UiO : Faculty of Medicine
University of Oslo

ETHICS AND COMPLIANCE POST-CLINICAL TRIAL APPROVAL

The Role of Research Ethics Committees

By

Shereen Annmarie Cox née Dawkins

A thesis submitted to the

Faculty of Medicine

Institute of Health and Society

University of Oslo

In partial fulfillment of the Requirements for the

Degree of Doctor of Philosophy (PhD) (Research Ethics)

Under the Supervision of

Professor Rosemarie de la Cruz Bernabe

Professor Jan Helge Solbakk

2023

Series of dissertations submitted to the
Faculty of Medicine, University of Oslo

ISBN 978-82-348-0279-9

Cover: UiO.
Print production: Graphic center, University of Oslo.

ABSTRACT (English)

Background

For approximately six decades, Research Ethics Committees (RECs), also known as Institutional Review Boards (IRBs), have played an integral part in the identification of ethical issues before the commencement of clinical research globally. The importance and relevance of the REC/IRB prospective review are widely acknowledged, admired, and critiqued. In many jurisdictions, legislative and policy frameworks are in place to prevent clinical research from taking place without prior review and approval by a REC/IRB. It is, therefore, reasonable to assume that research with a favorable opinion of a REC/IRB is ethically sound and scientifically appropriate. There is evidence, however, that researchers may deviate from the approved protocols. Many of these deviations are ethically relevant yet remain unaddressed. These unaddressed deviations form the basis for this interrogative thesis into the post-approval role of RECs/IRBs. It employs the sociological frame of role theory to illuminate concepts such as role expectations, identity, and behavior concerning REC/IRBs in the post-approval oversight of clinical trials.

Methods

Qualitative research methods were employed to explore the main objectives. The research approach includes hermeneutic content analysis combined with thematic analysis to guide data extraction, reading, interpretation, and reporting. The primary data sources were regional and international normative documents related to clinical research and REC/IRBs in Europe and the USA and US Academic health center IRBs' web page content. Stakeholder engagement included REC representatives in Europe using the European Network for Research Ethics Committee (EUREC) member list.

Results

The general post-approval role expectations of REC/IRBs are 1) to review significant protocol amendments and issue opinions or approval on these amendments, 2) to receive notification of safety and adverse events reports, and 3) to receive notification of the end of a trial and a final report. There is disagreement between regions on whether RECs ought to conduct continuing reviews. Within the EU and allied countries, continuing review is considered a form of active monitoring delegated to the regulatory authorities. Contrariwise, the law mandates continuing review within the USA, which is also distinguished from active monitoring. There are challenges with the use of and interpretation of clinical trial nomenclature. The authority of US IRBs to suspend and terminate trials is not commonplace in the EU.

Conclusion/Recommendations

The overarching role expectation of REC/IRBs after the approval of clinical trial protocols is to protect research participants. This may be achieved through post-approval activities such as continuing review, active monitoring, ethics support and education to researchers, and the issuance of an opinion on the final reports at the end of clinical trials. There may be hesitancy in European countries to conduct active follow-up of approved trials due to a lack of supporting legislation/policy, types of organizational structure, lack of expert administrative

staff, and other resource limitations. The European Medicines Agency's new clinical trial information system provides a unique opportunity to reduce bureaucracy and enable the follow-up of approved protocols. To avoid pushback, EU RECs may need stakeholder support and re-branding to shift the perception of RECs from mainly performing prospective reviews towards an end-to-end ethics oversight i.e. an oversight from start to finish.

ABSTRAKT (Norwegian)

Bakgrunn

I omtrent seks tiår har forskningsetiske komiteer (REC), også kjent som Institutional Review Boards (IRBs), spilt en integrert rolle i identifiseringen av etiske spørsmål før oppstart av klinisk forskning globalt. Betydningen og relevansen av den potensielle REC/IRB-gjennomgangen er allment anerkjent, beundret og kritisert. I mange jurisdiksjoner er lovgivende og politiske rammer på plass for å forhindre at klinisk forskning finner sted uten forutgående gjennomgang og godkjenning av en REC/IRB. Det er derfor rimelig å anta at forskning med en positiv oppfatning av en REC/IRB er etisk forsvarlig og vitenskapelig hensiktsmessig. Det er imidlertid bevis for at forskere kan avvike fra de godkjente protokollene. Mange av disse avvikene er etisk relevante, men forblir uadressert. Disse uadresserte avvikene danner grunnlaget for denne spørrende avhandlingen om post-godkjenningsrollen til REC/IRB. Den benytter rolleteori fra sosiologien for å belyse konsepter som rolleforventninger, identitet og atferd til REC/IRBs etter godkjenning av kliniske studier.

Metoder

Kvalitative forskningsmetoder ble brukt for å utforske hovedmålene. Forskningstilnærmingen inkluderer hermeneutisk innholdsanalyse kombinert med tematisk analyse for å veilede datautvinning, lesing, tolkning og rapportering. De primære datakildene var regionale og internasjonale normative dokumenter knyttet til klinisk forskning og REC/IRBs i Europa og USA og nettsidene til US Academic Health Center IRBs. I tillegg ble et utvalg av REC-representanter i Europa intervjuet. Disse ble identifisert ved å bruke medlemslisten til European Network for Research Ethics Committee (EUREC).

Resultater

De generelle forventningene til REC/IRBs rolle etter godkjenning er 1) å evaluere, kommentere og godkjenne substansielle protokollendringer, 2) å motta varsling vedrørende sikkerhet og uønskede hendelser, og 3) å motta melding om avslutning av en utprøving inkludert sluttrapport. Det er uenighet mellom regioner om hvorvidt RECs bør gjennomføre kontinuerlige vurderinger. Innenfor EU og allierte land anses kontinuerlig gjennomgang som en form for aktiv overvåking delegert til reguleringsmyndighetene. Motsatt gir loven mandat til å fortsette gjennomgangen i USA, som også skiller seg fra aktiv overvåking. Det er utfordringer med bruk og tolkning av nomenklatur for kliniske forsøk. Autoriteten til amerikanske IRBs til å suspendere og avslutte forsøk er ikke vanlig i EU.

Konklusjon/anbefalinger

Den overordnede rolleforventningen til REC/IRB etter godkjenning av kliniske utprøvingsprotokoller er å beskytte forskningsdeltakere. Dette kan oppnås gjennom aktiviteter etter godkjenning som kontinuerlig gjennomgang, aktiv overvåking, etikkstøtte og utdanning av forskere, og utstedelse av en uttalelse om sluttrapportene ved slutten av kliniske studier. Europeiske land synes nølende når det gjelder å

gjennomføre aktiv oppfølging av godkjente utprøvinger. Dette begrunnes i mangel på støttende lovgivning/policy, organisasjonsstruktur, mangel på administrativ ekspertise og andre ressursbegrensninger. Det europeiske legemiddelbyråets nye informasjonssystem for kliniske utprøvinger gir en unik mulighet til å redusere byråkratiet og muliggjøre oppfølging av godkjente protokoller. For å unngå pushback, kan EU-REC-er trenge stakeholder-støtte og re-branding for å endre forståelsen av RECs rolle fra hovedsakelig å utføre prospektive evalueringer til å føre etisk tilsyn med en studie til den er avsluttet.

PREFACE

A journey of a thousand miles begins with a single step (Lao Tzu)

My journey began on the island of Jamaica, where I embarked on a career as a community pharmacist but wanted to explore more in academia. Subsequently, I pursued graduate studies in Healthcare ethics and law at the University of Manchester, UK. During that period, I changed from community practice to regulatory pharmacy, where I worked as a Pharmacy Inspector at the Pharmacy Council of Jamaica. Upon completing my Master's degree, on the invitation of the then Permanent Secretary in the Ministry of Health, Dr. Grace Allen-Young, I began teaching ethics to undergraduate pharmacy students at the University of Technology, Jamaica. This was the first introduction of ethics into the course curriculum. In 2017, the University of the West Indies, Jamaica, commenced its Doctor of Pharmacy degree programme. The head of the school of pharmacy invited me to contribute to the drafting and teaching the pharmacy law and ethics course.

Despite these achievements in academia, I kept reflecting on the fact that Jamaica did not have legislation governing research. This reflection began when I was invited to be the Pharmacy Council representative on the Ministry of Health's Ethics and Medico-legal Affairs Panel. This panel is the committee that reviews and approves all research for government health facilities. My tenure on this committee led me to consider what happened to the approved research and the existing regulatory measures in Jamaica to address harm to research participants. These reflections led to a proposal submitted to the PhD programme at the Faculty of Law, University of the West Indies, Mona. However, the law faculty did not have anyone qualified in Ethics to provide supervision. The lack of supervision was a significant challenge.

In 2017, I attended an Ethics teacher training jointly hosted by the UNESCO Bioethics department for Latin America and the Caribbean and the Bioethics Society of the English-Speaking Caribbean. At that training, I met Professor Jan Helge Solbakk, who recognized my passion for bioethics, particularly the regulation of research. Jan Helge introduced me to Professor Rosemarie Bernabe who had done extensive work on ethical issues in post-trial authorization procedures. My background in regulatory pharmacy and ethics made the issues very real, coupled with my concerns about clinical research in my country and the wider Caribbean.

Fortuitously, in 2019, I became aware of a call for a PhD fellowship at the Centre for Medical Ethics, University of Oslo. The project was aligned with my initial research interest. Hence, being highly motivated by the topic and the possibility of working with expert Ethicists, I applied, was interviewed, and was subsequently informed that I was successful. Thus my journey from Jamaica to Oslo.

ACKNOWLEDGEMENTS

I want to first express thanks to God in accordance with my Christian faith. It is this faith that has been my guiding light throughout this journey called life (*Ephesians 3:20-21).*

My supervisors, Professors Rosemarie de la Cruz Bernabe and Jan Helge Solbakk for giving me the opportunity to work with them on this important project and their unwavering support throughout.

Professor Søren Holm who has been a de facto third supervisor. You provided critical but helpful comments. Your kindness is unique in academia.

Dr. Frederick Luthardt, for agreeing to give the US perspective and support with the third paper.

Reidar Pedersen and my colleagues at the Centre for Medical Ethics. I could not ask for a better work environment-the friendly faces and genteel personalities made life in Norway so much better.

Morten Ariansen, for the technical support during and after the pandemic.

Berit Hofset Larsen and Cecilie Hertz - my colleagues who are now like family.

Paul D. Brown and the members of the Jamaican Organization in Norway for the

camaraderie and taste of Jamaica.

The dedicated staff at Goodwill Pharmacy and Rxessentials Ltd- thanks for ALL you do!

Jason, who challenged me to do this PhD, and then listened to my reflections; the constructive feedback buoyed me towards the finish line.

Dahlia, Chavez, Ernestine, Syrena, Kerry, Valeria, and Simone-my cheerleaders who made me laugh, feel less alone, and gave me the impetus to keep going.

Vivienne, Chris, Mark, Marsha- the Ardenne Family: Deo Duce Quaere Optima!

Shandia- words are not enough to say thanks for your loyalty and friendship.

My mother, Carmen Williams, who checks on me every day. You are simply the best!

The Cox Family -Violet, Calvin, Barry, Daisy, and Rodney- I am forever grateful for the support especially with Apphia. I could not have done this without you.

Apphia Cox, my beautiful, delightful, funny, and intelligent daughter, who thinks I work too hard but unapologetically, enjoys the fruit of my labor. You are my forever sunshine!

I dedicate this thesis to my brother, Ian Dawkins, who passed away on 25.03. 2022.

Tusen Takk- A thousand Thanks!

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LIST OF PAPERS

The following is a listing of the three papers relevant to this thesis. Reference to the papers will be made based on their numerically assigned description-I, II, and III.

I. Cox, Shereen; Solbakk, Jan Helge & Bernabe, Rosemarie. (2021). The role of research ethics committees after the approval of clinical trial protocols in the EU and the USA: a descriptive content analysis of international and regional normative documents. Current Medical Research and Opinion. ISSN 0300-7995. 37(6), p. 1061–1069. doi: 10.1080/03007995.2021.1905621.

II. Cox, S., Solbakk, J. H., & Bernabe, R. D. L. C. (2022). Research ethics committees and post-approval activities: a qualitative study on the perspectives of European research ethics committee representatives. *Current medical research and opinion*, *38*(11), 1897–1907. https://doi.org/10.1080/03007995.2022.2115773

III. Cox, S., Solbakk, J. H., Luthardt, F., Jr, & Bernabe, R. D. (2023). Institutional Review Boards and post-approval monitoring (PAM) of human research: content analysis of select university (academic health center) web pages across the USA. *Current medical research and opinion*, *39*(3), 341–350. https://doi.org/10.1080/03007995.2023.2175999

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LIST OF ABBREVIATIONS

AHC	Academic Health Centers
CA	Competent Authority
CIOMS	Council for International Organizations of Medical Sciences
CITI	Collaborative Institutional Training Initiative
CRO	Contract Research Organization
CTIS	Clinical Trials Information System
CTSC	Clinical Trial Steering Committee
DoH	Declaration of Helsinki
DSMB	Data Safety Monitoring Board
EMA	European Medicines Agency
EUREC	European Network of Research Ethics Committees
GDPR	General Data Protection Regulations
IEC	Institutional Ethics Committees
ICH: GCP	International Council on Harmonization: Good Clinical Practice
IRB	Institutional Review Board
NIH	National Institute of Health
NSD	Norwegian Center for Research Data
IORGs	IRB Organisations
PM&R	Public Responsibilityin Medicine and Research
RA	Regulatory Authority
REB	Research Ethics Board
REC	Research Ethics Committees
UNESCO	United Nations Educational Scientific and Cultural Organization
US FDA	United States Food and Drug Administration
WHO	World Health Organization
WMA	World Medical Association

GLOSSARY

The following are key terms adopted from official source documents for this thesis. Definitions are exact quotes from the following official sources: International Council for Harmonization: Good Clinical Practice guidelines (ICH: GCP). Definitions for other relevant terms are expounded throughout the thesis.

Academic Health Centers	An academic health centre encompasses all the health-related components of universities, including their health professions, schools, patient care operations, and research enterprise (Alliance of Academic Health Centers International, 2022).
Clinical trial	Anyinvestigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s) and/or to identify any adverse reactions to an investigational product(s) and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous (International Conference on Harmonization, 2018)
Research Ethics Committee	An independent body constituted of medical, scientific, and non-scientific members whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trial protocol and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects. (Same as Institutional Review Board) (International Conference on Harmonization, 2018)
Regulatory authorities	Bodies having the power to regulate. In the ICH GCP Guidelines, the expression Regulatory Authorities includes the authorities that review submitted clinical data and those that conduct inspections. These bodies are sometimes referred to as competent authorities (International Conference on Harmonisation, 2018).

CHAPTER ONE

INTRODUCTION

1.1 Research Oversight -A Look beyond Prospective Ethics Review

Prospective review of clinical research is the well-established means by which RECs/IRBs execute their responsibilities to researchers and participants (Aguilar-Salinas et al., 2019; London, 2012). The emphasis on prospective review has its foundation in the origin of RECs/IRBs at the National Institute of Health in the 1950s (Hedgecoe, 2009; Moon & Khin-Maung-Gyi, 2009; Rice, 2008). At the time of conceptualization and subsequent implementation, the goal of the NIH was to have a committee review and identify potential ethical issues in the proposed research that their agency funded (Bradford Gray, 1977; Moon & Khin-Maung-Gyi, 2009; Rice, 2008). This review includes a comprehensive risk-benefit assessment, consideration of the social value and relevance of the study, the acceptability of the consent forms, and the capacity of research participants to consent and recommend changes before the commencement of the study (Emanuel et al., 2000; Habets et al., 2014). The REC/IRB should be independent, with sufficient expertise, and representative of a broad cross-section of persons (Mullings, 2007; Rice, 2008). The goal is to achieve consensus on the ethical acceptability of the proposed research. This approach to protecting research participants has had its fair share of critics (Abbott & Grady, 2011; C. Brown et al., 2020; Grady, 2015). The prospective review process has been described as tedious, stifling research, discouraging, and paternalistic (Brown et al., 2020; Edwards et al., 2004; Hearnshaw, 2004; Klitzman, 2011).

Researchers have argued for a shift from a highly paternalistic RECs/IRB to a more facilitative and inclusive one (Friesen et al., 2022; London, 2020; London, 2012; Moreno, 2001). One of the non-paternalistic arguments proffered is that RECs/IRBs should limit their interference and permit research providing the consent form is comprehensive and the participants are aware of the risks and are willing to participate in the research (Edwards et al., 2004; London, 2020). There is also the argument for a more collaborative stakeholder approach with less focus on research governance (institutional and researcher compliance) and more on the research ethics principles of respect for persons, beneficence, non-maleficence, and justice (London, 2020). Some scholars have argued that the aforementioned ethical principles do not adequately address ethical issues arising in new and emerging technologies (Brothers et al., 2019; Friesen et al., 2017).

Garrard and Dawson argue that there is a place for a paternalistic approach in how REC/IRB carries out its responsibilities (Garrard & Dawson, 2005). They posit that RECs/IRBs comprise people external to research with a wide range of expertise, including highly specialized scientists and laypersons who are competent, capable, and sufficiently objective to make decisions on behalf of research participants (Garrard & Dawson, 2005). They provide counterarguments to Edwards, Kirchin, and Huxtable, who argue that competent persons should be allowed, as far as they have sufficient information, to make decisions regarding the risks they wish to undertake (Edwards & Kirchin, 2004). Others have argued that characterising research participants as vulnerable have often resulted in a deficit in

knowledge generation about these individuals and, consequently, neglect in addressing their health needs. The neglected include young children and pregnant women (Friesen et al., 2017; London, 2020). However, Garrard and Dawson note that there are limits to the epistemic authority of sick individuals whose judgments may be influenced by "irrational fears, over-optimistic view, research, or a misplaced sense of altruism" (Garrard & Dawson, 2005). They asserted that "competent sick persons may be inclined to do research and take unjustified risks" (Garrard & Dawson, 2005).

There is sufficient evidence that informed consent processes are challenging even within the current systems (Klitzman, 2013; Paasche-Orlow et al., 2003). They argue, "many subjects find it difficult to judge relevant information appropriately, to the extent that we might….worry about their ability to give an informed consent" (Garrard & Dawson, 2005, p. 421). Wertheimer's discourse on "soft paternalism in research ethics" supports Garrard and Dawson's argument (Wertheimer, 2012). He notes that research participants with decisional deficits justify the protective oversight of the REC/IRB (Wertheimer, 2012).

Philosopher Alex London argues against the paternalistic model for research ethics (London, 2020; London, 2012). Nevertheless, he justifies the IRB's protectionist (albeit paternalistic) governance role. He posits what he describes as a framework for a "voluntary scheme of social cooperation that is stakeholder inclusive" (London, 2020, p. 4). Tusino and Furaro have also published a paper on the heels of the COVID-19 pandemic, asking for a rethinking of the role of research ethics committees (Tusino & Furfaro, 2022). They do not assert a non-paternalistic research governance model. Instead, they argue for "a reform that aims at improving the way we review, approve, monitor and conduct clinical research with human subjects that must find a way to preserve and promote the original goals of RECs" (Tusino & Furfaro, 2022, p. 44). This requires "ethical reflection inside research institutions that nourishes the culture of research ethics through three different functions: deliberating about the ethical acceptability of each research project, promoting bioethics education, and offering consultation and support to change" (Tusino & Furfaro, 2022, p. 44). Change is a common theme in recent scholarship on research governance and ethics.

Traditional research ethics is evolving as we learn from the many decades of scandals, challenges, and reflections of learned experts in the field (Beecher, 1966; Hedgecoe, 2017). The impetus for change is reflected not only in scholarly opinion pieces but also in legislation. During 2019 and 2022, the USA and Europe changed their primary legislation governing research (European Medicines Agency, n.d.; Menikoff et al., 2017). The US government updated a key clinical trials legislation – 45 CFR 46, also known as the Common rule in 2019 (Dove, 2019; Young, 2019). The change came into effect after several years of consultations with relevant stakeholders. The EU Regulations 536/2014 also came into effect in January 2022. It replaced the Clinical Trials Directive (EC) No. 2001/20/EC (Tenti et al., 2018). However, European and US-based scholars have contributed through a critical or complimentary lens, noting that the regulations changes are insufficient to address the myriad of social and ethical challenges that arise in research (Gefenas et al., 2017; Ostuzzi et al., 2020; Petrini, 2016). I will address some of these contributions in the literature review chapter.

This thesis aims to contribute to the ongoing dialogue by going beyond the traditional reflection on the prospective review model for REC/IRB analysis to examine its post-approval role. The motivation for this exploration lies in identifying ways to address the various challenges that arise during or after the completion of a clinical trial that is of ethical relevance. The central question is, what is the role, if any, of the REC/IRB after the approval of protocols?

There is support in published literature for a post-approval role for REC/IRBs. Dawson et al. note that:

> "Ethical issues arise during projects, especially with research in humanitarian settings, which is our particular interest, due to the instability and insecurity in such contexts. A regulatory and pre-approval approach to research ethics, focused on well-known ethical principles and issues, like informed consent or confidentiality, cannot address everything that is crucial in research ethics. What is missing is how topositively encourage ethical conduct" (Dawson et al., 2019, pp.1-2).

Scholars across various jurisdictions have published on the topic of REC/IRB monitoring and continuing review citing multiple benefits and challenges (Davis, 2018; Heath, 1979; Jadhav et al., 2014; Weijer et al., 1995a). In some jurisdictions, such as the United States and Australia, the legislation supports passive and active REC/IRB monitoring (Jadhav et al., 2014; McNeill et al., 1992; Pickworth, 2000). Dawson et al. proffer that REC/IRB should conduct critical reflections on completed trials in the form of a retrospective review. They claim an ex-post REC/IRB review would aim to:

> "Identify new insights and knowledge about ethical issues from looking back at research already conducted, increased sensitivity of researchers to relevant ethical issues, learning lessons from adaptations made during the research to how ethical issues were addressed, contributing to the development of ethical standards and guidelines in research, etc." (Dawson et al., 2019, p. 4).

