Biology and Medicine*, 42(3), S98-S114.

Lewis, S., Baird, P., Evans, R. G., Ghali, W. A., Wright, C. J., Gibson, E., & Baylis, F. (2001). Dancing with the porcupine: rules for governing the university–industry relationship. *Cmaj*, *165*(6), 783-785.

Lexchin, J., Bero, L., Djulbegovic, B., & Clark, O. (2003). Pharmaceutical industry sponsorship and research outcome and quality: Systematic review. *BMJ*, 326(7400), 1167-1170.

Lo, B., & Field, M. J. (2009). Institute of Medicine. Committee on Conflict of Interest in Medical Research, Education, Practice, & National Academies Press. Conflict of interest in medical research, education, and practice. Washington, DC: National Academies Press.

London, A. J. (2012). A non-paternalistic model of research ethics and oversight: assessing the benefits of prospective review. *The Journal of Law, Medicine & Ethics*, *40*(4), 930-944.

Lorell, B. H., Mikita, J. S., Anderson, A., Hallinan, Z. P., & Forrest, A. (2015). Informed consent in clinical research: Consensus recommendations for reform identified by an expert interview panel. *Clinical trials (London, England)*, *12*(6), 692–695. doi:10.1177/1740774515594362

Marcus, A. (2018). A scientist's fraudulent studies put patients at risk. *Science (New York, N.Y.), 362*(6413), 394.

McCarthy, C. R. (2008). The Origins and Policies that govern Institutional Review Boards. Emanuel, E. J., Crouch, R. A., Grady, C. C., Lie, R. K., Miller, F. G., & Wendler, D. D. (Eds.). *The oxford textbook of clinical research ethics*. Retrieved from https://ebookcentral-proquest-com.qe2a-proxy.mun.ca

McCusker, J., Kruszewski, Z., Lacey, B., & Schiff, B. (2001). Monitoring clinical research: report of one hospital's experience. *Cmaj*, *164*(9), 1321-1325.

McNeilly, P. J. (2001, October 3). Letter to Vice Dean for Research, Johns Hopkins University re: Human research subject protection under multiple project assurance. [accessed March 11, 2004]. [Online]. Available: http://ohrp.osophs.dhhs.gov/detrm_letrs/oct01a.pdf.

McNeill, P. M., Berglund, C. A., & Webster, I. W. (1992). Do Australian researchers accept committee review and conduct ethical research?. *Social Science & Medicine*, *35*(3), 317-322.

Medical Research Council (Canada). (1987). *Guidelines on research involving human subjects*. Medical Research Council of Canada.

Meyers, A.B. (2000, January 30). A LOOK AT . . . Informed Consent. The Washington Post. Retrieved from; https://www.washingtonpost.com/archive/opinions/2000/01/30/a-look-at-informed-consent/532b5992-0d7f-4271-9f0d-0a76108cf9aa/?noredirect=on&utm_term=.b93e1b322e08

Morse, M. A., Califf, R. M., & Sugarman, J. (2001). Monitoring and ensuring safety during clinical research. *JAMA*, *285*(9), 1201-1205.

Mosby, I. (2013). Administering Colonial Science: Nutrition Research and Human Biomedical Experimentation in Aboriginal Communities and Residential Schools, 1942–1952. *Histoire Sociale/Social History*, 46(1), 145-172.

Nardini C. (2014). The ethics of clinical trials. *Ecancermedicalscience, 8,* 387. doi:10.3332/ecancer.2014.387

National Bioethics Advisory Commission (NBCA). (2001). Ethical and Policy Issues in Research Involving Human Participants, volume 1, Report and Recommendations of the National Bioethics Advisory Commission, Maryland. Retrieved from; *http://bioethics.georgetown.edu/nbac/human/overvoll.pdf*.

Natural Sciences and Engineering Research Council-NSERC. (2012). ARCHIVED – Tri-Council Policy Statement: Integrity in Research and Scholarship. Retrieved from; http://www.nserc-crsng.gc.ca/nserc-crsng/policies-politiques/tpsintegrity-picintegritie_eng.asp

Ndebele, P., Mwaluko, G., Kruger, M., Ouwe Missi Oukem-Boyer, O. & Zimba, M. (2014). History of Research Ethics Review in Africa. In *Research ethics in Africa: a resource for research ethics committees*. Kruger, M., Ndebele, P., & Horn, L. (Eds.). African Sun Media. pp. 3-10.