The preceding arguments are a starting point for this empirical exploration of the role of RECs/IRBs beyond prospective review. The scholarship exists on the benefits of REC/IRB monitoring and continuing review (Davis, 2018; Shafiq et al., 2020; Weijer et al., 1995). However, others have argued that this type of monitoring is challenging for REC/IRBs and may negatively affect the relationship between RECs and researchers (Klitzman, 2011; Pickworth, 2000). Several scholars have argued for evaluation studies regarding the quality and effectiveness of RECs/IRBs prospective review and whether the intended outcome for protecting the research participant is being achieved (Abbott and Grady, 2011; Nicholls et al., 2012, Lynch et al., 2022; Tsan 2022; US General Accounting Office, 2023). There appears to be a disconnect between what is desired and what is practical. Nevertheless, in light of the discussions regarding an all-encompassing collaborative model for RECs/IRBs (stakeholder-inclusive) without losing the original protectionist mandate, the focus of this thesis on the post-approval role of REC/IRB is relevant. Aligned with this focus, the thesis' objectives, findings and discussions are restricted to role concepts such as expectations and identity and, to a limited extent, role behaviours. The thesis does not explore concepts such as the quality and effectiveness of RECs/IRBs, as this type of interrogation would require an in-depth examination of REC/IRBs' structures, processes, and outcomes in protecting research participants. However,

reference will be made to some scholarship in the Discussion chapter regarding the interconnectedness between role expectations and effectiveness and approaches to measuring quality and effectiveness.

1.2 Project Overview

1.2.1 Aim and Objectives

This thesis is the amalgamation of research for a University of Oslo project titled: **Incorporation of Ethics in Pharmaceutical Authorization Regulatory Procedures (REGULATORY ETHICS**). It combines sociological role theory (empirical) and a teleological (normative) framework to examine the post-approval role of RECs/IRBs. The project's aim and objectives were interrogative and comparative.

The interrogative research question throughout the project was, "What is the role of RECs after the approval of clinical trials?" To answer this question, it was imperative to identify what is documented and compare it to what is perceived as REC expectations and behaviours beyond prospective review. The first objective was achieved by way of content analysis of international and regional normative documents and a scoping review of scholarly literature. The content analysis results were published in Paper I. The intention is to publish the results of the scoping review as a fourth paper independent of this thesis. The second objective sought insight into stakeholder perspectives and experiences on REC's activities during ongoing clinical trials. Due to the unanticipated challenges presented during the COVID-19 pandemic, an additional objective was conceptualised during the project. This forms objective three, where we explored the post-approval activities of Academic Health Centres (AHCs) in the USA. The results of the three objectives enabled a comparison between some countries in the European Union (EU) and the USA. Objectives two and three results are reported in Papers II and III. We also intend to draft and publish the normative paper with recommendations outlined in objective four in a fifth paper independent of this thesis. The summarised aim and objectives are as follows:

Aim: To explore the post-approval role of Research Ethics Committees for clinical trials

Specific Objectives:

1. a) Perform a content analysis of relevant normative documents (guidelines and laws).

   b) Perform a scoping review of scholarly literature and REC mandates on the role of ethics committees during ongoing clinical trials (i.e. after approval).

2. Explore stakeholder (RECs) experiences and perspectives on the status quo in terms of RECs regulating ongoing clinical trials, if this status quo could be improved, and, eventually, in what ways.
3. To conduct a content analysis of webpages of Academic Health Centers (AHC) on IRB post-approval activities in the USA.
4. To provide normative reflection and guidance and propose recommendations about RECs and other relevant monitoring bodies' post-approval responsibilities based on the findings of objectives 1 – 3.

1.2.2 Study Context

The project explored the activities of RECs/IRBs in the USA and some European countries. According to clinicaltrials.gov, the USA and Europe are the leading regions for clinical trials globally, collectively managing over 65% of listed trials. The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) are also recognised as leading global regulatory agencies.

1.2.3 Justification, rationale, and relevance

Examinations of Good Clinical Practice (GCP) inspection reports in the USA and Europe indicate violations and departure from approved clinical trial protocols by principal investigators (Bernabe et al., 2019a, 2019b; Seife, 2015). Many of these violations are identified as ethically relevant (Bernabe et al., 2019a, 2019b). Post-clinical trial audits have identified deficiencies in monitoring trials by sponsors (funders) and contracted external agencies such as Data Monitoring Committees (DMC). Identified ethical violations are not considered relevant during pharmaceutical authorization procedures (Bernabe et al., 2019a, 2019b). The overall goal of this research project is to identify the role that RECs may have in clinical trials to (a) ensure scientific integrity and credibility, (b) protect research participants and (c) maintain public safety and trust. Scholars have argued that monitoring clinical trials from protocol approval to market authorisation is essential to achieving these goals. The findings will inform policymakers and regulators how RECs can and should play a role in ensuring compliance post clinical trial approval by addressing the ethically relevant issues identified while monitoring clinical research. By focusing on the situation in the USA and Europe, we hope the project findings will provide knowledge and inform RECs and regulatory agencies with global responsibilities for clinical trials.

1.3 Thesis Structure

The thesis is organised into seven chapters. Chapter 1 is the Introduction. Chapters 2, 3, and 4 include 1) the Literature review, 2) theoretical elaboration and conceptualisation, 3) research methodology and design, and 4) results and synthesis of the three papers. Chapters 5, 6, and 7 are the discussion, conclusions, and recommendations. Chapter 7 also includes the study limitations and suggestions for future research.

Chapter 2 delves into a historical reflection on clinical research, some noteworthy scandals, and the related normative responses that proscribed and changed clinical research from unregulated to a highly regulated social institution. The central theme in this chapter is clinical research and not research ethics in general. The chapter therefore will not expound on non-clinical research. Consequently, the cited historical research ethics and regulatory milestones will be examples directly or indirectly related to clinical human subject research. The review includes an overview of the various clinical research stakeholders and their responsibilities. Finally, there is an elaboration on recent examples of challenges within clinical research and its multiple stakeholders.

Chapter 3 is the theoretical chapter that elaborates on clinical research as a social institution with normative obligations. It incorporates role theory concepts to enable the characterisation and analysis of data. The normative theories are teleology, Alex London's common good approach, and William D. Ross' prima facie duties.

Chapter 4 outlines the theoretical and practical characteristics of the research methodology and design. I will briefly discuss empirical ethics, hermeneutics, thematic content analysis and their relevance to the research approach. The chapter will outline the overarching research design and then detail the data collection methods, analysis, and reporting of the three papers relevant to the thesis.

Chapter 5 summarizes the main results of papers I-III in two parts. Part one details the results of each article. Paper I presents the results of content analysis of 19 international and regional (Europe and USA) normative documents relevant to clinical trials. Paper I outlines the various types of post-approval activities expected of RECs/IRBs and considered in this thesis. The types of activities are discussed in the context of passive and active post-approval follow-up. This categorization enables a broad description of REC/IRB activities in Europe and the USA. It highlights some activities required by legislation in the USA and the wider European Union regulations. REC/IRB post-approval activities were not explored in individual countries within the EU. Paper II presents the results of interviews with representatives from European REC members. Paper III describes the content analysis results of US IRB AHCs' web pages. Part two includes two tables synthesizing the role expectations and factors contributing to divergence using extracts from the three papers. Role theory concepts frame the comparative analysis.

Chapter 6 is an analytical chapter elaborating on and discussing the research findings. The role theory frame highlights some identified challenges with role expectations, identity, and behaviours. The findings are also discussed in light of existing scholarly literature and emphasize how the identified challenges impact the divergence in role expectations.

Chapter 7 summarizes the conclusions in the thesis and presents recommendations on the way forward. The limitations are discussed, and suggestions are made for future research.

CHAPTER TWO

LITERATURE REVIEW

2.0 Overview

In this chapter, I will first briefly sketch the development of the clinical research enterprise, summarising historical examples of unethical research and the birth of a paternalistic governance model through enacting various guidelines. Secondly, I will outline the various stakeholders in clinical research and their respective mandates. Thirdly, I will provide examples of challenges that arise in ongoing clinical trials that the prospective review model of research governance does not adequately address.

All the world is a stage, and all the men and women are merely players; they have their exits and their entrances (William Shakespeare- As you like it)

Shakespeare's symbolic reference to the stage and players as a representation of how humans interact in life exemplifies role theory. The word role is ubiquitous. A word used in everyday jargon and academia to describe identities (status/positions), expectations, and behaviours/norms (Biddle, 1986). The term role originates from the French word "roule," referring to the piece of paper (or script) on which actors' parts are written (Merriam-Webster Dictionary, 2022). Within academia, role theory is used widely in sociology to examine multiple social phenomena (Anglin et al., 2022; Biddle, 1986; Hindin, 2007). When there is a clear understanding of roles and role expectations, it is easier for actors to know whether they are fully in character or go off-script, i.e. the manifestation of expected behaviours.

The sociologist Erving Goffman uses a metaphorical analogy of human interactions with actors in a theatre (Jacobsen, 2017). He proposed that social interactions can be examined using a theatrical lens (Jacobsen, 2017). Goffman referred to this metaphorical analogy as dramaturgy (Jacobsen, 2017). Dramaturgy is one of several methodologies in roletheory (Biddle, 1979). Although this is an unconventional way to begin the discourse for an ethics dissertation, creating a sense of direction for what I hope to accomplish was essential. This thesis attempts to elucidate the role of RECs within the clinical research enterprise.
More specifically, the role after the REC has approved what is known as the clinical research protocol. To achieve this objective, as a researcher, I have assumed the role of a critical reviewer and audience. As such, it would be imperative to ascertain the stage (clinical research enterprise) - that we seek to examine, the actors (stakeholders), and the role expectations, then give a critical review (normative reflection) of the findings. I will expound on whether RECs have a role in addressing ethical violations post-approval of protocols in clinical research. However, the project's general aim is to understand, by way of empirical ethics, whether and to what extent ethics committees have a role beyond the established ex-ante approach to protecting research participants. The literature review is a melting pot of several distinct but interrelated sub-topics. These are:

1. the evolution of the enterprise known as clinical research,
2. a brief reflection on the challenges of unregulated clinical research,
3. the shift from an unregulated to a highly regulated research governance system as a global social phenomenon highlighting current gaps in regulatory oversight, and
4. Some challenges with ongoing clinical trials.

2.1 Clinical Research Enterprise

Preamble

This section will focus on clinical research as a multi-stakeholder social institution, particularly clinical trials and the pharmaceutical industry. The intention is to elaborate on clinical research as a multi-stakeholder organization. For this reason, there will be less emphasis on Research Ethics in general or its broader discipline, Bioethics. Instead, the historical review on research and bioethics will center on how the concept of an ex-ante review of research proposals by way of a Committee began in the mid-1960s and is now a globally accepted norm. Chronologically, clinical research as a field predates the academic disciplines: Research ethics and Bioethics. Research Ethics became more prominent in the mid-1940 following the infamous Nuremberg trials, and Bioethics gained prominence as a discipline following the use of the term by biochemist Van Rensselaer Potter **(**Jonsen, 2012). Later in this chapter, the sequence of events will highlight that ethical challenges in early clinical research prompted normative responses in the form of international ethics guidelines and legislation to become a highly regulated industry.

2.1.1 The evolution of clinical research in Europe and the USA.

The term "clinical research" has root words derived from French and Greek origin, translated to mean "to search or go about searching at the bed of the sick." The search intends to find answers to the causes and treatments of the various ailments associated with the sick patient (Harper, 2020b, 2020a). Historians have traced medical/health research to as early as biblical days, 562 B.C., to compare dietary choices between the Hebrew enslaved people and the followers of then-King Nebuchadnezzar (Bhatt, 2010). It is claimed to be one of the first recorded "trial" of a public health nature (Bhatt, 2010).

Arun Bhatt gives a succinct outline of the history of oranges and lemons in 1747 to treat Scurvy to the milestone 1946/1947 first randomized trials in the UK for testing Patulin and Streptomycin (Bhatt, 2010). During the period between the treatment of Scurvy and the first randomized trial, several methodological changes took place for the scientific advancement of how clinical trials were conducted. Using a placebo in clinical research became part of this standardization process to eliminate inaccurate results. Eventually, concepts such as randomization, placebo controls, and other scientific/statistical approaches to conducting trials became part of the clinical trial jargon and the initiation of the randomized controlled method (Vickers & de Craen, 2000). Once randomized clinical trials became the norm for conducting clinical research, researchers emphasised the accuracy of scientific methods (Meldrum, 2000). In 1898, Johannes Fibiger addressed researchers' bias byintroducing the concept of blinding in the research approach. "Blinding" in clinical studies refers to random patient selection to allocate who gets the clinical intervention or the placebo (Meldrum, 2000). The randomized approach in patient selection evolved into what is described as "double-blind, randomized controlled clinical trials" – the gold standard for clinical research (Meldrum, 2000). Eventually, the term research protocol was coined for the document or documents relating to how an investigator or a sponsor organization intends to conduct clinical research. A research protocol is defined thus:

> "A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial" (International Conference on Harmonization, 2018).

The research protocol is shared with various stakeholders to clarify the scope of the research undertaking, the methods to be employed, the target subjects, and the associated risks.

Currently, clinical trials are the accepted methods of conducting research. At the time of drafting this thesis, clinicaltrials.gov reports over 400,000 research studies globally (US National Library of Medicine, 2022). This includes various sponsor organizations (academic and non-academic). The most significant sponsor organization is the pharmaceutical industry, the main sponsor of focus throughout this thesis discourse. The drug/device/clinical intervention process involves multiple stakeholders and extends over prolonged periods encompassing discovery phases to wide-scale manufacturing to reach the target market. Although academics and non-academics pursue drug discovery, manufacturing and marketing are the remits of the pharmaceutical industry.

2.1.2. The regulation of research - A paternalistic model.

The widespread manufacturing and distribution of drugs began in the 19th century. Before this, chemists or physicians compounded medications as needed for individual patients (Rägo & Santoso, 2008). Over time, there was a shift from an unregulated to a highly regulated research enterprise due to various challenges. One of the earliest pieces of legislation to govern pharmaceuticals is the Federal Pure Food & Drug Act of 1906, also known as the Wiley Act (Nasr et al., 2011). Nasr, Lauterio, and Davis outline examples of unregulated adulterated pharmaceuticals, such as morphine-laced soothing syrup as a "teething and colicky syrup" (Nasr et al., 2011). Another milestone was the Food, Drug, and Cosmetic Act of 1938. These follow what Nasr et al. describe as "disreputable incidents involving drug marketing claims which resulted in highly publicized deaths" (Nasr et al., 2011). The most significant at the time was the Sulfanilamide scandal. Sulfanilamide was an antimicrobial elixir dispensed in the solvent -diethylene glycol. Diethylene glycol is a poison known commonly as antifreeze. The ingestion of this product without timely medical intervention resulted in death (Ballentine, 1981; Nasr et al., 2011). Subsequent public outcries prompted the US congress to effect change in the law to "require evidence of safety for new drugs" (Nasr et al., 2011). Drug companies would prove safety by way of a New Drug Application to obtain regulatory approval (Nasr et al., 2011). Additional requirements would be listing active ingredients on the drug label and labelling with adequate directions for use and warning (Nasr et al., 2011). By 1948 and 1951, additional governance measures include prohibiting illegal drug sales and the enforcement of a distinction between prescription-only and non-prescription medicines (Fintel et al., 2009; Nasr et al., 2011).

In 1957, Thalidomide was first marketed in Germany as an over-the-counter treatment as a sedative and eventually used off-label to alleviate morning sickness in pregnant women. By 1961, the drug was used in over 40 countries globally (Fintel et al., 2009). In 1962, a significant event commonly described as the "Thalidomide disaster" discovered by an obstetrician, Dr William McBride, who identified that the drug was the cause of congenital disabilities such as phocomelia led to the regulatory changes that now govern clinical trials (Fintel et al., 2009). The USA, via its Food and Drug Administration (FDA), published the Kefauver-Harris Drug Amendments requiring drug manufacturers to prove the safety and efficacy of pharmaceuticals in stages. This legislative move became the platform for drug testing from pre-clinical (non-human) to clinical (in humans) (Fintel et al., 2009; Greene & Podolsky, 2012).

The various phases of a clinical trial include testing drugs on a healthy volunteer to ascertain safety and effective dose with minor side effects and subsequently in volunteers with the targeted disease (Phases 1-3) (Umscheid et al., 2011). The regulatory authorities approve the investigational new drug (IND) after its efficacy and safety are evaluated and proven at each stage (Umscheid et al., 2011). The regulatory process of requiring clinical trials significantly changed the pharmaceutical industry (Greene & Podolsky, 2012). With more controlled studies and regulatory oversight, the cost of drug manufacturing also increased and, consequently, the cost of drugs to the consumer (Martin, 2017). However, this did not negatively affect the profitability of the industry. The pharmaceutical business is now a multi-billion-dollar industry and one of the fastest growing in the world. Researchers ordinarily sell the rights to manufacture a drug product to a pharmaceutical company (Ehrismann &Patel, 2015). Traditionally, pharmaceuticals were chemical products; however, since the advent of biotechnology, biopharmaceuticals are now more prominent in the market and require additional scrutiny because of the costs for development and the subsequent cost to the patient. The biopharmaceutical industry is projected to value over 500 billion by 2027 (Mordor Intelligence, n.d; European Federation of Pharmaceutical Industries and Associations, 2022).

2.1.3 From unregulated to highly regulated- Declarations, legislations, and guidelines.

As research and development evolved, the industry's business side expanded, and the need to protect the research subjects became paramount. Since research began in the clinical setting, perhaps the first code for protecting the patient would be the Hippocratic Oath, named after the Greek physician Hippocrates. It was the adopted oath of the physician to “first do no harm” in his dealings with patients (Hajar, 2017). Rago and Santoso note that one of the earliest pieces of legislation regulating the manufacturing of drugs was promulgated in England. The Apothecaries wares, drugs and stuff Act was passed in 1540. The naming of the Act hints at the transition from the traditional apothecary physician-dominated practice to a regulated system (Rägo & Santoso, 2008).

While the US enacted legislation for drug efficacy and safety, the exploitation of research participants was also addressed in other regions (Hedgecoe, 2017). An important step in protecting research participants was the publication of the Prussian Regulations in the early1900s (Vollmann & Winau, 1996). This represents what may be the first regulation for protecting research subjects in the form of a Government directive. The motivation for enacting the Prussian Regulations was the outcry following well-known clinician Albert Neisser's syphilis studies with prostitutes without their knowledge (Vollmann & Winau, 1996). Vollmann et al. describes the Prussian Regulations as follows:

> “For the first time in history, written documentation of subjects' informed consent, theresearch process, and explicit clarification of personal responsibility for the experiment were required in the medical record. Furthermore, in the scientific reports upon which the directive was based, issues of social justice (protection of poor patients), medical self-experimentation, and the need for previous animal experimentation were raised.” (Vollmann & Winau, 1996, p. 10).

Albert Neisser, known for discovering gonorrhoea, sought to justify his actions by asserting that his patients would have inadvertently contracted syphilis from their profession

(Vollmann & Winau, 1996). The main ethical issue regarding the trial was the lack of informed consent from the patients (Vollmann & Winau, 1996). Following these regulations, in 1931, the German Government published additional guidelines for human experimentation (Vollmann & Winau, 1996). Ghooi notes that the 1931 Guidelines may have been the precursor to the 1947 Nuremberg Code, although no reference has been made to these guidelines during the Nuremberg trials (Ghooi, 2011). It is interesting that while the German government took the step to regulate clinical trials within its territories, some of themost significant atrocities in medical history took place during World War II by German medical doctors (Roelcke, 2004).

Following the war, these doctors were brought before a specially convened international court (Ghooi, 2011; Roelcke, 2004). Consequently, the Nuremberg Code was published, focusing on the research participants' rights (Ghooi, 2011). The ten ethical principles codified in Nuremberg are:

1. The voluntary consent of the human subject is absolutely essential.
2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.
3. the use of prior animal studies to establish safety,
4. avoidance of unnecessary physical and mental suffering and injury,
5. No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur, except, perhaps, in those experiments where the experimental physicians also serve as subjects.
6. degree of risk in a research undertaking should never exceed the benefits,
7. Proper preparations and adequate facilities participants must be made to protect the research subject against remote possibilities of injury, disability, and death
8. Experiments must be carried out only by qualified persons
9. During the course of the experiment, the human subject should be at liberty to bring the experiment to an end if he has reached the physical and mental stage where continuation of the experiment seems to him to be impossible
10. During the course of the experiment, the scientist in charge must be prepared to terminate the experiment at any stage. If he has probable cause to believe that a continuation of the experiment is likely to result in injury, disability or death to the experimental subject (Ghooi, 2011, p. 74).

Bhooi notes that although the Nuremberg Code is lauded extensively in history as the foundational code for modern research ethics, there are flaws in principles 5 and 10 that have not been examined and elucidated (Ghooi, 2011). The first flaw he notes is that principle 5 goes against natural justice, as it is not legally permissible to harm others if one knows beforehand that actions taken could cause death or disability. He argues that the caveat of the physician being the experimental subject is insufficient to justify the continuation of the experiment. He also notes that principle 10 requires the investigator to be prepared to terminate but does not explicitly mandate the investigator to stop the trial (Ghooi, 2011).

Following the Nuremberg Code, in 1964 the World Medical Association subsequently developed the Declaration of Helsinki (DoH), which bolstered the Nuremberg Code by reminding physicians of their primary commitment to the interest and well-being of persons in their care (Bhatt, 2010; Ghooi, 2011). The DoH has been revised multiple times to

address various ethical challenges as they arose. The primary ethical considerations of the DoH are:

- the duty of the physician to protect research subjects,
- the scientific validity and merit of the research,
- the balancing of risks and benefits,
- the prospective review of research by an independent committee
- the right of these committees to monitor ongoing research,
- informed consent for individuals and at community level,
- protecting vulnerable participants,
- Publication and dissemination of results
- the use of placebo, and
- Post-trial access to the benefits of research (World Medical Association, 2008).

Despite its moral authority and influence, the DoH is not without its critics (Carlson et al., 2004; Emanuel, 2013; Malik & Foster, 2016). Ezekiel Emanuel, US Bioethicist, in his 2013 article, described the DoH as follows:

> "It has an incoherent structure; it confuses medical care and research; it addresses thewrong audience; it makes extraneous ethical provisions; it includes contradictions; itcontains unnecessary repetitions; it uses multiple and poor phrasings; it includes excessive details, and it makes unjustified, unethical recommendations." (Emanuel, 2013, p. 1532).

Nevertheless, other scholars positively acknowledged the DoH and its various revisions, especially for guidance on research in limited-resource countries (Burgess & Pretorius, 2012; Rothman et al., 2000; Wolinsky, 2006). Including clauses that address post-trial access and the need for consideration of established standards of care received mixed global reactions (Iunes et al., 2019; Landes, 2005; Lie et al., 2004; Usharani & Naqvi, 2013). The main impetus for updating the DoH and related guidelines was addressing various developments regarding ethical issues in clinical research (Carlson et al., 2004; Iunes et al., 2019; Lie et al., 2004).

In 1949, the World Health Organization and UNESCO jointly established the Council for International Medical Organizations (CIOMS), which also published the International guidelines for Biomedical Research in 1982 (Council for International Organization of Medical Science, 2016).

In 1979, the Belmont report, issued by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, was published (Friesen et al., 2017; US Department of Health and Human Services, 1979). The commission was established in response to widespread public outcry regarding various scandals regarding unethical practices in the US (Beecher, 1966; Brandt, 1978). One of the most significant was the failure to treat almost 400 black men for syphilis without their informed consent between 1932 and 1972 due to their enrollment in a clinical trial conducted by the US Public Health Service and the Tuskegee Institute (Brandt, 1978). The Commission was mandated to "find the critical balance required to satisfy society's demands for the advancement of knowledge while abiding by its strictures to protect the dignity, privacy, and freedom of its individual members" (Friesen et al., 2017; US Department of Health and Human Services, 1979). The report emphasized three core principles that became the yardstick for assessing ethical issues

in clinical research. These are “respect for persons, beneficence, and justice (US Department of Health and Human Services, 1979). The main principles of the Report have been touted globally but are not without critics (Brothers et al., 2019; Friesen et al., 2017). Several have argued that the principles are inadequate to address the advances and complexity of research in the 21st century (Friesen et al., 2017). Issues of concern are the blurred lines between research and practice, transparency challenges, and difficulty predicting risks with novel technologies (Brothers et al., 2019; Friesen et al., 2017).Another concern was whether the principles adequately addressed harm to indigenous communities and the under-representation of minorities and those considered vulnerable patient groups (Friesen et al., 2017). The Belmont principles eventually became part of the ethical framework known as Principlism after non-maleficence was added as a fourth principle. The ethical framework of principlism and its relevance to clinical research and practice will be discussed in greater detail in the theoretical chapter.

Another significant milestone was the establishment of Good Clinical Practice (GCP) guidelines by the World Health Organization, then the International Conference on Harmonization (ICH) in 1995/1996 and adopted by the United States, the European Union, and Japan (International Conference on Harmonization, 1996; Otte et al., 2005). GCP became a standardized way of doing clinical trials to facilitate ease of drug registration for multi- country clinical trials (Vijayananthan & Nawawi, 2008). The cited legislations, codes, declarations and accompanying principles provided the framework for the worldwide development of over 1000 laws, regulations, and guidelines for protecting human research participants. Despite the tremendous progress of clinical research, the expansion of the pharmaceutical industry, and the establishment of various Codes of ethics and laws, there remain loopholes within this protectionist/paternalistic approach to research. This will be discussed later in the thesis.

2.2 Key stakeholders in clinical research

The shift from an unregulated to a highly regulated industry required the participation of multiple stakeholders. The Declaration of Helsinki and the ICH: GCP, the two most influential international normative documents for clinical research, note the roles and responsibilities of the principal investigator, usually a physician, and the independent ethics committees. The ICH: GCP acknowledges the contents of the DoH and further clarifies the other stakeholders' specific roles and responsibilities, such as the regulators and research sponsor organizations. The ICH: GCP emphasizes harmonizing clinical trials and drug authorization procedures across several continents. The following paragraphs will focus on the various stakeholders and their key responsibilities.

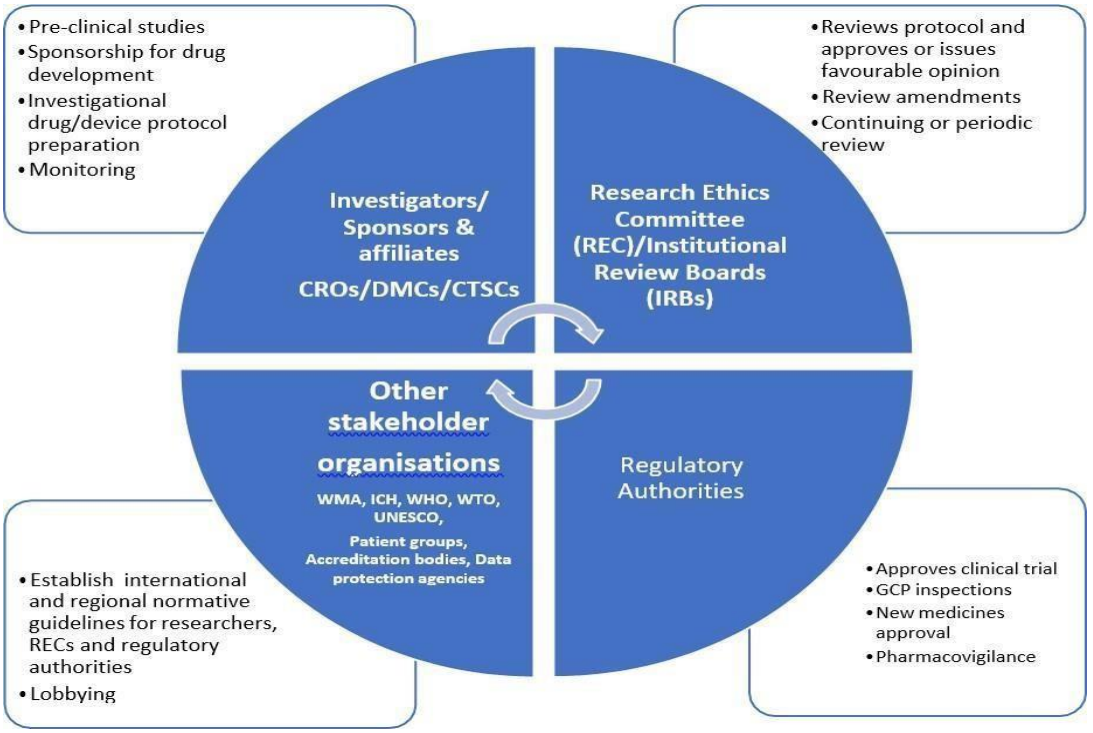

Figure 1.0 Stakeholders in the clinical research enterprise and their responsibilities

2.2.1 Principal Investigator

The principal investigators (PI) are essential stakeholders as they are the ones who undertake the research and interact with the research participants. The US National Institute of Health defines the PI as:

> "[…] the researcher, usually, a doctor or other medical professional, who leads the clinical research team and, along with the other members of the research team, regularly monitors study participants' health to determine the study's safety and effectiveness. A PI is primarily responsible for the preparation, conduct, and administration of a research grant, cooperative agreement, or other sponsored project in compliance with applicable laws and regulations and institutional policy governing the conduct of clinical research" (National Cancer Institute, 2022).

Essentially, it is the PI who would engage all stakeholders throughout the research process; hence may explain why the WMA DoH, as the principal normative agency for physicians globally, places particular emphasis on the conduct of the PI compared to other stakeholders. Principles 3, 4, 9, 10, 14, and 18 are directed to the physician investigator and his role obligations to the research participants, conformance with standards, and ensuring risk benefit assessments of any research under his purview (Appleyard, 2008). According to the DoH, the PI is expected to put the interests of the research participant above that of science and society. However, putting the interests is not always without repercussions. Thisis especially challenging when there is external funding for research. PIs endure threats and intimidation when the research sponsor wants to suppress unfavourable outcomes of research. According to Bennet et al., intimidation tactics employed towards PIs include:

> "[…] threats of lawsuits, […] public disparagement at conferences […], threats of loss of academic positions[…], threats of loss of grant funding […], delays in decisions regarding tenure […], and threats of reassignment to a low-level position" (Bennett et al., 2022, p. 11).

PIs also are under strict confidentiality agreements that may prevent their independence. These PIs face the possibility of severe reputational and financial damage. One example is that of Dr Nancy Olivieri, a Canadian pharmacy professor. She breached her confidentiality agreement with a pharmaceutical sponsor organisation and experienced reputational damage (Baylis, 2004). David Spurgeon reports Dr Olivieri's experience:

> "[…] neither the hospital nor the university, "both anticipating large donations from Apotex, supported me in fulfilling my ethical obligations to my patients or my scientific obligations to the public." […] after her announcement of her findings, she experienced "five years of personal vilifications, reprisals and harassment."(Spurgeon, 2001, p. 1085).

Spurgeon notes that the Academic Tenure and Freedom Committee of the Canadian Association of University Teachers subsequently exonerated Dr Olivieri in 1999 (Spurgeon, 2001).

2.2.2 Sponsor and affiliates

As stated prior, sponsors are the main financiers of clinical research. Sponsors may be government or private sector organizations such as the pharmaceutical industry (Davidson, 2018; Lewis et al., 2007). A sponsor organization usually has a vested financial or other interest in research outcomes, which may be secondary to the stated objective of scientific advancement and the public's ultimate good (Davidson, 2018; Lewis et al., 2007; J. Lexchin & Lexchin, 2012; J. R. Lexchin, 2005). The pharmaceutical industry is a significant contributor to research and development globally. Statista notes that the industry was valued at 1.42 trillion USD by the end of 2021, with 20% of its sales revenue reinvested in research and development (Mikulic, 2022). The industry's contribution to drug research, development, and supply is irrefutably significant for global health and the economy (International Federation of Pharmaceutical Manufactuers and Association, 2022; Mikulic, 2022). North America is the world's leading country in research and new drug development. While Europefollows closely, emerging markets such as China and Korea collectively generate new products (European Federation of Pharmaceutical Industries and Associations, 2022). The European Federation of pharmaceutical industries and Associations (EFPIA) notes that the industry spent 39 600 million euros on research and development in 2021 alone European Federation of Pharmaceutical Industries and Associations, 2022. Despite its invaluable contribution to research and development, employment and global health, some of the pharmaceutical industry's practices have been labelled corrupt (Lewis et al., 2007; J. Lexchin & Lexchin, 2012; J. R. Lexchin, 2005; Lundh et al., 2012; Sismondo, 2021).

According to Transparency International, a leading global agency focusing on corruption prevention, corruption is defined as "an abuse of entrusted power for private gain" (Kohler et al., 2016; Transparency International, 2022). In 2016, Transparency UK published a study on corruption in the pharmaceutical industry (Kohler et al., 2016). They note that corruption in this area may contribute to sub-standard, falsified, ineffective medicines (Kohler et al., 2016).

Multiple scholars over several years have published extensively on the issue of institutional corruption in the industry, citing issues with outcomes bias, suppressed negative data, use of ghost writers, and, more significantly, inappropriate influence on scientists and regulators (Kohler et al., 2016; Lexchin, 2012; Lexchin, 2005; Lundh et al., 2012). Many sponsor organisations faced sanctions and lawsuits when it was independently verified that there was deliberate manipulation or reporting of research data to achieve favourable outcomes (Krumholz et al., 2007; Lexchin, 2012). Scholars have described the industry's influence on medical research and practice as epistemic corruption (Lundh et al., 2012; Sismondo, 2021). He notes that epistemic corruption occurs "when a knowledge system importantly loses integrity, ceasing to provide the kinds of trusted knowledge expected of it" (Sismondo, 2021). Others have noted that industry-funded trials are more likely to publish positive outcomes than non-industry-funded entities. Conflict of interest and bureaucratic inefficiencies may also contribute to or mask corruption. Transparency International UK suggests some core areas of focus to combat corruption. These are:

1) Establishing leadership committed to addressing corruption

   All actors must display a genuine commitment to tackling corruption. Cooperation is key within and between governments, the pharmaceutical industry, global institutions and civil society organisations. This collaboration can be facilitated through the use of multi-stakeholder alliances.

2) Adopting technology throughout the pharmaceutical value chain

   Government agencies must adopt technology to reduce the opportunity for corruption by minimising actor agency and the need for face-to-face interactions. The increased use of digital record keeping facilitates the production and access of records that aids the discovery of corruption

3) Ensuring accountability through increased monitoring, enforcement and sanctions

   Actors in the pharmaceutical sector must be held accountable for their actions. Governments must implement processes to track activities and provide civil society organisations with access to data so they are able to act as watchdogs" (Kohler et al.,2016, p. 36).

Sponsors are responsible for addressing serious adverse events in research where participants may experience life-debilitating harm (Lineberry et al., 2016; US FDA, 2009). The sponsor organization assumes overarching responsibility for the engagement of the research team, including the PI and research monitors. During the last two decades, many sponsors have engaged and established external entities and committees such as contract research organizations (CROs), clinical trials steering committees (CTSCs), and Data Monitoring Committees (DMCs). The CRO's responsibility is to coordinate the clinical trial on behalf of the sponsor, while the DMC assesses trial data for statistically significant risks (Ellenberg, 2008; Fleming et al., 2018). Sponsors also disseminate/publish research results and in the case of successful clinical trials, they invoke proprietary rights to register and market the products (Conroy et al., 2015; Harman et al., 2015; Shuchman et al., 2007).

Contract Research Organization (CRO)

According to US FDA 21 CFR 312.3, a CRO is

> "[…] an independent contractor with the sponsor, one or more of the obligations of a sponsor, e.g., design of a protocol, selection or monitoring of investigations, evaluation of reports, and preparation of materials to be submitted to the Food and Drug Administration" (US Food and Drug Administration, 2022).

The CRO is a growing industry globally and is credited with improving the timeline for clinical trials and reducing human resource costs (Shuchman et al., 2007). The CRO is contracted by and reports directly to the sponsor organizations. The CRO assists the sponsors in a trial's pre-discovery and clinical phases and the investigational new drug or device application process with the regulatory authorities (Shuchman et al., 2007). Challenges that may arise with CROs are discussed further down in this chapter.

Data Monitoring Committee & Clinical Trials Steering Committees

The EMA's guideline on Data Monitoring Committee (DMC) defines this committee as follows:

> "A Data Monitoring Committee is a group of independent experts' external to a study assessing the progress, safety data and, if needed, critical efficacy endpoints of a clinical study. In order to do so a DMC may review unblinded study information (on a patient level or treatment group level) during the conduct of the study. Based on its review the DMC provides the sponsor with recommendations regarding study modification, continuation or termination. Data Monitoring Committees also go under different names like Data Monitoring Board or Data Safety Monitoring Committee". (Board) (European Medicines Agency, 2003, pp. 3-4).

The most significant role of the DMC is the ongoing monitoring of risks in a clinical trial. A DMC is engaged when studies have vulnerable participants, e.g., children diagnosed with life-threatening diseases, and there may be prior knowledge that an investigational treatment/intervention may cause harm (Calis et al., 2017; Damocles Study Group, 2005; EMA, 2003). If the risks are low, the sponsor is not obliged to contract a DMC. The Committee has primary responsibility for evaluating protocol adherence and participant withdrawal/dropout rates (Damocles Study Group, 2005; Ellenberg, 2008; EMA, 2003). These are important indicators of safety issues during the clinical trial that may require intervention. The EMA notes that the DMC ought to make recommendations to the sponsor on whether a trial should be suspended or terminated:

> "Based on the results of the monitoring activities, a central responsibility of a DMC is to make recommendations on further study conduct. Such recommendations include continuing or terminating a trial or modifications to the trial. With regard to the latter, such modifications should not violate the concepts behind the original study protocol. The proper communication of its recommendations is a major responsibility for a DMC" (European Medicines Agency, 2003, p. 5).

Although the EMA outlines this critical responsibility regarding identifying and communicating study risks and recommendations, whether the sponsor accepts and

implements the recommendations is discretionary. In fact, the wording in the guidelines suggests that the sponsor can completely ignore the DMC's recommendations:

> "The implementation of any DMC recommendation is solely the responsibility of the sponsor who is also free to neglect (in whole or in part) the recommendations ofa DMC" (European Medicines Agency, 2003, p. 6).

Calis et al. note that the concept of the DMC was introduced in 1967 (Calis et al., 2017). Subsequently, the US National Institute of Health (NIH) implemented this practice, and like RECs/IRBs, it became commonplace in the clinical research enterprise (Calis et al., 2017). They emphasized that the DMC is in a unique and privileged position to promote objectivity, increase credibility, and reduce bias in clinical trials (Calis et al., 2017). The foremost drive of the DMC is to use its members' expertise in clinical trials and statistical competence as part of the trial quality assurance process (Calis et al., 2017). Ultimately, the committee's recommendations are in the interest of protecting trial participants from harm. An essential characteristic for DMCs to operate optimally would be sponsor non-interferenceand influence. They note:

> "Independence from the trial sponsor is critical for the DMC to fulfil its central role of protecting vulnerable study participants from unpredictable harm that may arise during the course of a trial. Occasionally, this may require unscheduled meetings of the DMC and/or additional analyses without alerting the sponsor or study investigators." (Calis et al., 2017, p. 344).

It begs the question, then, why the EMA guidelines are laissez-faire (relaxed) in the wording regarding the recommendations? On the one hand, the DMC is a crucial independent expert assessor of clinical research safety, but conversely, the sponsor is free to neglect – in whole or in part, the recommendations of the DMC. The authors provide recommendations for best practices for DMCs (Calis et al., 2017). They suggest there should the written procedures for the interactions between the DMC and the Sponsor. Although it is entirely up to the sponsor to accept or reject the recommendations of the DMC, they argue that disputed DMC reports should be sent "promptly" to the IRB or Regulatory agency so they "may reach their independent conclusions and act accordingly within their respective authorities" (Calis et al., 2017, p. 346).

Fleming et al. support the need for what they describe as a mediator when there is a disagreement between the DMC and the sponsor (Fleming et al., 2018). They argue that this would benefit the sponsor's reputation regarding a trial's "science and ethics" (Fleming et al., 2018, p. 325). Unlike Calis et al., they do not indicate that the mediator should be the IRB or Regulators. It could be inferred that the authors were not confident that the FDA would take action. This assertion is based on several examples cited in the article discussing the US FDA's lack of action in a clinical trial after acknowledging that they were compromised (Fleming et al., 2018). Instead, they recommend industry agencies such as Pharmaceutical Research and Manufacturers of America and Public Responsibility in Medicine and Research (PR&MR) (Fleming et al., 2018). Another possible reason for this could be their cited concerns that members of DMCs may fear litigation for breach of confidentiality agreements (Fleming et al., 2018). What is common in the literature is that the DMC is a vital part of the clinical trial enterprise and perhaps should be independent of the sponsor's influence, especially when there is disagreement in implementing recommendations. The authors give

examples of the DMC role in trials for cardiovascular and oncology patients because of the high risk of harm. Calis et al. note:

> "DMCs have an important and unique role in trial oversight that is substantially distinct from institutional review boards, ethics committees, or trial steering committees, which do not see unblinded interim results." (Calis et al., 2017, p. 347).

In some jurisdictions, the DMC reports findings to a clinical trials steering committee (CTSC) authorized to make decisions on behalf of the sponsor regarding the continuation of a trial (Daykin et al., 2016; Harman et al., 2015). The CTSC usually comprises the PI plus two or more independent persons with varying expertise and clinical trial experience (Conroy et al., 2015; Daykin et al., 2016; Harman et al., 2015). While not all clinical trials may require a DMC, a CTSC is usually recommended. The purported role of the CTSC is quality assurance (Harman et al., 2015). Daykin et al. note that CTSCs may perceive themselves as advocates for the research participants (Daykin et al., 2016). Unlike the DMC, the CTSC is not allowed to review unblinded results (Conroy et al., 2015; Daykin et al., 2016). Still, the reports from the DMC, especially when there are risks of harm to participants, are reviewed by the CTSC. The CTSC would then decide or submit its recommendations to the sponsor (Conroy et al., 2015; Daykin et al., 2016). Harman et al. highlight ambiguity in the characterization of the CTSC. They also note that true independence is a challenge and the ability of the committee to identify and contextualize ethical issues (Conroy et al., 2015). They also report a lack of sufficient experts who can be truly independent and a lack of training. A sponsor organization usually establishes a trial steering committee as an independent committee to review DMC reports (Conroy et al., 2015).

2.2.3 Research Ethics Committees

Research Ethics Committees or Institutional Review Boards (IRB) came about in the 1950s at various US academic institutions, then formally established at the National Institute of Health (NIH) by James Shannon in 1964 (Moon & Khin-Maung-Gyi, 2009; Rice, 2008). The genesis of REC/IRB was an internal mechanism for reviewing research funded or conducted by NIH investigators. By 1966, the practice of ethics prospective review expanded nationwide. The expanding practice may be attributed to the US Surgeon General, who issued a memo to recipients of US Public Service grants. The memo notes that for grant recipients to be awarded new PHS grants for clinical research, applicants' institutions had to provide a prior review…

> "[…] of the judgment of the principal investigator in terms of the rights and welfare of the individual of the appropriateness of the methods used to secure informed consent, and of the risks and potential medical benefits of the investigation" (Hedgecoe, 2009, p. 335).

Since the US publicly funded grant holders were located globally, over time, other regions, such as the United Kingdom, began to establish ethics committees similar to what was established by the NIH (Hedgecoe, 2009). The prospective ethics review process became the means of independent review of the researcher's protocols before the commencement of the

research. Subsequently, the WMA codified the practice in its Declaration of Helsinki, which says:

> "All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation" (World Medical Association, 2018).

ICH: GCP requirements also note that all research should receive prior approval by an independent ethics committee (International Conference on Harmonization, 2018). With the adoption of GCP guidelines into legislation and policy of regulatory agencies in various countries, the prior review of research is now very commonplace for managing clinical trials.

2.2.4 Regulatory authorities

Regulators in clinical research trials have the significant task of setting standards through legislation and guidelines and enforcing these standards. According to the US Office for human research protections' international compilation of human research standards, there are over 1000 global research standards globally (U.S. Department of Health and Human Services, 2020). Enforcement may be in the form of education, inspections, warnings, and issuance of sanctions. In clinical research, particularly clinical trials, the ICH: GCP is one of the primary harmonizing documents for clinical research and an essential reference for regulatory agencies (Otte et al., 2005; Vijayananthan & Nawawi, 2008; WHO, 2005). GCP inspections are crucial to the identification of violations of protocols. Policymakers from the European Union, Japan, and the United States conceptualized the ICH: GCP guidelines with contributions from Australia, Canada, and the Nordic countries (Otte et al., 2005; Vijayananthan & Nawawi, 2008). However, the global landscape of clinical trials created a greater need for harmonizing regulatory standards. Subsequently, the World Health Organization published similar Good clinical practices and other guidelines for clinical research adopted by individual countries.

Drug Regulators approve new pharmaceutical agents and devices and issue marketing authorizations and recall in the interest of public health. The two leading regulatory agencies of focus in this thesis are the U S Food and Drug Administration (US FDA) and the European Medicines Agency. The US FDA, one of the first regulatory authorities, was established in 1906 (Nasr et al., 2011; US Food and Drug Administration, 2018). The agency was initially named the Bureau of Chemistry, then the Food, Drug, and Insecticides Administration (Nasr et al., 2011; US FDA,2018a). The current name was assigned in 1931 (Nasr et al., 2011; US Food and Drug Administration, 2018). The European Medicines Agency was established in 1995 to harmonize the authorization of new medicines in the EU (European Medicines Agency, n.d.). These two agencies are highly influential globally. The mandate of these regulatory agencies is to evaluate the safety and efficacy of medications approved for use by citizens in EU member countries and the USA (European Medicines Agency, n.d.; US Food and Drug Administration, 2018). The two agencies are guided by their respective legislations.