Ochieng, J., Ecuru, J., Nakwagala, F., & Kutyabami, P. (2013). Research site monitoring for compliance with ethics regulatory standards: review of experience from Uganda. *BMC Medical Ethics, 14,* 23. doi:10.1186/1472-6939-14-23

Okonta, P., & Rossouw, T. (2014). Misconduct in research: A descriptive survey of attitudes, perceptions and associated factors in a developing country. *BMC Medical Ethics, 15*(1), 25.

Okonta, P., & Rossouw, T. (2012). Prevalence of scientific misconduct among a group of researchers in Nigeria. *Developing world bioethics, 13*(3), 149–157. doi:10.1111/j.1471-8847.2012.00339.x

Onixt, M. R., & Sterling, R. L. (2009). Institutional review board liability for adverse outcomes. *AMA Journal of Ethics, 11*(4), 306-310.

Owens, B. (2018). Canadian science wins billions in new budget. *Nature*, 555(7695), 153.

Page, S. A., & Nyeboer, J. (2017). Improving the process of research ethics review. *Research integrity and peer review, 2*, 14. doi:10.1186/s41073-017-0038-7

Pickworth, E. (2000). Should Local Research Ethics Committees Monitor Research They Have Approved? *Journal of Medical Ethics, 26*(5), 330-333. Retrieved from http://www.jstor.org/stable/27718562

Pullman, D. (2002). Conflicting interests, social justice and proxy consent to research. The Journal of Medicine and Philosophy, 27(5), 523-545.

Pullman, D. (2001). Subject comprehension, standards of information disclosure and potential liability in research. *Health LJ, 9*, 113.

Pullman, D. (1999). General provisional proxy consent to research: Redefining the role of the local research ethics board. *IRB: Ethics & Human Research*, *21*(3), 1-10.

Racino, B. & Castellano, J. (2019, February 26). San Diego VA confirms liver samples taken from sick veterans without their consent. *Inewsource.* Retrieved from; https://inewsource.org/2019/02/26/san-diego-va-liver-study-veterans/

Ranstam, J., Buyse, M., George, S. L., Evans, S., Geller, N. L., Scherrer, B., ... Colton, T. (2000). Fraud in medical research: an international survey of biostatisticians. *Controlled clinical trials*, *21*(5), 415-427.

Rasko, J. & Power, C. (2017, September 1). Dr Con Man: the rise and fall of a celebrity scientist who fooled almost everyone. *The Guardian.* Retrieved from; https://www.theguardian.com/science/2017/sep/01/paolo-macchiarini-scientist-surgeon-rise-and-fall

Resnik, D. B. (2009). Re-consenting human subjects: ethical, legal and practical issues. *Journal of medical ethics*, *35*(11), 656-7.

Resnik, D. (2015). Paternalism and Utilitarianism in Research with Human Participants. Health Care Analysis, 23(1), 19-31.

Rice, T. W. (2008). The historical, ethical, and legal background of human-subjects research. *Respiratory care*, *53*(10), 1325-1329

Roberts, D. L., & John, F. A. S. (2014). Estimating the prevalence of researcher misconduct: a study of UK academics within biological sciences. *PeerJ*, *2*, e562.

Robertson, J. A. (1982). Taking consent seriously: IRB intervention in the consent process. *IRB: Ethics & Human Research*, *4*(5), 1-5.

Robbins, R. (2017, September 10). Most Experimental Drugs are Tested Offshore–Raising Concerns about Data. *Scientific American.* Retrieved from; https://www.scientificamerican.com/article/most-experimental-drugs-are-tested-offshore-raising-concerns-about-data/

Robinson, W. M. & Unruh, B.T. (2008). The hepatitis experiments at the Willowbrook state school. In *The Oxford textbook of clinical research ethics*, ed. J. E. Ezekiel, pp. 80-85. Oxford: Oxford University Press.

Rodriguez, L. L., Hanna, K. E., & Federman, D. D. (Eds.). (2003). *Responsible research: A systems approach to protecting research participants*. National Academies Press.

Romero, G. A. S. (2013). Clinical research monitoring: scenarios and challenges. *Revista da Sociedade Brasileira de Medicina Tropical*, *46*(1), 03-06.

Rosner F, Bennett AJ, Cassell EJ, Farnsworth, B.P., Halpern, A.L, Henry, JB., … Wolpaw, J.R. (1991). The ethics of using scientific data obtained by immoral means. *New York State Journal of Medicine*, 91(2), 54-59.