2.2.5 Other stakeholders

Several stakeholder organizations have evolved within the clinical research enterprise. Some provide normative guidance, others focus on harmonization, and some work closely with the sponsors and PI to ensure quality assurance, education, and general management of clinical research.

Normative and quality assurance agencies

Some normative agencies include the World Health Organisation (WHO) and its subsidiaries, The United Nations Educational, Scientific and Cultural Organization (UNESCO), the World Trade Organisation (WTO), the World Medical Association (WMA), the Council for International Organizations of Medical Sciences (CIOMS), and the International Council for Harmonization of technical requirements for pharmaceuticals for human use (ICH). Regional and local stakeholders include training and accreditation bodies, research integrity organizations, and data protection agencies. Stakeholders generate guidelines for harmonized research governance and enable cooperation between countries. As mentioned earlier, the two main guidelines for clinical research are DoH and the ICH: GCP. However, depending on the region or jurisdiction, the various agencies have varying authority and influence on clinical research.

Patient organizations

A vital stakeholder is a patient organization. According to the EMA, patient organizations are:

> "Not-for-profit organisations which are patient-focused, whereby patients and/orcarers (the latter when patients are unable to represent themselves) represent a majority of members in governing bodies" (European Patients Forum, 2022).

Deidre O'Connell et al. note that patient organisations are involved in "training initiatives, the administration and conduct of research, and lobbying for increased funding" (O'Connell & Mosconi, 2006). Patient organisations have grown significantly over the past 80 years (European Patients Forum (EPF), 2022). Their influence is significant in providing advocacy in seeking new treatments for diseases such as cancer and leukaemia trials and developing treatments for rare diseases (European Patients Forum, 2022; O'Connell & Mosconi, 2006). Patient organisations engage sponsors and regulatory agencies to provide a perspective reflecting the patient's real-life experiences in clinical trial development and post-authorisation phases. The EMA and the US FDA established a patient forum cluster in 2016 (Srijanee, 2016). A significant milestone indicating the influence of patient organisations is the successful lobbying for the Right to Try Act in the USA (US Food and Drug Administration, 2020).Unquestionably, patients and patient organisations are essential stakeholders in clinical trials. However, scholars have raised awareness and concerns regarding the potential lack of transparency in the operations of these organizations (Fabbri et al., 2020; Roennow et al., 2020). Patient organisations work closely with sponsors and receive funding (Karas et al., 2020). The main challenge was the potential conflict of interest in the absence of transparency and proper reporting and disbursement of funds (Fabbri et al., 2020; Karas et al., 2019).

2.3 Challenges after the approval of clinical trials

2.3.1 Ethical issues at the early phase of clinical trials – Outsourcing, recruitment, inducements

Recruitment of sufficient trial participants is essential to the success of a clinical trial. For this reason, many sponsor organizations have outsourced this critical task (Shuchman et al., 2007). Contract research organizations (CROs) are a very profitable industry because of their ability to attract and retain trial participants on behalf of pharmaceutical companies (Shuchman et al., 2007). Miriam Shuchman outlines what she describes as a CRO Boom-the rise of the industry but with questionable ethics and accountability. She gives several examples where CROs operate facilities that exploit financially vulnerable participants, ignore severe adverseevents reported by participants, and employ inadequately trained personnel (Shuchman et al., 2007). Shuchman cites incidents where CROs identified and reported fraud and adverse events to sponsors who failed to act. This raises the vital consideration of independence of oversight and accountability. The key strategy attributed to the success of CROs is the ability to complete clinical trials in a shorter timeline and at a lower cost than sponsors (Shuchman et al., 2007). Despite the obvious economic benefits of CROs, it is claimed that the "commodification" of research projects has begun "to kill" clinical research (Shuchman et al.,2007)). Schuchman highlights that CROs are data-driven as "everyone is very focused on the data" rather than on the totality of the knowledge required to determine whether a drug is worth pursuing further (Shuchman et al., 2007).

As discussed earlier, sponsors engage DMCs if study risks are high and require additional monitoring. Like CROs, DMCs play an essential part in trial oversight-However, this is limited to data analysis, and questionable findings are reported to the sponsor (Ellenberg, 2008; Fleming et al., 2018). Although guidelines for DMCs require that members declare a conflict of interest, especially if they have a financial stake in a company, the organizations have been scrutinized for bias and lack of actual independence (Fleming et al., 2018; Sydes et al., 2004). Like the CRO, DMCs report to the sponsor, not the REC/IRB or RA. Drazen and Wood highlight this challenge in their editorial, citing examples of when the DMCs could not execute their functions because of sponsor interference (Drazen & Wood, 2010). While acknowledging that the DMC play a critical role in managing trial data by assessing, identifying, and recommending when a study should be terminated, they note examples of sponsor interference that compromised the achievement of the stipulated objectives (Drazen & Wood, 2010). When DMCs cannot carry out their responsibilities adequately due to conflicts of interest, further reflection is needed on coping with these challenges. Indeed, the engagement or convening of entities/committees to create independence from the sponsor does not mean an absence of conflicts or interference. If these entities/committees are compromised, it only causes more challenges with answerability by creating distance between the sponsor and the actual study participants (Damocles Study Group, 2005; Drazen & Wood, 2010; Fleming et al., 2018).

Another controversial challenge in clinical trials is inducements. Some ethicists argue that incentives in research are fair compensation for participants (Denny & Grady, 2007; Dickert, 2009; Grant, 2002). However, there are concerns by others that financial incentives may impair the judgements of research participants, especially those who are economically

constrained (Denny & Grady, 2007; Grant, 2002; Walker et al., 2018). The ICH: GCP guidelines address inducements as an ethical consideration to be assessed by the REC/IRB. However, IRB/REC review has been on the amount paid to research participants and less on the socioeconomic situation of the participants. This was highlighted in a series of publications, culminating in a book on the ethics of phase one studies and the vulnerabilities of research participants, especially health volunteers (Fisher, 2020; Walker et al., 2018). When a REC/IRB reviews a protocol, the goal is to ensure that payments to research participants do not cause exploitation. Recently, more focus has been on healthy volunteers and exploitation possibilities (Johnson et al., 2016; Karakunnel et al., 2018). Fisher notes that many health volunteers in her US-based study were from ethnic minorities or ex-convicts with challenges being employed (Fisher et al., 2018). Fisher notes:

> "US Phase I trials are fundamentally built upon and shaped by social inequalities, and the resulting system exploits participants to make pharmaceutical products appear safer than they really are" (Fisher, 2020, p. 11).

Inducement is acknowledged as an ethical challenge that may impede research participants from making decisions and acting in their best interests (Denny & Grady, 2007; Grant, 2002; Groth, 2010). Williams and Walter note that there is a fine line between coercion and undue influence (Williams & Walter, 2015). Undue influence occurs "when the compensation or incentive is sufficient to induce prospective participants who otherwise would not enrol to enter studies in which there might be significant risks" (Williams & Walter, 2015, p. 1117). However, inducement must be distinguished from compensation, which is acceptable based on the ethical principle of justice as long as the benefits outweigh the risks (Grant, 2002; Permuth-Wey & Borenstein, 2009). Incentivising research is a delicate balance in which the REC/IRB plays a critical role. The appropriateness of incentives is assessed mainly during the prospective review (US FDA, 2018b). It would be essential to consider the opinions of RECs/IRBs on what is paid to the research participants and the socio-economic background of recruited participants. Walker et al. argue, "Traditional biomedical research oversight offers inadequate ethical and policy guidance for phase 1 health volunteer research." (Walker et al., 2022, p. 1).

They propose five ethical criteria: "translational science value, fair opportunity, burden sharing, fair compensation for service, experiential welfare, and enhanced voice and recourse" (Walker et al., 2022, p. 6). Explaining each criterion, they sought to expound on the benefits for healthy volunteers. To remain focused on the scope of this thesis, I will refrain from an extensive discussion on each criterion but briefly emphasise experiential welfare, enhanced voice and volunteers. These terms stress trial site conditions and the empowerment of research participants to share their "concerns regarding their experiences" and have "direct recourse for wrongful treatment or harm" (Walker et al., 2022, p. 6). Of the five criteria outlined, these would require post-approval activities in the form of site visits and complaints mechanisms (Walker et al., 2022).

2.3.2 Weak ethics oversight and international research

Ethics dumping and helicopter research are terms used to describe the challenges of international research, particularly in LMICs with lax regulatory and ethics governance and insensitivity to cultural norms (Adame, 2021; Schroeder, 2021). In response, some research funders, such as the EU, have adopted codes of conduct for international research (Schroeder et al., 2018; Schroeder, 2021). While many global research issues can be addressed in the prospective review, there is a growing concern that active follow-up or research monitoring is also critical (Hunter, 2014). Brown et al. have raised the question of post-approval monitoring for US IRB-approved research (Brown et al., 2014). They recommend using technology to facilitate remote monitoring to maintain quality (Brown et al., 2014). Doris Schroeder et al. document ethics dumping and its implications in LMICs and suggest an ethics framework to address these issues. Although global awareness is increasing, there is still the need to strengthen regulatory oversight capacity in LMICs (Schroeder et al., 2018; Schroeder, 2021).

2.3.3 Ethically relevant protocol deviations and violations

Several publications highlight that despite a highly regulated clinical research industry directed by many legislations, guidelines, and systems, there are unaddressed protocol violations of ethical relevance at the end of some clinical studies on human subjects. A protocol violation is defined as:

> "A divergence from the protocol that **materially** (a) reduces the quality or completeness of the data, (b) makes the Informed Consent Form inaccurate, or (c) impacts a subject's safety, rights, or welfare" (Bhatt, 2012, p. 117).

Arun Bhatt distinguishes violations from deviations. "Deviations are activities on a study that diverge from the Institutional Review Board-approved protocol" (Bhatt, 2012, p. 117). However, these are usually not considered critical or consequential to the study's findings but may compromise the research process's integrity (Bhatt, 2012). The line between violations and deviations is, at times, blurred. There are examples of protocol violations that are not immaterial enough to be classified as a deviation yet not significant enough to be classified as a sufficiently serious breach hence left unaddressed by the GCP inspector (Bernabe et al., 2019a; Bernabe et al., 2019b; Seife, 2015). Bernabe et al. refer to these as relevant (ERF) protocol violations. They report that the 4014 GCP inspection reports for 2008 - 2012, 1452, could be considered ethically relevant (Bernabe et al., 2019a, 2019b). The GCP inspectors categorized the non-compliance findings as critical, major, or minor. Bernabe et al. report that most ERFs belong to the major category (Bernabe et al., 2019a, 2019b; Bernabe et al., 2016).

A follow-up study to identify what regulators do about ERFs revealed that these non-compliance issues were not considered relevant in the product deliberations for European marketing authorization (Bernabe et al., 2019a). This failure to take action could be construed as treating the identified violations as irrelevant. Alternatively, it could be postulated that in the grand scheme of things, after significant investments into clinical research, these deviations from the approved protocol may not be sufficient reasons to prevent a product from getting marketing authorization. This could be argued as pragmatic

and reasonable from a purely utilitarian perspective. However, should regulators continue to ignore these ethically relevant violations?

These overlooked violations are incongruent with the normative arguments presented to the scientific community, research participants, and the wider society that products placed on the market (made available to the public) have satisfied all legal and ethical requirements. Many identified protocol violations could be argued to be a matter of research integrity (issues with the PI/Sponsor) and not so much research ethics (regulation of the research process and protection of research participants). Primarily when the regulators identify, report and take action as deemed necessary. However, what is fundamental to the preceding study by Bernabe et al. for consideration is that there exist situations that would be categorized as unethical but do not breach any strict regulations. As such, no action is taken. This is a lacuna (Bernabe et al., 2019a; Bernabe et al., 2019b). Zarin and Tse, in an article addressing protocol deviations such as "unacknowledged changes to the primary outcome measure" argues that "trust us is not good enough (Zarin & Tse, 2013, p. 66). They note "in the face of serious concerns about the quality and validity of the medical evidence base, physicians and patients deserve better" (Zarin & Tse, 2013, p. 66) They argue for registration of protocols to facilitate open scrutiny by comparing the between the initially approved protocol against what is published in the results of the trial (Zarin & Tse, 2013).

2.3.4 Questionable regulatory approvals and diminishing trust in drug regulators

So far, I have shared some challenges with ERFs at the end of the clinical trials, a lack of independence of outsourced contractors and committees, and exploitation of vulnerable persons. It is essential to underscore that stakeholders have different goals; for the sponsors, the overarching goal is to make a profit. While there is a contribution to knowledge generation and public health, sponsor organizations are primarily businesses. After significant investments in a product, the expected end is to ensure that product reaches the market. Any attempts by regulators to address challenges may delay the process from discovery to market.

Consequently, governance agencies such as RECs and RAs face criticisms of bureaucracy from sponsors and patient organizations (Greener, 2009; Gribben et al., 2020). In response to this criticism, regulators have tried cultivating a more research-friendly environment for sponsors. However, at what cost? In 2021, Nature published an editorial, "a carte blanche approval in Alzheimer's" (A carte blanche approval in Alzheimer's, 2021). This editorial raised concerns about the approval process of the biopharmaceutical drug, Aducanumab. The US FDA approved the drug against the advice of its scientific advisory committee. The drug showed marginal benefit and has a high risk of brain swelling at high doses (A carte blanche approval in Alzheimer's; Mahase, 2021). The projected annual cost for a patient was 56000 USD (A carte blanche approval in Alzheimer's, 2021). This raised concern about one of the world's most recognized regulatory agencies giving way to external pressure to authorize new products. The Editorial queried whether approving a questionable drug is a signpost for the future. The European Medicines Agency has not approved the drug due to the company's inability to prove its efficacy in treating early-stage Alzheimer's (Mahase, 2021).

This controversy occurred during the COVID-19 pandemic when there was much furore about vaccines and treatments for COVID-19. Scientists and the wider society openly challenged regulators' authority (Front Line Covid-19 Critical Care Alliance, n.d; Reich,

2021; Scott, 2021).Since a pandemic is not an ordinary situation, the examples from the pandemic may be considered an anomaly. Another example of questionable approval arose with the drug Amylyx. This drug was approved without sufficient clinical data to support its use. The USFDA was scrutinized for how much weight it should give to patients and other outside voices (Mullard, 2022).

Charles Seife, who did a cross-sectional analysis of publicly available clinical trial documents between 1998 and 2013, highlights a lax US FDA governance of clinical trials. He found what he described as "significant evidence of objectionable conditions or practices" identified by the US FDA (Seife, 2015, p.567). Onakpoya, Heneghan, and Aronson report a global increase in drug recalls due to adverse drug reactions and, at times, death. Although drug recalls are a regulatory mechanism to address reports of unsafe medical products, the implications for science, industry, and, most significantly, the public is significant and far-reaching (Onakpoya et al., 2016a, 2016b). They note:

> "The removal of previously approved products from the market can result in a loss of confidence in medicines by the public, loss of effective compounds (i.e. effective for treating the specific indication but for which the benefit-to-harm balance was considered unfavourable), and loss of revenue for drug manufacturers" (Onakpoya et al., 2016a, pp. 1-2).

While reducing bureaucracy is an important consideration, when there are financial gains from research that involves human subjects, the exploitation of vulnerable persons must be of significant concern. Subsequently, any highlighted gaps should be addressed to ensure the research enterprise does not merely appear to be ethical but is, in fact, ethical. One of the challenges is that many exploits are discovered long after the product has been approved for sale. Consequently, the benefits are so great in terms of the number of persons that it presents a challenge to address any misadventure for an individual or minority group. How does one applying the utilitarian principle, deny approval of a drug that can benefit millions or save lives? There was an accepted norm for emphasizing the risk-benefit assessment of finished drug products during the marketing authorization process. However, there appears to be a shift with the recent questionable approvals. If regulators make decisions based on external pressures and not on sound clinical data, could clinical research take a retrograde step? Moreover, if yes, which of the stakeholders in the clinical research enterprise would be sufficiently independent and less susceptible to conflicts of interest to address this situation? Is this a regulatory or ethical situation? Somebody could argue that acting in the patient's best interest is the remit of the REC/IRB. Addressing this situation may be outside the purview of the regulators since the regulators are demonstrating a propensity to deviate from established norms. What are the reasonable ways to address this lacuna? Is it fair to assert that assessment of ethics in clinical trials ought to be throughout the entire drug development process and redress entrenched in law so that governance in research occurs from discovery to market and not simply handed over to the Regulators?

2.3.5 Ethical issues with gene therapy and advanced technologies

The examples of ethical challenges in the clinical research enterprise cited earlier are predominantly chemical drugs. However, technological advancement has impacted clinical research and medical interventions. One breakthrough was CRISPR/Cas (Clustered regularly interspaced palindromic repeats/CRISPR-associated enzymes) (Zhang & Baohong Zhang, 2021). This technology allows scientists to explore and conduct medical experimentation through genetic splicing and manipulation. Scientists and Ethicists have lauded the possibilities but warned of safety implications beyond our reach if not managed appropriately. To this end, research on the human germline was prohibited (Brokowski & Adli, 2019).

Nevertheless, two cases in recent history highlight the importance of oversight in this developing field. The first is the case of Jesse Gelsinger, an 18-year-old who participated in a trial to treat a metabolic disorder-ornithine transcarbamoylase (OTC) deficiency (Rinde, 2019). Jesse was enrolled in the trial at the University of Pennsylvania and received a corrective OTC gene (Rinde, 2019). He died within four days of receiving the injection. The family sued the researchers based on inadequate informed consent (Dettweiler & Simon, 2001; Savulescu, 2001). This case led to the FDA's nationwide investigation of gene therapy trials across the USA. In response to this unintended death, the FDA established the Gene Therapy Clinical Trial Monitoring plan, emphasizing the post-approval monitoring aspect of the trials (Stephenson, 2000; US FDA, 2020). The other example is Dr He Jiankui, a Chinese researcher who created the first gene-edited baby. Gene editing on the germline is considered illegal and unethical. Although sanctions were meted out to him in fines and incarceration, scientists are still deliberating on the implications of editing the germline. He was also banned from doing any work in biotechnology. Commentators note the need for strengthening research governance in China (Cyranoski, 2020; Roskams-Edris et al., 2019).

Hirsch et al. emphasize that:

> "[…] an ethics review process must be efficient, not necessarily blocking the innovative project cycle but still having enough strength to stop it at any point in time in case any violation of the agreed ethics norms and principles is detected" (Hirsch et al., 2019, p. 5).

He cites the EU ethics monitoring process that allows the EU Commission to "closely monitor project implementation and possibly stop the project process at any time in case the ethical dimensions of the project are not respected" (Hirsch et al., 2019, p. 6).

Genome editing using advanced technologies such as CRISPR provides novel treatments for complex diseases (Attarwala, 2010). Novel and emerging technologies, including the increasing use of artificial intelligence and man-machine interfaces, present unique challenges that prospective review may not adequately address. In response to the existing and anticipated challenges, the WHO and UNESCO have established expert committees to draft recommendations for artificial intelligence governance and human genome editing. Regarding genome editing, the WHO notes the following:

> "The technology of human genome editing can expand human knowledge, improve human health and contribute to both collective well-being and the common good. To

> maximize the positive impact and minimize the potential harms of this technology, procedural and substantive values and principles should guide policies and practices”(World Health Organization, 2021b, p. 12).

The Committee recommends a governance framework requiring the requisite technical expertise to consider the legal, ethical, and social implications. Regarding AI, emphasis is placed on protecting human rights –well-being, safety, the public interest, respecting persons' right to privacy, inclusiveness and equity, and transparency (World Health Organization, 2021a, 2021b). The WHO also notes that governments ensure that research ethics committees review and approve clinical trials using these technologies (World Health Organization, 2021b). Additionally, local ethics guidelines should be updated to facilitate the registration of these trials and ongoing monitoring.

2.4 Summary

The clinical research enterprise is becoming more technical, and governance is more complex. While the benefits of clinical research are important for society, the risk of harm, exploitation, and injustice are integral ethical factors of consideration. Research governance structures should continue to be strengthened to respond adequately to the various ethical challenges that may arise. Throughout this literature review, I have shared historical and recent examples of PIs/sponsors that deviate from the approved ethical standards during the research process, stakeholders such as DMCs with conflicts of interest, and RAs making questionable decisions that may not be in the best interests of patients and society. Irrefutably, prospective reviews by RECs/IRBs do not adequately address all these gaps within research governance. REC/IRB post-approval follow-up has been deliberated in research ethics for many years. Some jurisdictions, such as the United States, are ahead in implementing measures for this type of research oversight. Nevertheless, many cited examples of digression from acceptable ethical standards are from the USA. Hence, it would be difficult to assert that REC/IRB oversight is the only solution.

CHAPTER THREE

THEORETICAL ELABORATION AND CONCEPTUALIZATION

Overview

Earlier it was established that clinical research involves multiple stakeholders with various roles and responsibilities. Some of which overlap. A fulsome discussion on the post-approval role of RECs would be difficult without demonstrating the relationship with other stakeholders and carefully highlighting the individual roles in the research enterprise to identify how they interact to achieve the collective goal. To this end, consideration was given to the fact that an empirical normative framework is necessary to address the research question adequately. Consequently, several theoretical perspectives informed and guided this thesis's approach and data analysis.

This thesis integrates role concepts – expectations, identity, and behaviours within the collaborative social enterprise of clinical research. Given that the overarching objective at the outset of the project is to seek an answer to the question of whose responsibility it is to address issues of ethical concern in clinical research, a role theory framework is considered relevant. This theory elucidates the REC/IRB's role expectations, identity, and behaviours. The normative approach is an ambitious adaptation of Seumas Miller's teleological individualistic approach to social institutions. Miller's theoretical model enables the contextualizing and discussing of research findings. This teleological account will be supported by Alex London's arguments for a new approach to considering the philosophical foundations for research ethics. Finally, the thesis is buoyed by the methodological philosophies of hermeneutics and phenomenology under the umbrella of empirical bioethics. These will be discussed in the methodology chapter.

3.2 Role theory and its related concepts

Bruce Biddle describes role theory as "the study of roles, or patterns of behaviour characteristic of persons and contexts." He organizes the theory into 1) parts or identities that social participants assume), 2) scripts or expectations for behaviours that are understood by all, and 3) patterned and characteristic social behaviours." Role concepts may therefore be analyzed based on social status (positions/identity), expectations (beliefs), or behaviours (actions) (Biddle, 1979, p. 20).