Rutter, T. (1998). Short Course of Zidovudine Cuts Transmission of HIV. *BMJ: British Medical Journal*, *316*(7132), 645-645. Retrieved from http://www.jstor.org/stable/25178385

Saver, R. S. (2004). Medical research oversight from the corporate governance perspective: Comparing institutional review boards and corporate boards. *Wm. & Mary L. Rev.*, *46*, 619.

Savulescu, J. (2001). Harm, ethics committees and the gene therapy death. *Journal of medical Ethics*, *27*(3), 148-150.

Schooler, N.R. & Baker, R.W. (1999). Providing quality care in the context of clinical research. In Pincus, H. A., Lieberman, J. A., & Ferris, S. (ed). Ethics in psychiatric research: a resource manual for human subjects protection. American Psychiatry Association. Washington, DC

Schroeder, D., Cook Lucas, J., Hirsch, F., Fenet, S., & Muthuswamy, V. (2018). *Ethics dumping case studies from North-South research collaborations*. Springer International Publishing.

Schwarz Jr, R. P. (1991). Maintaining integrity and credibility in industry-sponsored clinical research. *Controlled clinical trials*, *12*(6), 753-760.

Scott-Lichter, D. (2006). Editorial Policy Committee, Council of Scientific Editors. CSE's white paper on promoting integrity in scientific journal publications. Retrieved from; http://www.councilscienceeditors.org/wp-content/uploads/entire_whitepaper.pdf

Sieber, J. E., Plattner, S., & Rubin, P. (2002). How (not) to regulate social and behavioral research. *Professional Ethics Report*, *15*(2), 1-4.

Silberman, G., & Kahn, K. L. (2011). Burdens on research imposed by institutional review boards: the state of the evidence and its implications for regulatory reform. *The Milbank Quarterly*, *89*(4), 599-627.

Silverman, H. (2007). Ethical issues during the conduct of clinical trials. *Proceedings of the American Thoracic Society*, *4*(2), 180-184.

Schneider, W. H. (2005). The establishment of institutional review boards in the US background history.

Shekelle, P. G., Ruelaz, A., Miake-Lye, I. M., Beroes, J. M., & Newberry, S. (2012). Maintaining Maintaining Research Integrity: A Systematic Review of the Role of the Institutional Review Board in Managing Conflict of Interest [Internet]. Washington (DC): Department of Veterans Affairs (US); EXECUTIVE SUMMARY. Available from: https://www.ncbi.nlm.nih.gov/books/NBK98423/

Sheehan, J. G. (2007). Fraud, conflict of interest, and other enforcement issues in clinical research. *Cleveland Clinic journal of medicine*, *74*, S63.

Shetty, Y. C., Jadhav, K. S., Saiyed, A. A., & Desai, A. U. (2014). Are institutional review boards prepared for active continuing review?. *Perspectives in clinical research*, *5*(1), 11–15. doi:10.4103/2229-3485.124553

Stark, L. (2012). *Behind closed doors: IRBs and the making of ethical research*. University of Chicago Press.

Steinbrook, R. (2008). The Gelsinger Case. In Emanuel, E.J., Grady, C., Crouch, R.A., Lie, R.K., Miller, F.G., & Wendler, D. (Eds.), The Oxford Textbook of Clinical Research Ethics (110-120). New York: Oxford University Press.

Sugarman, J., Getz, K., Speckman, J. L., Byrne, M. M., Gerson, J., & Emanuel, E. J. (2005). The cost of institutional review boards in academic medical centers. *New England Journal of Medicine*, *352*(17), 1825-1827.

Steen, R. G. (2011). Retractions in the scientific literature: do authors deliberately commit research fraud? *J Med Ethics* 37: 113–117.

Steen, R. G., Casadevall, A., & Fang, F. C. (2013). Why has the number of scientific retractions increased?. *PloS one*, *8*(7), e68397.

Stephens, J. (2006, May 7). Panel Faults Pfizer in '96 Clinical Trial In Nigeria. *The Washington Post.* Retrieved from; http://www.washingtonpost.com/wp-dyn/content/article/2006/05/06/AR2006050601338.html?noredirect=on

Stern, A., Grant, S., & Fang, F. (2014). Financial costs and personal consequences of research misconduct resulting in retracted publications. ELife, 3, E02956.

Stolberg, S. G. (1999). The biotech death of Jesse Gelsinger. *NY Times Mag*, *28*, 136-140.