Biddle notes that roles are "shared normative expectations that prescribe and explain behaviours" or expected behaviour based on an associated social position (Biddle, 1979, p.20). Roles are either prescriptive (functional or structural)-shared understanding of expectations or learned through social interaction- a phenomenon identified as symbolic interactionism (Biddle,1986). Biddle notes that although role theorists' empirical research should focus on the origin,dynamics, and effects of roles, social positions, and expectations, the interest has been on practical questions and concepts. He discusses role concepts (expectations, identity, and behaviour) within five perspectives in role theory. These are 1) functional role theory, 2) symbolic interactionists, 3) structural role theory, 4) organizational

role theory, and 5) cognitive role theory (Biddle, 1986). However, since this thesis is not sociological, the discussion of role theory and its related concepts will serve only as the frame.

Biddle notes that the following propositions underpin the application of role theory:

1. Role theorists assert that some behaviours are patterned and are characteristic of persons within contexts (i.e., form roles)
2. Roles are often associated with sets of persons who share a common identity (i.e., who constitute social positions)
3. Persons are often aware of roles, and to some extent, roles are governed by the fact of their awareness (i.e. by expectations)
4. Roles persist, in part because of their consequences (functions) and because they are often imbedded within larger social systems.
5. Persons must be taught roles (i.e., must be socialized) and may find either joy or sorrow in the performances thereof (Biddle, 1979, p. 8).

Extracting from the above propositions, assumptions were made about the data for the analysis, discussion, and recommendations regarding RECs/IRBs: The common identity (social position) is the relationship on or with the research ethics committee. Using qualitative research approaches, our endeavour sought to pinpoint expectations of REC/IRB and related functions within the clinical research enterprise. We also explored what REC/IRB members considered their post-approval roles, whether their role perceptions were legitimized (e.g., laws, training), and to identify some patterns, if any, in behaviours (practice) regarding conformity (or lack) to the expected role.

3.2.1 Role Expectations

Biddle's discourse on role expectations focuses on persons and statuses, which he describes as a "statement that expresses a reaction about a characteristic of one or more persons" (Biddle, 1979, p.119). He further explains that expectations consist of "subject-held or emitted statements that express a modal reaction about characteristics of object persons" (Biddle, 1979, p.132). He categorizes expectations as overtly expressed (enunciations), covertly expressed, and written (Biddle, 1979, p. 132). Examples of overt expressions are testimonies, usually verbal conversations regarding behaviour. Sometimes this is in the form of denouncements or approval of a behaviour. Covert expectations are usually observed actions but not verbalized. Written expectations are self-explanatory; one example is rules oflaw or journalistic accounts. Written expectations are the easiest to study; however, overt expectations may be captured in a recording such as an interview (Biddle, 1979). He summarizes the various expectation modalities and forms in the table below:

TERMS FOR EXPECTATIONS[2]

EXPECTATIONAL MODES	EXPECTATIONAL FORMS		
	Conceptions (covertly held)	Enunciations (overtly expressed)	Inscriptions (written)
Prescription	Norm	Demand	Rule
Cathexis	Preference	Assessment	Appraisal
Description	Belief	Assertion	Representation

Table 1.0 Biddle's Role expectational forms and modes (Biddle, 1979, p. 132)

Although Biddle focuses on personal role expectations, the modalities and forms may be adapted to study social institutions. For this project, we chose to focus on the prescriptive (norm, demand, rule) and descriptive (belief, assertion, representation) expectation modes in the forms of enunciations (overtly expressed in interviews) and inscriptions – that which are detailed in legislative documents, declarations, guidelines, and scholarly articles. Conceptions were explored in a very limited sense, as observations would require more significant resources. Role consensus occurs when two or more persons share or hold compatible expectations. Dissensus happens when two or more persons do not share comparable expectations (Biddle, 1979, p. 195).

3.2.2 Role Identity

Social psychology scholars, Stryker and Burke, note that identity theory is an outgrowth of role theory and is most related to symbolic interactionism, a role perspective posited by George Mead (Stryker & Burke, 2000). Stryker and Burke succinctly describe Mead's symbolic interactionism as "society shapes self-shapes behaviour" (Stryker & Burke, 2000, p. 285). They share three usages of identity: 1) culture, 2) common identification with a collectivity or social category, or 3) references to parts of a self, composed of meanings that persons attach to multiple roles they play (Stryker & Burke, 2000, p. 285). One approach in identity theory is to examine how "social structures affect the structure of self and how the structure of the self- influences social behaviour" (Stryker & Burke, 2000, p. 285). A second approach is to examine "the internal dynamics of self-processes as they affect social behaviour" (Stryker & Burke, 2000, p. 286). Stryker and Burke focused much of their work on the first approach, looking at the external social structure and the relationship with the individuals. They note that:

[2] Biddle defines norms as privately held prescriptions. Preferences as private reactions to characteristics. Belief assess human characteristics against the criterion of subjective probability. Demands, assessments, and assertions are overtly enunciated forms of expectation. Rules are prescription forms of inscriptions and appear in law, in manuals of etiquette, or in job description in industry. Appraisals may be in a review and representations included all attempts to describe human characteristics in literate records such as newspaper accounts and histories (Biddle, 1979, p.132-133).

> "[…] social roles are expectations attached to positions occupied in networks of relationships; identities are internalized role expectations…role choices are a function of identities so conceptualized, and that identities within self are organized in a salience hierarchy reflecting the importance of hierarchy as an organizational principle in society (Stryker & Burke, 2000, p. 287).

The main point of consideration is the relationship between role perception (identity) and the direct influence on role commitment (behaviours). Consequently, Stryker and Burke modified Mead's phrase to "commitment shapes identity salience shapes role choice behaviour" (Stryker & Burke, 2000, p. 286). The authors expounded the work of Burke and Reitzes on what they call "shared meanings," noting this as the link between identity and behaviour. They argue that role is external and linked to social positions within a social structure while identity is internal- *internalized meanings and expectations associated with a role* (Stryker & Burke, 2000). Social structure is thus defined as "interconnecting positions and associated roles, linked through the activities, resources, and meanings that are controlled mutually or sequentially" (Stryker & Burke, 2000, p. 289).

Applying the preceding to this project would require bearing in mind additional sociological concepts such as authority, legitimacy, and consensus. Acknowledging the research enterprise as a social structure enables one to identify how RECs situate within this network and subsequently strive to understand how stakeholders, particularly REC members, identify- that is, express shared meanings attendant to such a role. Biddle notes authority as one of several criteria for acknowledgement of role status. Authority is essential because it legitimizes the degree to which others follow the dictates of position members (Biddle, 1979).

Legitimacy is "a belief that a rule, institution, or leader has the right to govern" (Hurd, n.d., para. 1). Ian Hurd notes that legitimacy exists only in "the beliefs of an individual about the rightfulness of rule" (Hurd, n.d., para.4). Legitimacy, he concludes, impacts society as it has collective effects when shared widely in the community. He references Tom Tyler's assertion that "social regulation is more difficult and costly" if authorities are not considered legitimate (Hurd, n.d., para.2).
Therefore, a practice can be authorized by law or other policy but still not widely accepted as legitimate (Hurd, 2022). This is a crucial consideration to explore any apparent disconnect between written expectations not demonstrated in behaviours or widely incorporated in practice. Hurd emphasizes that compliance is not congruent with legitimacy:

> "[…] compliance with rules is not evidence that the rules are seen as legitimate, and non-compliance is not evidence against legitimacy. There are many reasons that actors might comply with sources of authority, legitimacy being only one of them. It is an internal condition of belief whose existence is not directly observable. The second problem is that actors have an incentive to portray their rule as legitimate and challengers to that rule have an incentive to portray it as illegitimate" (Hurd, n.d.,para.3).

This is not an assertion that a lack of consensus in role identity would solely be based on a lack of legitimacy. However, this brief insertion only highlights that this concept is an important and relevant consideration, especially as we examine the various stakeholders in clinical research and the dissensus that perpetuates the role of the REC/IRB.

3.2.3 Role Behaviours

Role behaviours are the overt actions or performances that may be observed and characterize the persons observed (Biddle, 1979). This role concept is fundamental. It is what is done or not done based on internalized role expectations (Biddle, 1979, 1986). This project did not examine role behaviour because its primary objective was to explore the role of RECs/IRBs, a question more suited for role expectations and identity. However, to a limited extent, questions were developed to identify what RECs/IRBs representatives say they do after they approve clinical trial protocols. To this end, any identified role behaviours would not be from direct observations. Biddle argues that although possible, the study of role behaviour has challenges (Biddle, 1979, 1986). This concept is essential because role conformity or compliance is based on comparing expectations with actual behaviour. Therefore, it is critical to understand behaviours to identify challenges and make recommendations. As noted earlier, much of Biddle's work is based on individual role identities, expectations, and behaviours and less on social institutions. However, the explication of the various role concepts serves only as a frame for this thesis to enable a structured reporting of the findings, a context-specific discussion, and recommendations for further studies. Another essential theoretical claim for this study was acknowledging the clinical research enterprise as a social institution.

3.3 Research enterprise as a social institution

Suemas Miller notes that an institution is "an organization or system of organizations that consists of an embodied (occupied by human persons) structure of differentiated roles" (Miller, 2019, p. 6). Miller describes a teleological account of social institutions theory. He notes that one can examine the normative role of institutions if one scrutinizes the collective end and the interconnectedness of the various players within that institution (Miller, 2019). Miller claims that if social institutions individually have specific roles that are joined with each other to achieve a collective end, which is a collective good, then this creates duties and rights and, as such moral responsibilities (Miller, 2010, 2019). However, he notes that although the joint effort of the individual organizations achieves a collective end, each role actor's telos (purpose) is individual and collective (Miller, 2019). He presents the following conditions for examining social institutions: structure, function, culture, and sanctions (Miller, 2019).

3.3.1 Structure and Function

Miller notes that social institutions define their roles as "tasks and rules regulating the performance of those tasks" (Miller, 2019, p. 6). He notes that interdependence exists between this institution's roles to the extent that one role cannot be performed unless the otherrole has been undertaken or is being undertaken. He argues that "the constitutive roles of an institution and their relations to one another can be referred to as the *institution's structure*" (Miller, 2019, p. 6).

The role expectations of the various players within the institution of clinical research governance, illustrated in Fig 1.0, are defined by the rules of the various normative documents regulating their tasks. There is interdependence, as the PI/Sponsor must have ethics approval or a favourable opinion (Cox et al., 2021). This approval/opinion is usually a prerequisite for the Regulatory Authorities to authorize the commencement of a clinical trial.

(Cox et al., 2021). Only after the REC and RA approve can the PI/Sponsor legally and ethically proceed. Further oversight is required to ensure compliance with the approved protocol (Heath, 1979; Weijer et al., 1995).

Miller notes a hierarchical relationship between status levels and authority degrees (Miller, 2019). Research governance structure seems to place RAs at the top of the hierarchy, followed by RECs/IRBs. Notably, the IRBs in the USA are answerable to government authorities such as the US FDA and OHRP (Office for Human Research Protections, 2016; US Food and Drug Administration, 2019). These entities influence IRB programs and can issue sanctions for nonconformity. In Europe, RECs are accountable to health agencies that may or not be the Drug and Medicines board.

According to Miller, the functional role of social institutions is to generate a collective end and, in the case of the research enterprise, a collective good. He asserts that this collective end could only be achieved through joint actions and joint institutional mechanisms (Miller, 2019). This joint action is at the core of his teleological account. He notes that within this teleological account, joint actions consist of the intentional individual actions of a number of agents directed to the realization of a collective end (Miller, 2019). The joint institutional mechanisms consist of "(a) a complex of differentiated but interlocking actions (the input to the mechanism), (b) the result of the performance of those actions (the output of the mechanism), and; (c) the mechanism itself" (Miller, 2019, p. 30). Clinical research enterprise aims to generate scientific knowledge and produce clinical products/devices/interventions that benefit public health- a social value. Most importantly, this system is established to create safe, effective products (collective end) and ethically appropriate, scientifically sound knowledge relevant to public health (collective good).

Ethicists, Habets, Van Delden, and Bredenoord have explored the concept of social value in clinical research. They contextualize the concept of social value as follows:

> "[…] the expected improvement the intervention can bring to the wellbeing of (future) patients or society […]For the sole purpose of gaining knowledge, we should not expose humans to potential harm; the ultimate justification of involving humans in research lies in the *anticipated social value* of the intervention (Habets etal., 2014, p. 1).

They emphasize an anticipated social value, i.e., a value for future patients and wider society. This responsibility, they posit, is the responsibility of the sponsors (funders) and RECs (Habets et al., 2014).

3.3.2 Culture and Sanctions

Another salient feature of social institutions is that of culture. Miller notes institutional culture as "the informal attitudes, values, norms, and the ethos or "spirit" which pervades an institution" (Miller, 2019, p. 8). He notes that culture differs from formal rules and usually explicitly stated or defined tasks and rules. Culture, in the narrow sense, influences much of the activity of the members of that institution, or at least the manner in which that activity is undertaken. Biddle notes culture as both role expectations (norms) and behaviours (Biddle, 1979). Non-conformity to expected roles, especially norms and written policy/guidelines/law, may lead to sanctions. Social institutions necessarily involve

sanctions. It is uncontroversial that social institutions involve informal sanctions, such as moral disapproval following on non- conformity to institutional norms. However, Miller notes that some theorists such as Jon Elster argue that formal sanctions, such as punishment, are a necessary feature of institutions. Formal sanctions are certainly a feature of most, if not all, of those institutions that operate within a legal system. However, they do not appear to be a feature of all institutions (Miller, 2019, p. 9). Within the clinical research enterprise, sanctions are usually the remit of regulatory agencies. However, in some jurisdictions, the REC/IRB is empowered to sanction researchers.

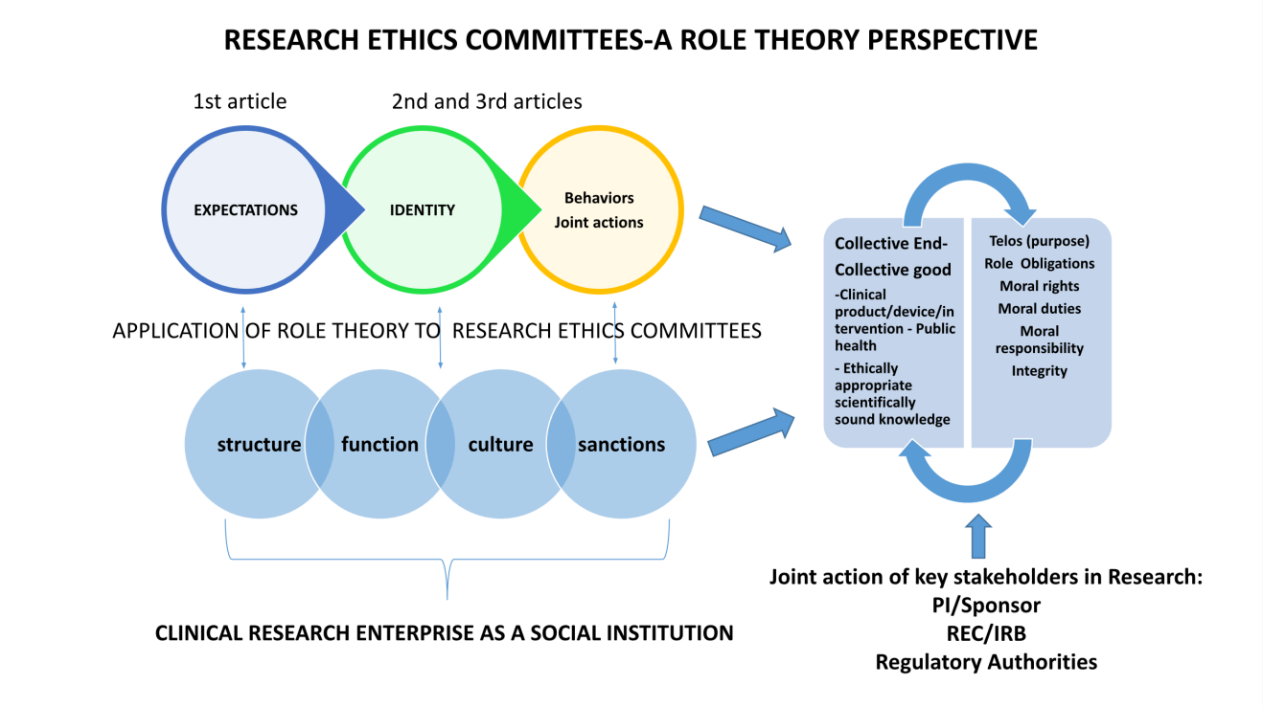

Figure 2.0 Conceptual framework combining Biddle's role theory and Suemas Miller's teleological account of social institutions

3.3.3 REC/IRB- Structural, functional, cultural, and sanction similarities and differences in EU and USA

The USA - IRB

Sarah Babb gives a historical account of the development of the social institution of research governance in the USA (Babb, 2020, 2021). As a sociologist, she examines the factors influencing the changes in human research regulations over several decades (Babb, 2020, 2021). Babb's book documents the changes during the evolution of the IRB as an organization from volunteerism to hyper-compliance, then compliance with efficiency (Babb, 2020). IRBs in the USA were initially university-based and consisted of faculty members who volunteered their time and expertise, a period she describes as approximate compliance. This period was from the inception of IRB reviews in the 1960s to the early 1990s (Babb, 2020).

Following several scandals arising from lax IRB oversight, regulatory authorities began to sanction IRBs boards, creating a need for compliance expertise and, ultimately, the genesis of IRB administrators and staff trained and certified in human research regulations (Babb, 2020). Babb outlines that this period created national IRB training and certification entities such as the Collaborative Institutional Training Initiative (CITI) and PRM&R (Babb, 2020). She describes this as the period of the hyper-compliance risk-avoidant era. IRB offices, afraid of sanctions from regulators such as the OHRP, focused on hiring compliance professionals to interpret and ensure that systems were in place (Babb, 2020). One primary sanction of concern was the loss of federal funding. This significantly influenced the research environments of many higher-learning institutions (Babb, 2020). These entities also developed their internal policies and procedures. However, while there were fewer sanctions and more compliance, the culture of IRBs in the USA became a bureaucratic challenge for researchers who found that they had extremely lengthy timelines before IRB decisions and significant paperwork that seemed more than was required by law (Babb, 2020).

Accreditation of IRB was a welcomed concept as it allowed standardization and support that under-resourced and strained regulatory agencies could not provide. Nevertheless, researchers pled for greater IRB efficiencies and consistencies. Additionally, many IRBs sought independent accreditation, creating another set of rules or standards that IRBs professionals were now expected to meet (Babb, 2020).

Subsequently, the IRB system became reoriented to what Babb describes as the era of compliance with efficiency. This period emerged in the mid-2000s (Babb, 2020). However, this period was still not without its challenges. The IRB offices have more personnel and a more significant delegation of decision-making to the administrators of these offices (Babb, 2020). Babb notes unintended consequences such as "the exercise of bureaucratic authority over research design and goal displacement" (Babb, 2020, p. 12). Eventually, the IRB system in the USA became more privatized, and technology was incorporated to ensure standardization and efficiency (Babb, 2020, 2021). One important observation made by Babb was the variation in interpretation across the institution and the imposing of rules on non-federally funded research, especially those that would ordinarily be considered exempt research. In response to this, there was a shift towards compliance with flexibility (Babb, 2020). This was followed by a revised Common rule, the primary legislation governing federally funded institutions engaged in research (Babb, 2020).

Europe

The practice of prospective review by Ethics Committees evolved in Europe as it did in the USA. The presence of Ethics Committees within Europe began in the mid-1960s (Hedgecoe, 2009). Adam Hedgecoe details how RECs became part of the regulatory structure in the United Kingdom during the period 1967-1972 (Hedgecoe, 2009). He notes that the first committees were established in teaching/research hospitals after a 1966 memo from the US Surgeon General (Hedgecoe, 2009). The memo instructed all entities that received grant funding for clinical research from the US Public Health Service to ensure a prior review of the judgment of the principal investigator. The new requirement prompted the ad hoc establishment of RECs at various institutions in the UK and Sweden (Hedgecoe, 2009). Initially, these RECs were the remit of the governance of the individual hospitals and served an advisory role. Eventually, the system of RECs expanded to regional and centralized committees with government oversight (Hedgecoe, 2009, 2017). By the early 2000s, there were over 200 RECs in the UK (Hedgecoe, 2009, 2017). Other European countries established ethics governance systems by RECs following scandals and adopting normative documents such as the Declaration of Helsinki, the ICH: GCP and the CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects (Hedgecoe, 2017). Between the 1960s to mid-2000, almost all European countries adopted legislation governing clinical trials on human subjects. The general governance structure of RECs in Europe was either government-controlled or institutional, with government reporting responsibilities (Hedgecoe, 2009, 2017). Similar to the USA, RECs in Europe comprised mainly of volunteers who were faculty members in Universities and predominantly of the medical profession (Hedgecoe, 2009, 2017). In 2001, the European Commission sought to address challenges faced by researchers within the EU by issuing the Clinical Trials Directive 2001/20/EC. The Directive's objective was to harmonize the administrative provisions governing European clinical trials (European Commission, 2019).

Unfortunately, the intended purpose of the Directive was not achieved (Frewer, Coles, Champion, et al., 2010; Van Doorn et al., 2015). Several studies published post-implementation of the Directive across member states note increased bureaucracy, workload, and costs impeding clinical research progress (Frewer et al., 2010; Hartmann, 2012). Subsequently, Europe began experiencing a decrease in the number of clinical trials. One possible reason was that member states varied in their adoption of the Directive in their respective legislations. Galbraith et al. echo concerns that the evidence negatively affected European clinical research (Galbraith et al., 2006). The European Federation of Pharmaceutical Industries and Association’s 2022 report corroborates this claim. It notes thatbetween 2016- 2021, Europe experienced only a 5.8% growth in the research and marketing of pharmaceuticals compared to emerging markets such as Brazil, China, and India, which experienced growth of 11.7%, 6.7%, and 11.8%, respectively (European Federation of Pharmaceutical Industries and Association, 2022). Hartmann et al. note that some member states developed best practices to address the shortfall after these challenges (Hartmann, 2012). Similarly, Frewer and co-authors. submitted recommendations on how the EU policymakers could forge a way forward (Frewer, Coles, Champion, et al., 2010). These are:

1) Require only once clinical trials authorization (CTA) for all multinational clinical trials, irrespective of participating nations, either by the development of a single CTA application across Europe or mutual recognition of authorizations by competent authorities
2) Simplify and harmonize the procedures for clinical trial approval (for example, use just one set of forms) and safety reporting
3) Better define and harmonize the roles and review processes of ethics committees (achieve the so-called single opinion) and competent authorities)
4) Adopt a risk-based approach-adapt i.e., the regulatory requirements to consider the risk associated with the trial with regard to safety reporting (for example, limited safety reporting for commercially approved drugs), data monitoring, insurance, application dossiers, substantial amendments
5) Allow co-sponsorship in the case of multinational trials, with the aim of facilitating collaboration between research groups
6) Better define terms and concepts
7) Increase public financial support for investigator-driven trials
8) Harmonize insurance requirements – for example, uniform costs per country, minimum and maximum indemnity payments, total duration of coverage, and time to permit claims (Frewer et al., 2010, p. 3)

Several critical reviews of the impact of the EU directive on research and subsequent recommendations, such as the ones mentioned above, and the results of an EU-initiated study on the implications of European legislation on clinical research caused EU policymakers to go back to the drawing board and identify a way forward. This led to the new EU Regulations 2014 being implemented in January 2022 (Tenti et al., 2018). The new Regulations aim to create greater harmonization than its predecessor (Tenti et al., 2018). The Regulations have the prima facie aim of standardizing the application and assessment procedures for clinical trials in member States, asserting that these measures would increase the number of clinical trials within the EU. Of note in the new Regulations is its emphasis on simplicity and the reduced timeline for clinical trials. To achieve this, the EMA has created the Clinical trial information system (CTIS) programme, a single portal accessible by sponsors, regulators, RECs, and the public (European Medicines Agency, 2020). The programme allows sponsors to upload clinical trial applications, submit notifications of serious unexpected adverse events, submit annual safety reports, and indicate the end of the trial. The public can access to identify the various clinical trials taking place in their countries (European Medicines Agency, 2020). The impact of the new Regulations would have to be measured over time to determine if it is achieving its intended goals.

Before its implementation, the new Regulations were criticized. Several commentators, mainly those with expertise in Ethics, have indicated a reduction in the emphasis on ethics within the Regulations. “We just lost our chance”- summarizes the concerns of the European Network of Research Ethics Committees (EUREC) and ethics experts across Europe in the article “A European consistency for the functioning of REC?” (Waligora, 2013). Marcin Waligora notes the EUREC’s concern regarding the Regulations’ “wide discretion in constituting national assessments processes,” which may inadvertently facilitate sponsors shopping for countries with the weakest regulatory systems (Waligora, 2013, p. 408). Waligora highlights Eugenijus Genfenas and Richard Ashcroft's comments that the new EU

Regulations represent an “ethics rubber stamp” and “moral figleaf” for research (Waligora, 2013, p. 409). He notes the lost opportunity to address inconsistencies in EU RECs (Waligora, 2013). There was also a call for a “transparency quality and accreditation system for RECs in the EU” (Waligora, 2013, p. 408).

The concerns raised by these commentators were precisely the problems faced and addressed by IRBs in the USA, where pressure from regulators and threats to research funding caused a shift to hyper-compliance and subsequent complaints from researchers (Babb, 2020). The discussion regarding the increasing loss of clinical trials in the EU concentrated on the bureaucratic challenges due to inconsistencies across the member countries (Gefenas et al., 2017; Hearnshaw, 2004; Lukaseviciene et al., 2021). Suppose the European countries emulate the US model of improving ethics review. In that case, consideration could be given to employing expert professionals and establishing quality agencies such as PRIM&R (Public Responsibility in Medicine and Research, 2022). Babb notes that PRIM&R facilitates the collaboration of ethics professionals to discuss best practices. These deliberations led to US IRBs achieving what Babb describes as compliance with efficiency. Additionally, training IRB members by a single entity (CITI), accreditation by the Association for the Accreditation of Human Research Protection Programs (AAHRP), and incorporating technology with standardized application procedures enabled what Babb describes as compliance with efficiency research culture in the USA (Babb, 2020).

The literature highlights the difference in research culture when comparing the USA with Europe. Nevertheless, the basic social structure of the research enterprise remains the same despite the cultural and sanction differences.

3.4 A teleological account for the clinical research enterprise

Having discussed the research enterprise within the context of Miller’s criteria for social institutions, I will now reflect on the moral obligations/responsibilities of the clinical research enterprise. Miller argues that contemporary social institutions that aim to generate a collective good to which citizens may assert a justified claim may have moral obligations to fulfil such claims. He uses Emile Durkheim’s argument that social groups have moral power based on how they organize themselves as a collective with an end that is also a collective good. Miller returns to the seldom-used understanding of teleology, i.e., telos meaning end or purpose. He describes this as an *individualist teleological (normative) theory of social institutions* (Miller, 2010, p.54). He notes, aggregated needs-based and non-needs-based rights generate moral responsibilities hence the normative basis for institutions (Miller,2019).

The emphasis is what he posits as the collective end theory (CET), i.e., “joint actions (macro or micro) are directed to the realization of a collective end” (Miller, 2010, p. 41). In summary, a society's communal needs engender claims, which spawn a moral responsibility tomeet those needs through joint activities that yield the collective good arising from the demand (Miller, 2010, 2019). The collective good, he explains are:

(1) “[…] produced, maintained, or renewed by means of the joint activity of members of organizations or systems of organizations, that is, by institutional actors,
(2) they are available to the whole community, and

(3) they ought to be produced (or maintained or renewed) and made available to the whole community because they are desirable goods and ones to which the members of the community have an (institutional) joint moral right" (Miller, 2010, p. 4).

He applies this theory to several institutions, such as governments, universities, the police, and businesses. He acknowledges a range of possible rights that may cause the generation of several institutions (Miller, 2009, 2019). However, he also asserts human rights as one of the strongest, citing the example of the police and the citizens (Miller, 2009, 2019). If citizens need to be protected from harm, the right to life becomes a normative obligation of the State. This right to life essentially forms the basis for institutions such as the police. The theory aligns its foundational norms (formal or informal) with deontic properties on the part of the institutional actors, guiding individual actions towards proximate or ultimate ends (Miller, 2009, 2019). Applying this theory to clinical research is relevant because it presents a structured yet multi-faceted argument for examining the moral responsibilities of all social actors within the research enterprise.

Earlier, I shared that norms (formal – laws, policies, guidelines, and informal culture) guide the activities of the role occupants within research. Additionally, each role occupant (PI, sponsor, REC, RA), both individual and through joint interconnected action, aims to achieve the ultimate (collective) end (good) to which research participants may assert justified claims (rights), subsequently generating moral responsibilities. One of the challenges in this thesis is arguing that any single actor within the research enterprise would be responsible for ethics. It may be an impossible task because each stakeholder has ethics embedded in how it will execute its duties at the foundation of its individual norms and proximate end. Nevertheless, the interconnectedness makes the ultimate end a joint effort. In other words, every actor would have some responsibility for ethics. Within each of these is the normative expectation of protecting research participants. The PI is guided by the DoH, which clearly outlines in its preamble that the declaration is primarily addressed to physicians (usually the PI) but encourages "others who are involved in medical research involving human subjects to adopt" (World Medical Association, 2013). Ethics is a continuum throughout research, and each social actor has moral obligations within the research enterprise.

The ICH: GCP is established to harmonize standards for clinical trials to enable regulatory authorities in collaborating countries to have similar clinical trial requirements (International Conference on Harmonization, 2018; Otte et al., 2005). This facilitates sponsor organisations doing multi-centre clinical trials and seeking marketing authorization post-clinical trials in collaborating countries (Otte et al., 2005). Nevertheless,it is essential to consider that although the role obligations vary among actors within the research enterprise- the normative force of each role ought to be primarily considered based on the proximate end of each actor. Clearly, the ultimate goal is to contribute to generating knowledge, thereby addressing a fundamental need- to treat/cure/prevent diseases and improve public health. However, it is also understood that in pursuing this end, one ought not to infringe on the rights of research participants.

It could be asserted that the proximate end of the sponsor is generating a product that will yield profit, albeit the collective good being public health. In addition, it could be proffered that the proximate end of the PI is generating scientific knowledge and ultimately contributing to social good. Some may argue that the proximate end of RAs is to ensure

compliance with the law and the provision of a public good through its marketing authorization process. Of all the stakeholders involved in the research enterprise, the REC/IRB is noted to ensure that the proposed research is ethical and, to this end, may be the actor most responsible for ensuring that the research participants, especially those most vulnerable, are protected. The proximate end is to approve only ethical studies. However, this is the crux of the paternalistic argument regarding RECs/IRBs but is this protectionist role unfounded? I will now explore the concept of teleology and its relevance to the clinical research enterprise.

3.4.1 Teleology – purpose, outcomes, and behaviours

Teleology has its roots in the Greek word telos, which means purpose, end, and goals (Merriam-Webster, 2022). Both ancient and modern philosophers have deliberated extensively on teleology, especially in their attempt to explain the nature of things, God, goodness, and ethics (Bedau, 1992; McDonough, 2020c, 2020a). Philosophers such as Plato, Aristotle, Kant, Spinoza, and Hegel have proffered arguments on whether teleology sufficiently has a place in explaining causality (Bedau, 1992; McDonough, 2020b, 2020c, 2020a). Jeffrey McDonough presents summaries of various accounts of the different views regarding teleology. He summarizes teleology's central questions: whether it is extrinsic or intrinsic, its intentionality, scope, and its explanatory power (McDonough, 2020c). He notes Plato's account of teleology as "extrinsic, intentional, all-encompassing, and explanatory" (McDonough, 2020c, p. 6). On the other hand, Aristotle's account of the teleological interpretation of the nature of things is regarded as intrinsic and non-intentional (Bedau, 1992; Mayr, 1992; McDonough, 2020c, p. 7).

Several other accounts where philosophers' arguments regarding teleology diverge or converge exist. However, this thesis considers teleology's central question about the purpose or end of a thing or that for which something exists. Therefore, I will not explore the other philosophical considerations regarding teleology. This central question of purpose will be discussed in the context of intentionality or, as McDonough explains it, "the aboutness" of a thing (McDonough, 2020c, p. 2). What was the purpose for which RECs/IRBs were created?

Supported by Miller in his account of social institutions, the emphasis on REC/IRB in the clinical research enterprise is on the original purpose for which they were created and how this individual purpose contributes to a collective end that is also a social good. Suppose intentionality is an essential consideration for the purpose (telos) of REC/IRB in research. In that case, one could argue that since every research is subject to ethics review, the institutional actors intend to ensure the research is executed ethically and not simply a paper approval before the start of a study. The telos of the REC/IRB would be throughout the entire research process. If this is the accepted norm, then there ought to be expectations that dictate the post-approval behaviour of RECs/IRBs.

It is important to pause to acknowledge that most modern scholarship describes teleological ethics only as consequentialist, i.e., only outcomes (Ronzoni, 2009; Wininger, 1986). However, the carte blanche characterization of teleological ethics as consequentialism is a misnomer. Some consequentialist accounts perpetuate the interpretation of teleology as only an outcome (consequence) (Ronzoni, 2009; Wininger, 1986). Although consequentialism is, in fact, a form of teleology, i.e., the application of the end meaning of telos - it fails to

recognize the intentionality argument (Bedau, 1992; McDonough, 2020c; Wininger, 1986). This may create confusion about successfully applying a teleological (purpose-focused) approach (Wininger, 1986). There are two possible scenarios in clinical research. Scenario 1 is the generation of a collective end, i.e., a clinical product/device or intervention in an unregulated environment, and ethical conduct is not a consideration. Scenario 2 is the generation of a collective end that produces a collective good, a clinical product/device/intervention in a regulated environment where ethical conduct is foremost. The first scenario does create an end that can benefit millions. Utilitarian consequentialists would proffer arguments in support of the market authorization of any outcome (product/device/intervention) that can yield positive effects on the health of a population. However, history has sufficient evidence to support the assertion that an unregulated environment (where ethics is not foremost) has dangerous implications for science, research participants, and the public (Beecher, 1966; Brandt, 1978; Hedgecoe, 2017).

For this reason, there was a shift to the highly regulated clinical research enterprise that now exists with norms, rules, and guidelines to ensure that the rights of individuals who participate in generating the collective end (the product/device/intervention) are not infringed. These individuals have justified claims/rights not to be exploited for the greater good. In fact, the DoH emphasizes this point in its eighth principle:

> "[…] While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects" (World Medical Association, General Principles 8, 2008).

The rights and interests of research participants generate moral responsibilities on the part of the various actors within the research enterprise. In scenario 2, the collective good is ethically appropriate scientific knowledge contributing to public health. It is more than just a scientific discovery. A singular outcomes-based focus solely on scientific discovery is the antecedence of what has been achieved since the Nazi doctor medical crimes, Tuskegee, and many other examples of unethical research (Beecher, 1966; Hedgecoe, 2017; Roelcke, 2004). The current clinical research enterprise ought to be purpose-driven- with its telos centred on intentionality, not only on ends. As noted by Miller in his teleological account, the collective good – ethically appropriate scientific knowledge has deontological foundations (Miller, 2009, 2019). The summum bonum - the highest moral good, ought to be the aim of the clinical research enterprise. If this is the ultimate intention, then the relationship between purpose and behaviour must be illuminated.

"The road to hell is paved with good intentions" is a famous quote that is often shared when persons end up in a bad situation, albeit unintentionally (Wikipedia, 2022). This quote challenges the concept of intentionality and asserts that one can have good intentions, but it does not always work out as planned. Applying this to the thesis, one could argue a claim that telos, i.e., purpose, is not sufficiently strong to support a post-approval role for RECs/IRBs. There must be some connection between intention and the achievement of a goal. This is usually action-oriented. Moving from intention -that which is conceived (expectations) to that which is, achieved (behaviour). Arturo Rosenblueth, Norbert Wiener, and Julian Bigelow drafted an essay in 1943 on Behaviour, purpose, and teleology (Rosenblueth et al., 1943). Although the examples used to illustrate their main points are not relevant to the current focus on social institutions, the observations regarding behaviour, purpose, and teleology may be worth considering:

> "[…] in classifying behaviour, the term teleology was used as synonymous with purpose controlled by feed-back. Teleology has been interpreted in the past to imply purpose and the vague concept of a final cause has been often added. This concept of final causes has led to the opposition of teleology to determinism…It may be pointed out, however, that purposefulness, as defined here, is quite independent of causality, initial or final. Teleology has been discredited chiefly because it was defined to imply a cause subsequent in time to a given effect. When this aspect of teleology was dismissed, however, the associated recognition of the importance of purpose was also unfortunately discarded. Since we consider purposefulness a concept necessary for the understanding of certain modes of behavior we suggest that a teleological study is useful if it avoids problems of causality and concerns itself merely with an investigation of purpose" (Rosenblueth et al., 1943, p. 23).

They argued for restricting teleological behaviour "only to purposeful reactions" (Rosenblueth et al., 1943, p. 24). Teleological behaviour would be only those "which are controlled by the error of the reaction, i.e., by the difference between the state of the behavingobject at any time and the final state interpreted as the purpose; teleological behaviour, thus becomes synonymous with behaviour controlled by negative feedback, and gains" (Rosenblueth et al.,1943). In other words, based on a strict definition of teleology, independent of causation, they categorized behaviour into teleological (purposeful) or non-teleological (without purpose). Citing various examples of biological/animal mechanisms/behaviour, they attempted to elucidate that intentional conduct requires "negative feedback" (Rosenblueth et al., 1943). They argued:

> "[…] if a goal is to be attained, some signals from the goal are necessary at some time to direct the behavior. By non-feed-back, behavior is meant that in which there are no signals from the goal, which modify the activity of the object in the course of the behavior" (Rosenblueth et al., 1943, pp. 19-20).

One example is the voluntary action of drinking a glass of water. Thought is not given to the act of lifting the glass- the thought is given to raising the glass- to drink water (Rosenblueth et al., 1943). Therefore, the actions of the brain and body align towards that purpose, simultaneously prohibiting alternate activities (Rosenblueth et al., 1943). However, the contrast is a patient with cerebellar damage who may have the same intention but cannot execute the function, as the cerebellum cannot restrict feedback that prevents the achievement of the intended act (Rosenblueth et al., 1943). Hence, while attempting to drink the water, the patient with cerebellar damage will spill that water, and the purpose will be defeated (Rosenblueth et al., 1943). This analogy is worth considering for exploring the role of RECs/IRBs in that without a teleological (purpose-driven) approach, ethically appropriate research would not be achieved. Instead, there would be breaches from the time of approval throughout the life of the trial – little spills of water (unethical behaviour) in the end. Suppose we accept that the purpose of the currently regulated clinical research enterprise is to generate ethically appropriate research. In that case, any deviation from that should be construed as non-teleological-i.e., not aligned with purpose. I dare to go a bit further and piggyback on the example of the cerebellum as a feedback mechanism of the body to enable the intention of drinking water to be fulfilled (teleological). I want to assert a claim that the REC/IRB ought to be considered the main feedback centre on what is ethically appropriate research- not just at the point of conceptualizing but the complete execution of that purpose.

3.5 Research Ethics, Belmont Report and William D Ross' Prima facie duties

For a social institution to have a purpose or goal, it would be reasonable to assume that moral principles guide the purpose (telos). Previously, I discussed that most scholarship has deviated from teleology's intentionality (motive) root meaning. Instead, scholars have contextualized teleology as purely outcome-based ethics, i.e., the utilitarian type of ethics;- best outcome for the greatest number. Since this thesis focuses on the purpose of RECs/IRBs in the context of role expectations, identity and behaviours, it is essential to disentangle teleology from the outcomes-based tradition to focus on purpose or intention. To this end, it would be necessary to identify an appropriate ethical framework for analyzing the role of RECs/IRBs within the clinical research enterprise that would not confine its foundation to the traditional utilitarian (outcome-based) or deontological (duty-based) arguments for what is right or wrong.

This thesis discussed several normative guidelines adopted or agreed on as fundamental to research governance. One of the earliest was the Prussian guidelines, which emphasized informed consent and avoidance of harm (Moll et al., 2012; Vollmann & Winau, 1996). The Nuremberg Code which followed reiterated a) the voluntary consent of research subjects, b) the minimizing or avoiding injury in experimental procedures, and c) the right to withdraw or for a researcher to be prepared to terminate a study was codified (Ghooi, 2011). The subsequent passage of various legislation in the USA codified the importance of the safety of pharmaceuticals- reiterating the avoidance of harm to human subjects while seeking to benefit society (risk-benefit ratio) (Fintel et al., 2009; Nasr et al., 2011). Despite these various laws and guidelines, several ethical atrocities in the USA prompted a discussion towards developing an ethical framework for the evaluating research for the protection of research subjects. The framework was the Belmont Report briefly introduced in chapter one. At the time of its conceptualization, the National Commission for the Protection of Human Subjects sought to address the main concerns regarding unethical conduct of research by examining research protocols using the lens of the three overarching principles; respect for persons, beneficence, and justice (Brothers et al., 2019; Friesen et al., 2017). Over time, these principles have gained wide attention and influence through the different versions of Thomas Beauchamp and James Childress' textbook "Principles of Biomedical Ethics" as reflected in various guidelines in REC/IRB review and clinical practice. The principles reflect a framework for ethical reflection.

3.5.1 Belmont Principles- Respect for persons, Beneficence, and Justice

The principle of respect for persons reflects consideration for the right of individuals to self-determination/autonomy and to protect persons who have diminished capacity to make autonomous decisions, i.e., vulnerable persons. An important aspect of the Report was distinguishing between research and clinical practice (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979). In the context of research, the research participant should 1) receive sufficient information to enable them to have full comprehension of the risks and benefits of the proposed research, 2) be capable of understanding the information given, 3) voluntarily consent to the participation (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979). Although the concept of informed consent was already an integral part of what was considered ethical research since the Nuremberg Code, the Belmont Report through the

National Health Research Act made it a legally mandated consideration for all IRB reviews in the USA.

The second principle beneficence, requires researchers to ensure the well-being of research participants. To this end, researchers are expected to "do no harm" and to "maximize possible benefits and minimize possible harms" (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979). This is the guiding principle for risk-benefit assessments during prospective REC/IRB review.

The third principle of justice addresses concerns concerning the fair distribution of the benefits and burdens of research. It is closely connected to the arguments for research generating a social good and to, as much as reasonably possible, not unduly burden some members of society - especially vulnerable participants, and benefit others. The principle of justice has been discussed widely in scholarship. There has been debate about the inclusion/exclusion of some populations/persons based on what may be considered a vulnerability, e.g., children, pregnant women, racial and ethnic minorities, and prisoners. The fair selection of persons implies ensuring they are not chosen because of availability, compromised position, or manipulability (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979). Deviations or violations of ethical relevance in clinical research usually constitute a breach of one or more of these principles. Conversely, adherence to these principles implies that the research outcome is not only a good one but implies the duty of ethical execution throughout the research process.

These principles underpin the basis for emphasizing that prospective review and subsequent follow-up to ensure compliance with the approved protocol are aligned with outcomes and intentions. Principle-based ethics is normatively focused on the research participants and their rights. They guide how stakeholders ought to act towards research participants. However, there is uncertainty regarding how well these three principles adequately address the individual or collective obligations of actors (stakeholders) within the social institution that is clinical research. The consideration, therefore, is to identify how other normative frameworks may complement the principles. While acknowledging that the priniciplist framework is widely applied in Bioethics, a duty-based normative framework is applied to this thesis's interrogation of the role of the REC/IRB in the multi-stakeholder clinical research enterprise. The assumption is that the principles are foundational for protecting research subjects. As noted in the discussion regarding ends, the collective goal of the stakeholders within the clinical research enterprise is not only to achieve a product of social value but one that is ethically acceptable. The principles of respect for persons, beneficence, justice, and non-maleficence remain the normative framework for determining whether a clinical research outcome is ethically justified.

Therefore a greater deliberation or justification of the principles may not be necessary for what is being examined, i.e., which of the several actors within the clinical research enterprise is chiefly responsible for following up to ensure that approved research is conducted ethically. The aim is to reflect on the social institution of clinical research and how RECs/IRBs situate within this institution regarding moral obligations. To this end, William D Ross's ethical framework of prima facie duties is applied, with the core consideration that REC/IRBs have moral obligations to meet their normative role expectations as part of their duties. Ross presented an argument for seven prima facie duties, two of which are part of the

Belmont principles. Consequently, the prima facie duties of emphasis in this thesis are 1) fidelity -the duty to keep promises; 2) reparation; 3) gratitude; and 4) self-improvement.

Earlier, I expounded on Suemas Miller's teleological account of social institutions, highlighting that the deontic properties of individual organisations are based on their delegated role expectations within a social institution. To further strengthen this teleological account and its application to RECs/IRBs and clinical research, I will briefly expound on prima facie duties with further elaboration in the Discussion chapter on how I wish to connect the various theories (role/teleology/prima facie duties) to my argument for shifting attention from the predominant focus on prospective ethics review to the post-approval activities and obligations of RECs/IRBs.