Stone, J. (2015). Why The U. Of Minnesota Research Scandal Threatens Us All. Forbes. Retrieved from; https://www.forbes.com/sites/judystone/2015/05/27/why-the-umn-research-scandal-threatens-us-all/#53358c1e2e74

Swartz, M. K. (2012). The range of scientific misconduct. *Journal of Pediatric Health Care*, *26*(5), 317.

The Nuremberg Code. (1949). *Trials of war criminals before the Nuremberg military tribunals under control council law*, *10*, 181-182.

Tierney, W. M., Meslin, E. M., & Kroenke, K. (2016). Industry support of medical research: important opportunity or treacherous pitfall?. *Journal of general internal medicine*, *31*(2), 228-233.

Titus, S., Wells, J., & Rhoades, L. (2008). Repairing research integrity. *Nature*, *453*(7198), 980-982.

Thomson, J. J., Elgin, C., Hyman, D. A., Rubin, P. E., & Knight, J. (2006). Research on human subjects: academic freedom and the institutional review board. *Academe*, *92*(5), 95-100.

United States Adjutant General's Department. (1947). Trials of War Criminals Before Nuremberg Military Tribunals Under Control Council Law No. 10 (October 1946-April, 1949). The Medical Case. U.S. Government Printing Office, Washington, D.C. Vol. 2: 181-183

US Department of Health and Human Services. (2014). Federal policy for the protection of human subjects ('common rule'). *DHHS version, 45*.

Webb, G. P. (2017, March 27). Research fraud – Ranjit Kumar Chandra and his faked "cure" for dementia. Retrieved from; https://drgeoffnutrition.wordpress.com/2017/03/27/research-fraud-ranjit-kumar-chandra-and-his-faked-cure-for-dementia/

Weeks, C. (2015, October 28). Journal retracts study by Canadian researcher, citing scientific fraud. *The Globe and Mail.* Retrieved from; https://www.theglobeandmail.com/life/health-and-fitness/health/journal-retracts-study-by-canadian-researcher-citing-scientific-fraud/article27023169/

Weijer, C. (1995). The breast cancer research scandal: addressing the issues. *CMAJ: Canadian Medical Association Journal*, *152*(8), 1195.

Weijer, C. (2001). Continuing review of research approved by Canadian research ethics boards. *Canadian Medical Association Journal*, *164*(9), 1305-1306.

Weijer, C., Shapiro, S., Fuks, A., Glass, K. C., & Skrutkowska, M. (1995). Monitoring clinical research: an obligation unfulfilled. *CMAJ: Canadian Medical Association Journal*, *152*(12), 1973.

Weindling, P., von Villiez, A., Loewenau, A., & Farron, N. (2016). The victims of unethical human experiments and coerced research under National Socialism. *Endeavour*, *40*(1), 1-6.

Weiss, R. & Nelson, D. (1999, September 29). Teen Dies Undergoing Experimental Gene Therapy. *The Washington Post.* Retrieved from; https://www.washingtonpost.com/wp-srv/WPcap/1999-09/29/060r-092999-idx.html?noredirect=on

Wendler, D. (2017). The Ethics of Clinical Research. *The Stanford Encyclopedia of Philosophy* (Winter 2017 Edition), Edward N. Zalta (ed.), URL = <https://plato.stanford.edu/archives/win2017/entries/clinical-research/>.

Wilson, R. F. (2009). Estate of Gelsinger v. Trustees of University of Pennsylvania: Money, prestige, and conflicts of interest in human subjects research. *Health law and bioethics: Cases In Context*, 229.

Willyard, C. (2007). Pfizer lawsuit spotlights ethics of developing world clinical trials. *Nature Medicine*, 13(7), 763.

Woollen, S. W. (n.d.). Misconduct in Research - Innocent Ignorance or Malicious Malfeasance? Retrieved from; https://www.fda.gov/media/75682/download

World Medical Association (WMA). (2014). Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. Available from: http://www.wma.net/en/30publications/10policies/b3/index.html. [Last cited on 2016 Feb 26].

World Medical Association (WMA). (2018). Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. Available from: http://www.wma.net/en/30publications/10policies/b3/index.html. [Last cited on 2016 Feb 26].

World Health Organization. (2000). *Operational guidelines for ethics committees that review biomedical research* (No. TDR/PRD/ETHICS/2000.1). Geneva: World Health Organization.

Wurtzurg, S. J. (2016). Tuskegee Experiment In S.E Boslaugh (Ed), The SAGE Encyclopedia of Pharmacology and Society. (pp. 1448-1455). Thousand Oaks: SAGE Publications Inc.