3.5.2 William D. Ross Prima Facie duties

In his Stanford Encyclopedia of Philosophy entry, Anthony Skelton notes that William D Ross sought to find a middle ground between pure deontology and ideal utilitarianism (Ross & Stratton-Lake, 2002; Skelton, 2022). Skelton highlights that Ross challenged the works of deontologist Immanuel Kant and utilitarian G. E. Moore (Skelton, 2022). According to Skelton, Ross argued that deontology and ideal utilitarianism is "oversimplified and distorted" moral life (Skelton, 2022). In his rejection of pure deontology and ideal utilitarianism, Ross accepted that we have moral duties (Skelton, 2022). Still, it is not limited to monistic concepts such as the categorical imperative proffered by Kant. Instead, he presents a pluralistic form of deontology- a spectrum of duties (Skelton, 2022). Regarding utilitarianism, Skelton notes that Ross argued that there is more to moral deliberation than consequences (Skelton, 2022). He shared the following example:

> […] when deciding whether to fulfil a promise we think much more of the fact that in the past we have made a promise than of the consequences its fulfilment promotes…Our common-sense moral thinking includes the idea that what we ought to do depends in part on retrospective considerations, e.g., that we have made a promise in the past or previously incurred a debt" (Skelton, 2022, p. 8).

Ross explains his approach to moral deliberation in his book "The Right and the Good" (Ross & Stratton-Lake, 2002). He argues for rightness and goodness as irreducible objective moral properties that cannot be defined but physically manifested (Skelton, 2022). The rightness of an act and the goodness of its motive are based on a set of duties he describes as prima facie duties and values (Ross & Stratton-Lake, 2002; Skelton, 2022). The values are considered intrinsically good. The prima facie duties are:

1. "[…] a duty of fidelity, that is, a duty to keep our promises
2. A duty of reparation, that is, a duty to correct a previous wrong we have done
3. A duty of gratitude, that is, a duty to return services to those from whom we have in the past accepted benefits
4. A duty of beneficence, that is, a duty to maximize aggregate or general good
5. A duty of non-maleficence that is, a duty not to harm or injure others" (Skelton, 2022, p. 10)

The complementary values are virtue, knowledge, justice, and pleasure within a hierarchy where virtue is ranked the highest (Skelton, 2022). Although Skelton outlines five duties, other interpretations outline seven duties, including self-improvement and justice, as additional prima facie duties and not values (Simpson, 2022). Skelton notes that Ross emphasized flexibility in prima facie duties (Skelton, 2022). Hence, the rightness of action varies based on considering all possible factors and then concluding having addressed "all things considered," i.e., balancing the rightness of all possible acts and deciding, intuitively, which becomes the most compelling or actual duty (Skelton, 2022, p. 14). He notes:

> "[,,,] to figure out which of the acts open to you has the greatest balance of prima facie rightness over prima facie wrongness, you look at all the acts open to you and determine all the ways in which they are prima facie right and all the ways in which they are prima facie wrong and then figure out in each case the balance of prima facie rightness over prima facie wrongness. You then compare the acts open to you in terms of their balance of prima facie rightness over prima facie wrongness. The act with the greatest balance of overall prima facie rightness is the one you ought all things considered to do and what you ought all things considered to do is what you ought, or it is right to do" (Skelton, 2022, p. 14).

Skelton notes that the above approach may be challenging. Ross's work, although commendable, is heavily predicated on ethical intuitionism and non-naturalism, which makes it subject to scrutiny and rebuttals (Skelton, 2022). Ross also distinguishes between actual and prima facie duties, where actual duties are primary moral obligations and unconditional, while prima facie duties are conditional and flexible. In situations of conflicts of duty, there ought to be a comparison between the two duties, and the more stringent duty should be considered the right action (Skelton, 2022). Ross asserts that our intuition would guide us to identify which duty is more suitable when compared to another in a given situation. Thornton notes that philosophers Tom Beauchamp and James Childress' "Principles of Biomedical Ethics" referenced Ross's prima facie duties as foundational in the development of the principlist framework of biomedical ethics (Thornton, 2006). Exploring Ross' prima facie duties in the context of ethics review could prove beneficial in broadening the scope of understanding the moral responsibilities of RECs/IRBs.

To some extent, the prima facie duties of reparation, gratitude, and fidelity are implicitly acknowledged in the examples of compensation and insurance for research subjects (Ghooi & Divekar, 2014; Minacori et al., 2012). Post-trial access would imply the duties of reparation and gratitude (Usharani & Naqvi, 2013). At the same time, fidelity represents the relationship between the REC/IRB and the research participant. Fidelity is about promise keeping and trust. Trust in science and scientists is imperative to achieve the collective good (Parikh, 2021). Ross did not have a hierarchy for the prima facie duties because he emphasized context as crucial for examining the moral rightness of a situation. Skelton demonstrates this by breaking the promise to meet a friend to assist someone in an accident with an immediate need. Although it is important to keep promises, circumstances may arise where one deviates from fulfilling the promise.

The crux here is the intentionality argument, as the intention was to keep the promise, but the duty of non-maleficence, all things considered, became the more stringent duty. This flexible, pluralistic approach is already embedded in biomedical research. Critics of the foundational

principles of research ethics have noted that some principles (beneficence and autonomy) are over-emphasized while others are neglected. One critic is Alex London, who argues for more attention to the principle of justice (London, 2020). The central theme of London's critique was an emphasis on research ethics and the need for a paradigm shift from over-emphasizing principles, particularly beneficence and respect for persons to greater consideration for what he describes as the common good. This common good is centred around the principle of justice. He expounded on the human development approach as central to achieving this common good. Contextually, to avoid digressing from the aim of this thesis, I will share excerpts of London's reflection on research ethics, highlighting his emphasis on clinical research being a social enterprise with several stakeholders working towards a common good.

3.6 For the common good – is it relevant to a teleological account for clinical research enterprise?

In 2020, Alex London published a book asserting a new vision for the philosophical foundations of research ethics (London, 2020). London claims that the key to understanding research is to accept the research enterprise as a social undertaking with a division of labour between multiple stakeholders. He notes that this paradigm shift is necessary:

> "[…] to provide concrete and credible social assurance that the research enterprise constitutes a voluntary scheme of cooperation; that this scheme of social cooperation offers an avenue through which diverse stakeholders, often pursuing their personal ends and interests, can contribute to the common good, that this cooperative enterprise includes checks and balances designed to prevent it from being coopted to unfairly advance the parochial ends of particular parties at the expense of the common good." (London, 2020, p. 299).

The common good to which London refers lends support to Miller's teleological account of social institutions-joint interconnected actions leading to collective ends that are a collective good. The common good is one in which all stakeholders cooperate to ensure a research enterprise hinged on the principle of justice (London, 2020). The interests of science are treated as paramount but not to the disadvantage of the research participant. However, London is disinclined to perpetuate what he describes as orthodox paternalistic research ethics ((London, 2020). He argues that if deficiencies were remedied in clinical research, it would be essential to examine not the agents but "the structural features of the strategic environment" (London, 2020, p.300). He notes that to achieve an effective system of research ethics, there needs to be a sustainable scheme of social cooperation by helping stakeholders resolve coordination problems that threaten its ability to advance the common good (London,2020). My interpretation is that London is asserting a research ethics that is dynamic and continuous. Most of London's discourse is that he argues for aligning research ethics toward considering the common good at all times (London, 2020). In his reflection on the role of the IRB, London asserts that the error surrounding this institutional actor is based on what is known as the IRB triangle –the relationship between the IRB, the researcher, and the research participant (London, 2020). He notes that this triangle is the moral epi-centre of clinical research (London, 2020). London, however, does not address the influence of other stakeholders outside the triangle. Despite arguing against the parternalistic nature of the foundations of research ethics, London does not argue against the

protectionist position the IRB holds. On the contrary, he seems to justify the position by outlining the benefits while acknowledging the limitations:

> "[…] IRBs are limited in their ability to influence the full range of stakeholders who make decisions that shape the way research is conducted. Nevertheless, my contention is that we should jettison the paternalistic justification for prospective review and, with this, its protectionist stance and instead more explicitly align IRB review with the requirements of the egalitarian research imperative. The goal of these reforms is to more explicitly and directly shape the incentives for researchers to ensure that proposed studies contribute to the production of public good while respecting the status of participants as free and equal" (London, 2020, p. 323).

London claims that while he acknowledges the various challenges researchers encounter, particularly in the social sciences with prospective review, he believes that the IRB may be able to address coordination issues, provide quality assurance in research, and enable trust (London, 2020). My interpretation of London's discourse on IRBs is that his argument is centred on prospective review. It raises the question of whether examining IRBs beyond prospective approval would generate the same reflections ((London, 2020). London's use of the IRB triangle is representative of only a few key stakeholders in the clinical research enterprise.

Perhaps IRBs are not as limited in their ability to influence stakeholders, as post-approval activities would mean increased interactions primarily with researchers that could further enhance the quality of research and identify areas where more support may be given to researchers. Perhaps another way of achieving London's egalitarian research imperative is to address the research challenges by examining the stakeholders' prospective and post-approval roles, particularly the REC/IRB. Research ethics review is a continuum and not just ex-ante. It facilitates research but does not negatively represent researchers by asserting a claim to protect participants. London proffers a non-paternalistic (egalitarian) approach towards the common good- knowledge generation and public health (London, 2020).

3.7 Application to the thesis

In the preceding literature, I have presented a hybrid theoretical framework for approaching and analyzing REC/IRB role within the research enterprise-combining role theory with Miller's teleological account for social institutions. I proffered that examining role expectations, identity, and behaviours would be challenging without understanding the social institution being examined. Acknowledging the clinical research enterprise as a social undertaking with various norms (formal and informal) helps contextualize the problems within the enterprise. It also enables pragmatic recommendations on whether or not more research is needed. A role theory approach to examining this enterprise allows us to identify norms, understand how the actors identify with their respective roles, and how the joint actions or inactions facilitate or delay the achievement of the collective end. For the purposes of this thesis, the collective end (good) is the generation of ethically appropriate, scientifically sound knowledge to address public health needs. However, the moral foundation is within the traditional claim of protecting research participants. This is achieved using a teleological lens (purpose-driven) to understand each role actor within the clinical research enterprise. If research ethics is considered flexible (not fixed) and a continuum (not

ex-ante nor ex-post), then I hope to assert that the REC/IRB role is research oversight that goes beyond the widely accepted view of prospective review.

CHAPTER FOUR

METHODOLOGY & RESEARCH DESIGN

4.0 Overview

This thesis fits what Alexander Kon describes as a "lay of the land" empirical ethics research. Kon defines this type of research as "studies that seek to define current practices, opinions, beliefs, or other aspects that may be considered the status quo" (Kon, 2009, p. 60). This lay of the land research's scientific and philosophical premises fall within the theoretical framework of empirical ethics. This chapter seeks to demonstrate that empirical ethics is an appropriate methodological approach for exploring the role of RECs/IRBs and reflect on some issues regarding research design, data collection, analysis, and reporting.

Theoretical underpinnings of the research methodology

4.1. An Empirical normative approach to a study on RECs

Empirical ethics (EE) has been the subject of bioethics discourse for over two decades (Borry et al., 2013; Mertz et al., 2014; Molewijk et al., 2003). Bioethicists have presented compelling arguments for its place in evidence-based practice (Borry et al., 2013; Molewijk et al., 2003). According to Mertz et al., three key elements classify a research study as empirical ethics. The study must encompass: "(i) empirical research as well as (ii) normative argument or analysis, and (iii) attempts to integrate them in such a way that knowledge is produced which would not have been possible without combining them" (Mertz et al., 2014, p. 2). In the social sciences, the term empirical refers to the social context of a research study which may be "*institutional, relational, cultural, social, spatial or virtual dimensions of human and animal life*" (Singh, 2016, p. 68). Empirical data is extracted from instruments such as "*interviews, surveys, observation, and text"* (Singh, 2016, p. 68). Scientific data, particularly in the natural sciences, is often considered value-neutral, therefore facilitating objectivity (Chalmers, 1982).

Objectivity is a value that natural scientists aim to attain because it facilitates trust. Objectivity in this context is considered "faithfulness to facts," "absence of normative commitments," and "absence of personal bias" (Reiss & Sprenger, 2020, p. 3). However, empirical data obtained using instruments such as interviews may be subjective and value-laden (Borry et al., 2004, 2013). In our attempt to explore the role of RECs, although the aim would be to be value-neutral, the questions in and of themselves that were asked of the respondents and the responses have some underlying normative assumptions. Therefore, it would be disingenuous and almost impossible to ignore that there is a relationship between facts and values (Borry et al., 2004, 2013; Schleidgen et al., 2010). Molewijk et al. suggest that empirical ethics addresses this relationship by integrating moral theory and empirical data. They argue that this integration would facilitate "a normative conclusion with respect to a specific social practice" (Molewijk et al., 2003). Integrated empirical ethics has some underlying beliefs/assumptions: "1) facts produced by descriptive sciences are interwoven with discipline-specific epistemic values, 2) moral theory is inherently based on empirical background assumptions, 3) ought implies can- feasibility argument" (Molewijk et al., 2003, p. 58).

Empirical data can guide the identification of ethical problems and contributory factors. This would be followed by extensive normative reflection incorporating values, culture, and norms. Molewijik et al. suggest three ways bioethicists may use empirical data; 1) bioethicists may need the results of empirical research to be able to apply a moral theory to judge a certain policy or action (i.e. to accomplish the prescriptive goal of a moral theory, 2) the results of empirical research can be used to assess the validity of empirical background assumptions of a moral principle, and 3) empirical data may generate insight into a social practice that allows ethicists to improve an existing moral theory (Molewijk et al., 2003).

The preceding laid the foundation for applying an empirical approach to the study of RECs/IRBs. The third point is the most relevant to this thesis, as the main goal is to understand the social practice of research in the context of clinical trials to address perceived gaps. The perceived gap is whether there is a role for RECs/IRBs in addressing the issue of ethically relevant protocol violations.

4.1.2 Hermeneutics

Hermeneutics is a theory of textual interpretation, particularly by scholars in theology, jurisprudence and medicine (Byrne, 1998; George, 2021; Mccaffrey et al., 2012; Paterson et al., 2005). It includes a spiral reading, interpreting and understanding process, described as the hermeneutic circle (George, 2021; Paterson et al., 2005; Vieira K A L & de Queiroz, 2017). The process of understanding requires the interpreter to acknowledge biases and own pre-understandings that may influence how the text is understood (Paterson et al., 2005; Vieira K A L & de Queiroz, 2017). Hermeneutics is widely applied in the social sciences methodologies, especially textual analyses. Several philosophers have contributed to the discourse on hermeneutics. The most notable contributors to the theory are Friedrich Schleiermacher, Wilhelm Dilthey, Martin Heidegger, Hans-Georg Gadamer and Paul Ricoeur (Byrne, 1998; George, 2021; Mccaffrey et al., 2012).

4.2 RESEARCH DESIGN

The thesis has a qualitative research design. The research paradigm is interpretivist with a relativist ontology and a subjective epistemology (Kivunja & Kuyini, 2017). The primary data analysis methods in the first paper were hermeneutic content and thematic analysis. This enables an understanding of facts and contexts. Content analysis has its roots in hermeneutics. The first objective required significant interpretation and understanding of the texts' semantic and latent meanings. According to Mariette Bengtsson, a structured approach to content analysis includes the following phases: 1) planning, 2) data collection, 3) data analysis, and 4) reporting results (Bengtsson, 2016). The overall project was structured accordingly:

4.2.1 Planning - Aim, objectives and research strategy

All researchers met to discuss and outline the research aim and objectives, identify data sources, and agree on the appropriate data collection and analytic tools for achieving these objectives. The main researcher drafted the proposal and interview guide. The interview guide was written based on Michael Patton’s six categories of qualitative research questions in the social sciences (Patton Michael, 2002). These are questions related to behaviour or

experience, opinion or belief, feelings, knowledge, sensory, and background or demographic (Appendix) (Patton Michael, 2002). We had weekly research meetings to finalize the proposal and assess the appropriateness and clarity of questions. Once finalized, the proposal with the interview guide was submitted to the Faculty department and to the Norwegian Center for Research Data for review and approval (Norsk Senter for Forskningsdata | NSD, 2022). According to the Norwegian law on health research (Lov om medisinsk og helsefaglig forskning, helseforskningsloven, LOV-2008-06-20-44, this project was exempt from REC approval since it did not aim at generating knowledge about health and disease. Only approval from the NSD was necessary.

4.2.2 Research setting- The USA and Europe

The regions of focus for this thesis were Europe and the USA. Paper I focused on governance documents for member countries within the EU. However, the stakeholder participants for Paper II were REC representatives of member countries in EUREC and the United Kingdom. Three of these countries, Norway, Switzerland and the United Kingdom, are not members of the EU but are members of EUREC or previously affiliated with the EU and European Network of Research Ethics Committees (EUREC). Unlike Europe that comprises of many individual countries, the USA was comparatively easier as it is one country with multiple states hence governed by federal and state regulations. We focused on the US Federal regulations during the content analysis of normative documents in Paper I based on a selection process, 54 AHCs in 30 US States in Paper III.

Figure 3.0 European countries represented in Paper II

	States	Institutions
1	Alabama	University of Alabama, University of Southern Alabama
2	California	Chapman University, University of California, University of Southern California
3	Carolina	Charlotte University, Duke University, East Carolina, University of North Carolina, Wake Forest
4	Colorado	University of Denver
5	Connecticut	University of Connecticut, Yale
6	Delaware	University of Delaware
7	Florida	Florida State University, Nova Southeastern University, University of South Florida
8	Georgia	University of Georgia
9	Hawaii	University of Hawaii
10	Illinois	Northwestern University, University of Illinois
11	Indiana	Indiana University, Purdue University
12	Louisiana	Tulane University
13	Maryland	John Hopkins University, University of Maryland
14	Massachusetts	Boston University, University of Massachusetts
15	Michigan	Michigan State University, University of Michigan, Wayne State University
16	Missouri	St Louis University, University of Missouri
17	Nebraska	Creighton University
18	New Jersey	Princeton
19	New Mexico	University of New Mexico
20	New York	Albany University, Binghamton University, University of Rochester
21	Nevada	University of Nevada
22	Ohio	Case Western University, Ohio State University
23	Pennsylvania	Penn State University, Thomas Jefferson University
24	Virginia	Virginia Tech University
25	Rhode Island	Brown University , University of Virginia
26	Washington	Washington State University
27	Wisconsin	University of Wisconsin
28	Tennessee	University of Tennessee at Chattanooga
29	Texas	Texas A&M University, Texas Tech, University of Houston, University of Texas
30	Utah	University of Utah

Table 2.0 States (30) and names of selected AHCs (54) in Paper III

4.2.3 Participant selection and characteristics

For paper II we interviewed participants from nineteen European countries. Sixteen were member countries of the EU. The Countries were Belgium, Denmark, Estonia, Finland, France, Germany, Greece, Ireland, Italy, Latvia, Netherlands, Norway, Poland, Portugal, Slovakia, Spain, Sweden, Switzerland, and the United Kingdom. The other three countries were Norway, Switzerland, and the United Kingdom. Norway and Switzerland are members of EUREC. Although the UK recently left the EU, the research team decided to include this country because of its history and influence in clinical trials development in Europe (Cox et al., 2022).

The participants held positions as follows: REC chair (4), members (12), secretary (1), advisor (1), and chair of an ethics appeals committee (1). Their qualifications range from Masters to PhD degrees in philosophy, medicine, law, pharmacy, immunology, toxicology, microbiology, clinical pharmacology, and psychology. Three participants note qualifications in applied ethics at the Master's level. The years of experience in their respective RECs range were from 5.5 to 30 years (Cox et al., 2022).

4.2.4 Inclusion/exclusion criterion

In keeping with the overall project objective, the participants for Paper II were informed in the invitation letter and at the beginning of the interview that the questions were regarding the post-approval role of REC/IRBs that approve clinical studies, particularly drugs and devices in humans. We were not considering non-human studies.

4.3 Data Collection

4.3.1 Normative Document review (Paper I)

Our research question in paper I was whether and to what extent normative documents support a monitoring role for RECs in the United States and the European Union. We adopted Eurostat, the statistical office of the EU with regard to definition and categorization of normative documents. The adopted definition is "the broad category of documents that provides rules, guidelines, or characteristics for activities or their results" (Eurostat, 2020). The three categories for normative documents are: (1) legal Acts, (2) standards, and (3) other normative documents (see table 3.0) (Eurostat, 2020). We identified the US Department of Health and Human Services International Compilation of Human Research Standards of the Office for Human Research Protection as a comprehensive data source. The list is updated annually and is reliable for identifying normative documents. The 2020 list was screened using pre- established inclusion/exclusion criteria (International Compilation of Human Research Standards 2020 Edition, 2020). We considered a broad perspective on the research topic to simplify the process, and excluded documents explicitly developed for particular subject areas, such as low-resourced countries or conditions such as HIV or genetic studies. Only documents written in the English Language were included. The final list of normative documents is reported in Paper I.

Type	Definitions
Legal documents	**the documents which provide binding legislative rules that are adopted by an authority**
Standards	**established by consensus and approved by a recognized body that provides for common and repeated use, guidelines or characteristics for activities or their results, aimed at the optimum degree of order in a given context**
Other normative documents	**documents approved by a group of persons who are not entitled to adopt standards**

Table 3.0 Categories of normative documents

Guidelines	Legislations
World Medical Association's Declaration ofHelsinki (2013) **UNESCO's Universal Declaration onBioethics and Human Rights (2005)** **The International Conference on harmonization for technical requirements forpharmaceuticals for human use (ICH): GoodClinical Practice (1996 & 2015)** **Council for International Organizations ofMedical Sciences: International Ethical Guidelines for Health-related research involving humans (2016)** **World Health Organisation:** **-Good Clinical Practice (1995)** **-GCP Handbook (2005)** **-Updated Standards and Operational Guidance for Ethics Review of Health-Related Research with Human Participants(2011)** **Council of Europe Guidelines for Ethics Committees Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) (1997)** **EU Reflection paper on ethical and GCP aspects of clinical trials of medicinal productsfor human use conducted outside of the EU/EEA and submitted in marketing authorisation applications to the EU Regulatory Authorities (2012)** **Guidance for IRBs, Clinical Investigators, and Sponsors: IRB Continuing Review afterClinical Investigation Approval (2012)**	**The Council of Europe's Convention for the Protection of Human Rights and Dignity of the Human Being with regardto the Application of Biology and Medicine (1997) and its additional protocol concerning Biomedical Research (2005)** **The Common Rule and US Code of Federal Regulations (CFR) Title 45 (public welfare), Part 46 (protection of humansubjects)** **The FDA Code of Federal Regulations (CFR) Title 21 (foodand drugs),** **Part 50 (protection of human subjects),** **Part 56 (Institutional Review Boards)** **Part 312 (Investigational New Drug Application)** **The European Union Clinical Trial Regulation EU No.536/2014.**

Table 4.0 Normative documents reviewed in paper I

4.3.2 Stakeholder interview (Paper II)

The objective of paper II was to ascertain stakeholder perspectives on the post-approval activities of RECs/IRBs in the EU and USA. Initially, we set out to explore the perspectives of REC members, GCP inspectors, sponsors, and patient organizations. Invitations were sent to stakeholders (RECs/IRBs, sponsors, and patient organizations). However, the response rates were low. The COVID-19 pandemic affected many stakeholders whose offices were closed because of a work-from-home mandate (Galanti et al., 2021). We deliberated and decided to adjust the research scope to the REC representatives across Europe as the responses from this group were the most positive.

The list of member countries of the European Network of Research Ethics Committees (EUREC) was identified as a comprehensive listing of countries from which we could objectively identify countries and, subsequently, participants (European Network of Research

Ethics Committees, 2022). The list includes countries within the European Union, hence governed or influenced by EU Regulations. Norway and Switzerland are members of EUREC signatories and are influenced by the Regulations. We included the United Kingdom because of its prior membership in the EU and EUREC. We emailed letters of invitation and consent forms to the listed organizations of the named European countries, which included details of the study objectives. The respondents reviewed, signed the informed consent forms, and returned them via electronic mail before the scheduled interview date. We persistently pursued referred contacts in countries from which we did not initially receive any response or from which we received a negative response. One of the challenges is that the focus of the study was to ensure we interviewed participants who served on RECs that reviewed human subjects research in their countries. Some initial contacts noted they did not sit on those RECs and referred us to colleagues who met the criteria. This strategy is called snowballing/respondent-driven technique (Handcock & Gile, 2011).

We used the virtual platform Zoom for the interviewing and recording. At the beginning of each interview, we reminded the participants of the study's objectives and the possible length of the interview and asked permission to record. The interviews lasted, on average, 45–60 min. With the supervisors' support, the PhD researcher conducted the interviews at different times. Although the interview schedule guided the process, additional questions were asked to clarify some responses. The interview schedule was updated with the new questions. The recordings were transcribed and saved under a pseudonym to protect the identity of the participants. The transcripts were uploaded to NVIVO 12 for coding and analysis. The interviews and data analysis took place between April 2021 and March 2022.

4.3.3 Webpage Content - Paper III

Paper III discusses the post-approval activities of IRBs in the USA. Similar to paper II, the method was adjusted due to recruitment challenges. Guided by the results of the first paper, an observation was made that US normative documents mandate various IRB post-approval activities, such as continuing review and observation of consent procedures. Since the research team is based in Europe, we conducted a preliminary google search regarding post-approval activities of US based IRBs using the search terms "monitoring, IRB, and post-approval". These search terms revealed that some US academic institutions had a program described as post-approval monitoring (PAM). The program description was featured on the university websites or, as they are officially known in the US, Academic Health Centers (AHCs). The research team reviewed these web pages and noted that it forms part of a Human Research Protection Program with oversight by the Office for Human Research Protection (OHRP). The decision was made to proceed with a content analysis of IRB web pages describing this program and to invite representatives to participate in interviews via the Zoom platform. Unfortunately, the response rate was also low because many of the AHCs' IRB staff were working remotely, and the offices were closed. Two AHC compliance program directors consented to the interview. These interviews took place in September 2021. Although the interviews gave us further insight into programmes, the research team decided not to include the interviews in the data analysis because of low representativeness.

We searched the OHRP database of registered IORGs and IRBs to identify the number of active IRBs in the USA. Of the 2598 registered university and hospital-based IRBs, 1581 were active. Only IRBs with designate IRB#1 for AHCs with multiple IRBs listed were selected to prevent duplication. The final number for analysis was 235.

Of the 235 IRB websites, 24 explicitly used the title Post-approval monitoring (PAM) or noted the term in the general web content. Based on the relevance of the content described, we identified other programs under headings such as quality improvement, quality assurance, routine monitoring, research congruency, audits, and research or compliance monitoring. The selected AHCs described post-approval monitoring as a heading and noted post-approval activities related to compliance checks of IRB-approved protocols. Web pages that referred to non-human studies were excluded. We note that the pages broadly described post-approval activities for human studies that were not specific to clinical trials only. We selected fifty-four (54) active AHC's IRB web pages from 30 States and the content extracted for analysis. A spreadsheet was created of the active registered OHRP/FDA University-based IRBs and imported into Microsoft Excel 2016. A list of the web pages that met the eligibility criteria was generated. The relevant content for selected webpages was copied into Microsoft word and uploaded to QRS NVIVO 12 Pro for coding and coding,

4.4 DATA ANALYSIS

After collecting the data relevant to each objective, we discussed and agreed on the appropriate data analysis methods. The primary strategy throughout the research was content analysis using Braun and Clarke's textual analysis approach (Braun & Clarke, 2006, 2020). The process required contextualization, re-contextualization, and data categorisation (Braun & Clarke, 2006, 2020). Braun and Clarke's six-step approach to thematic analysis was necessary for refining the data into an intelligible, coherent report that reflects both the manifest and latent interpretation of the data (Braun & Clarke, 2006, 2020). The steps include 1) familiarization, 2) coding, 3) theme generation, 4) reviewing of themes, 5) defining and naming themes, and 6) writing up and reporting the findings (Braun & Clarke, 2006, 2020).

4.4.1 Familiarization and coding

The familiarization process entails reading the documents multiple times to identify patterns. All the documents were printed and organized in a folder. The PhD researcher read each normative document. Phrases were highlighted, and notes were made when terms were identified as relevant to the research question. I also recorded my reflections during the reading process. When patterns were observed, these were discussed in meetings with supervisors. After several readings, the electronic versions of the documents were uploaded into a qualitative data analysis software, NVIVO Pro version 12. The NVIVO files were shared with the supervisory team, reviewed, and categories revised when there was disagreement. Coding was an iterative process as large categories were condensed into sub-categories. We first identified patterns across the documents that could be described as activities of RECs/IRBs after they approve protocols. These patterns were coded, and sub-nodes were created to ensure that all the data was thoroughly reviewed. After several meetings and discussions, the research team agreed on the main themes, with accompanying activities defined.

As previously stated, the analytical process employed a hermeneutic approach, i.e., a spiral process of reading and re-reading the text to ensure one understands the context and word meanings. The process was both descriptive and interpretative. Legal terms and context meanings were significant. Words such as *shall* or *must* have different interpretations in the legal field (Schmidt et al., 2010). Additionally, Europe and the USA have different judiciary systems and structures. Therefore, an awareness of the differences was necessary for the interpretative process. Different terms were also used to describe ethics committees within the various documents. We acknowledged and adopted the following terms as representing

research ethics committees throughout the project and for analytical purposes: (1) Research Ethics Committee (REC), (2) Institutional Review Board (IRB), (3) Institutional Review Committee (IRC), and (4) Independent Ethics Committee (IEC).

4.5 RESEARCHER CHARACTERISTICS AND REFLEXIVITY

My pharmacy, health law, and ethics background enabled me to approach this project with a good understanding of the normative guidelines that informed and governed clinical research. However, my experience was limited to theory and not practice. My preunderstandings were challenged when I read the various normative documents and engaged with REC members. I had no prior experience in Europe and the USA and a limited understanding of the European Union's and US legislative frameworks. I had to undertake extensive preparation to acquaint myself with the legal structure and systems in the respective regions. However, the interpretation of the legal instruments was positive because of my health law qualification and experience working as a pharmacy inspector in Jamaica. I enjoyed the process of familiarization with the actual legal documents in Paper I.

The interactive part of the research was personally challenging because many participants did not speak English as their first language. There were moments as a researcher when I wondered if the English word used by the participant was what the individual truly meant or whether I was hearing what was said correctly because of the various accents. There were times of self-doubt on whether we accurately interpreted and represented the findings. However, the response from the participants when asked to review the results and subsequent publication was positive. Additionally, one of the project supervisors is fluent in several languages and participated in several interview sessions where translation may be required. This is usually for the rare moment when the participants struggle to find the appropriate English equivalent of a word or phrase in their mother tongue language.

4.6 TRUSTWORTHINESS, CONSISTENCY, AND APPLICABILITY

The subjective nature of the interpretative process of data analysis requires that researchers acknowledge biases and employ techniques to enhance trustworthiness. According to Noble and Smith, qualitative research is credible if it demonstrates 1) truth value, 2) consistency, 3) neutrality, and 4) applicability (Noble & Smith, 2015). Truth-value is enhanced when the researcher demonstrates reflexivity and reflection on their perspectives (Noble & Smith, 2015). They note some credibility strategies, which were incorporated in Paper II. The strategies include reasonable sampling of research participants, recording interviews that can be audited, use of verbatim extracts to support themes, and inviting participants to comment on the themes generated before the publication of results (member-check) (Noble & Smith, 2015).

4.6.1 Member checks

According to Creswell, member checking is a technical strategy to reduce researcher bias in the interpretive process by asking participants to review extracted themes and the final report (Creswell, 2014). Participants were therefore invited to comment on the accepted peer-reviewed article. A majority responded to indicate agreement with the extracted themes and data, while a few suggested minor adjustments. The pdf copy of the final edited article was

again sent via electronic mail with a deadline for responding. Only one person had a minor correction.

4.6.2 Verbatim Quotes and Triangulation

Admittedly, researcher influence was unavoidable during the generation of themes because of the interpretative nature of the process, particularly in relation to the normative documents and webpages in papers II and III. To minimize this influence on the results, verbatim quotes were extracted from normative documents (paper I), transcripts of participants (paper II) and webpages (paper III). According to Eldh et al., the use of verbatim quotes "relies profoundly on the appraisal and skills of individual researchers and teams; they must decide whether the quotations inserted into a paper or report are presented verbatim or are edited or condensed." They note that verbatim quotes are used to "demonstrate how the findings and interpretations have arisen from the data" (Eldh et al., 2020, p. 3).

Another key validation strategy is triangulation. According to Heale and Forbes, triangulation is a technique used in qualitative research design to "increase confidence in the findings through the confirmation of a proposition using two or more independent measures" (Heale & Forbes, 2013, p.98). Triangulation was employed using different data sources (documents, interviews, and webpages) and cross-checking with scholarly literature, guidance documents, regulatory websites, and researcher expertise in the subject area (Creswell, 2014; Heale & Forbes, 2013).

4.6.3 Structured Reporting and Peer review

Our reporting of the research process was detailed enough to be repeated and yield the same results. We structured the paper according to consolidated criteria for reporting qualitative research (COREQ) (Tong et al., 2007). The three papers underwent peer review processes (Creswell, 2014; Heale & Forbes, 2013). Critical comments from anonymous peer-reviewers contributed to improvements in the manuscripts (Creswell, 2014).

4.6.4 Applicability/transferability

The applicability or transferability of results to a situation with a similar or identical context is considered a reasonable alternative to the generalizability principle in natural science research. The study's findings were similar to published papers investigating similar questions and data collection methods. One example is a 1992 Australian study by McNeill et al. They explored researchers' experience with REC review via a mixed-method approach (McNeill et al., 1992). The second is a 1997 UK study by Jonathan Berry where RECs mailed questionnaires to research participants to explore the feasibility of REC monitoring (Berry et. al., 1997). De Miguel Berain et al. published a study in 2020 that also exemplifies the comparative content analysis of normative documents governing RECs and practice between the USA and select European Countries (De Miguel Berain et al., 2020). Generalizability, however, is limited because of potential differences in individual countries' legislative framework and culture. The sample size of the participants in paper II was insufficient to reflect the representativeness of all RECs. However, the participants had varied expertise and experience in research ethics and working with RECs. The expert interview is a qualitative research technique aimed at "gaining information about or exploring a specific field of action" (Döringer, 2020, p. 265).

4.7 RESEARCH ETHICS

The main ethical concerns for this type of qualitative research are informed consent, anonymity, confidentiality, and the researcher's impact on participants and data interpretation (Goodwin et al., 2019). According to the Norwegian Health Research Act, the project was not health research and hence exempt from review. The project overview included the study rationale, objectives, interview schedule of questions, participant invitation letter, and consent form submitted to the Norwegian Centre for Research Data (NSD). The NSD approved the proposal on November 11, 2019 (reference number 360856). Interview transcripts were de-identified using codes and stored in a password-secured server. The recorded data will be destroyed at the end of the project.

4.7.1 Rights of Data Subjects –Disclosure, informed consent, right to withdraw

We sent invitation letters to target participants for the stakeholder interviews and detailed consent forms. All targeted participants were experienced REC members who were competent and fully aware of their rights as data subjects in accordance with the General Data Protection Regulations 2016/679 (GDPR)(Wolford, 2022). The consent form and process documented the right to withdraw from the study at any time, the method and length of time for storage and storage and how the data would be used. The participants returned the signed consent forms via electronic mail.

4.8 Instruments and Technologies

This project took place during the COVID-19 pandemic. Some objectives and data collection methods were modified. In place of in-person interviews, we used the zoom video conferencing platform. Zoom is considered a suitable platform for qualitative research. The essential features are "convenience, ease of use, security, interactivity, unique features (e.g., screen sharing, video record option), and its ability to facilitate personal connections between users" (Archibald et al., 2019, p. 1). The QSR International NVIVO analytical software for qualitative data was used for the coding process. NVIVO provides a convenient medium for organising the data and searching for keywords and phrases throughout the text. The use of NVIVO is complimentary or may be used in place of manual coding techniques (Welsh, 2002). We used NVIVO version 12 for data analyses in the various stages of the project (Welsh, 2002).

Article	Design strategy	Dataset	Data analysis	Participants
1	Qualitative	Documents	Hermeneutic content & thematic analysis	N/A
2	Qualitative	Interview transcripts	Thematic analysis	Representatives of RECs from countries aligned with EUREC
3	Qualitative	Webpages	Content & thematic analysis	N/A

Table 5.0 Overview of research design for three Papers

CHAPTER FIVE

RESULTS

5.0 PART 1 –SUMMARIES OF PAPERS I-III

The first papers were published in March 2021 (Paper I) and August 2022 (Paper II). Paper III was submitted for peer review, sent back for revision, and resubmitted in October 2022. The following is a summary of the main findings in each paper.

5.1 PAPER I

Cox, S., Solbakk, J. H., & Bernabe, R. (2021). **The role of research ethics committees after the approval of clinical trial protocols in the EU and the USA: a descriptive content analysis of international and regional normative documents**. *Current medical research and opinion*, *37*(6), 1061–1069. https://doi.org/10.1080/03007995.2021.1905621

Hermeneutic content analysis of 19 normative documents identified fourteen (14) possible post-approval activities of RECs/IRBs. The coded activities are at the beginning, during, and end of clinical trials. The activities are described as either passive or active. Passive describes those predominantly paper-based activities, while active refers to activities where REC/IRB members/staff or other representative visits the trial/research sites. These activities will be discussed within the context of role expectations (see below). Examples of themes and sections coded are detailed in paper I. These are visual representations of the actual activities, the identified documents, and the frequency of codes.

5.1.1 Activities at the commencement of the trial

Of the 19 documents reviewed, only the EU Regulations 2014 requires that notification of the start of a trial should be sent via the EU Portal.

5.1.2 Activities during and at the end of the trial

The identified post-approval activities were:

- Conduct continuing review
- Receive notifications of protocol amendments
- Receive notifications of adverse events
- Receive notifications of protocol deviations
- Receive notifications of protocol violations
- Receive notifications of premature suspension or termination of a trial
- Receive end of the trial declaration

- Receive final report
- Verification of trial procedures-e.g., observation of informed consent process,
- Authority to suspend/terminate a trial
- Maintain records
- Communicate with Regulatory Authorities

Depending on the jurisdiction, on receipt of notification of significant protocol amendments, serious adverse events, and communication on any of the above, the REC/IRB is expected to issue an opinion or withdraw a prior favourable opinion on protocol amendments (Cox et al., 2021b). It was not explicitly stated that REC/IRBs should respond or give an opinion on the final report (Cox et al., 2021). In the USA, the IRB can suspend or terminate clinical trials if necessary.

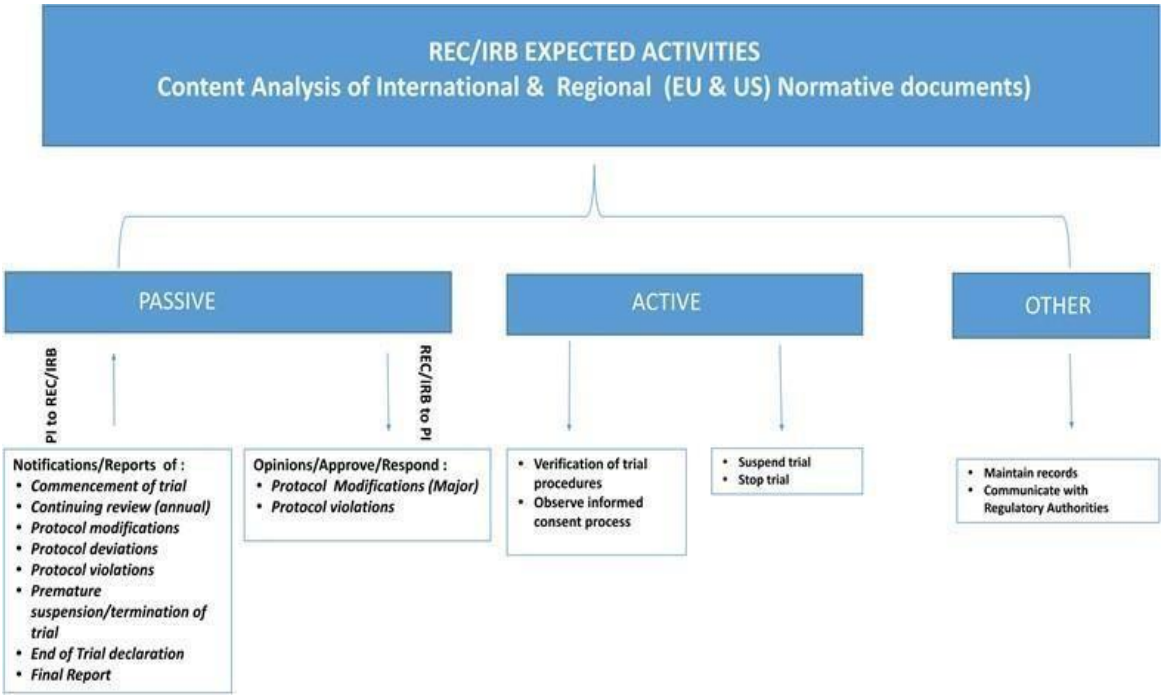

Figure 4.0 REC/IRB normative role expectations (activities)

5.1.3 Word meanings and interpretations in themes explanations

We observed ambiguous interpretations of terms in the examined normative documents. The researchers had to contextualise each meaning based on the accompanying activity description to ensure that the reporting was reflected as intended by the various jurisdictions. The continuing review was interpreted to be an annual review of the activities of an ongoing trial. Based on the FDA guidance document on continuing review, the written report was sent to the REC/IRB by the PI before the expiration of the initial approval. The continuing

review report was also mentioned in the ICH: GCP guidelines, but it was unclear whether this was an annual report similar to the USA.

We interpreted adverse events as unanticipated severe side effects that may cause injury or harm to research participants. Anticipated side effects were not classified as adverse events. The terms modification and amendment had the same basic interpretation of a change in the protocol. However, we note that modification meant *any* change in the protocol (major or minor). At the same time, amendments would be a significant change that may influence the initial approval, subject to REC/IRB review. It was not clear what was meant by significant amendments. A protocol deviation is a minor unreported change discovered by a monitor or inspector. In contrast, a protocol violation was a more serious unreported deviation that may affect the rights of the trial participants and influence the scientific validity of the results.

Safety reports were unclear and, as such, were categorized under adverse events. We observed a difference in the use of the word opinion in European documents while approval in US documents. This may imply a stricter enforcement responsibility on the part of the US IRBs compared to Europe.

5.2 PAPER II

Cox, S., Solbakk, J. H., & Bernabe, R. (2022). **Research ethics committees and post-approval activities: a qualitative study on the perspectives of European research ethics committee representatives**. *Current medical research and opinion*, 1–11. Advance online publication. https://doi.org/10.1080/03007995.2022.2115773

The EU participants note that PIs must submit protocol amendments (significant changes) to the REC for re-evaluation and a new opinion/approval. There was consensus that serious adverse events such as death should be reported to the REC/IRB. However, they thought that non-life-threatening safety reports were the RA's remit. Continuing review was not a term that representatives used in describing their activities. However, they note that annual reports were either mandated by law (depending on the law in the country) or may be voluntarily submitted to the REC by the sponsor/PI or they were unaware of this type of reporting. They note that the REC office personnel or Chair may review any submitted annual reports. Some representatives note that end-of-the-trial reports are to be sent to their RECs. Some representatives indicated these reports were not a requirement, while a few noted that the report was mandated in law. They also note that limited human resources and the voluntary nature of their positions as REC members would make it challenging to review annual, safety, or end-of-the trial reports. Minor protocol modifications were not expected to be submitted to the RECs. A majority of the representatives note that protocol deviations and violations were the remits of the Regulatory authorities. However, two countries note that their RECs may take action if they become aware of serious protocol violations.

Many of the REC representatives note resource challenges when asked their opinions on the active monitoring of clinical trials by RECs/IRBs. These resources were human, financial, capacity, and time. Weak organizational structure was also identified as a challenge, as most RECs are structured to have minimal support to receive protocols for prospective review and

essential administrative functions. Some REC members emphasized that they were volunteers appointed by the Government. Some questioned the legitimacy of active monitoring by RECs, citing a lack of legislative support. Others expressed concern about the perception by researchers that RECs may be acting outside their role, thereby creating an unwelcoming environment for sponsor organizations. One representative noted that additional fees might have to be charged to facilitate active monitoring. As such, RECs that currently charge to review protocols may have to increase the fees, or new fees may be created for those countries that do not now have a fee system. Emphasis was placed on trust between RECs and researchers. They note that active follow-up may negatively influence an already strained relationship. Concern was also raised about RECs being perceived as assuming a regulatory role. On the other hand, some representatives were of the opinion that it ought to be the responsibility of the REC to follow up to identify if the trials were conducted as approved.

5.3 Paper III

Cox, S., Solbakk, J. H., Luthardt, F., Jr, & Bernabe, R. D. (2023). **Institutional Review Boards and post-approval monitoring (PAM) of human research: content analysis of select university (academic health center) web pages across the USA**. *Current medical research and opinion*, *39*(3), 341–350. https://doi.org/10.1080/03007995.2023.

Using thematic analysis, we identified three categories with various sub-themes. The main categories are 1) Goals of PAM, 2) Reasons for study selection, and 3) PAM procedures. (See thematic map below).

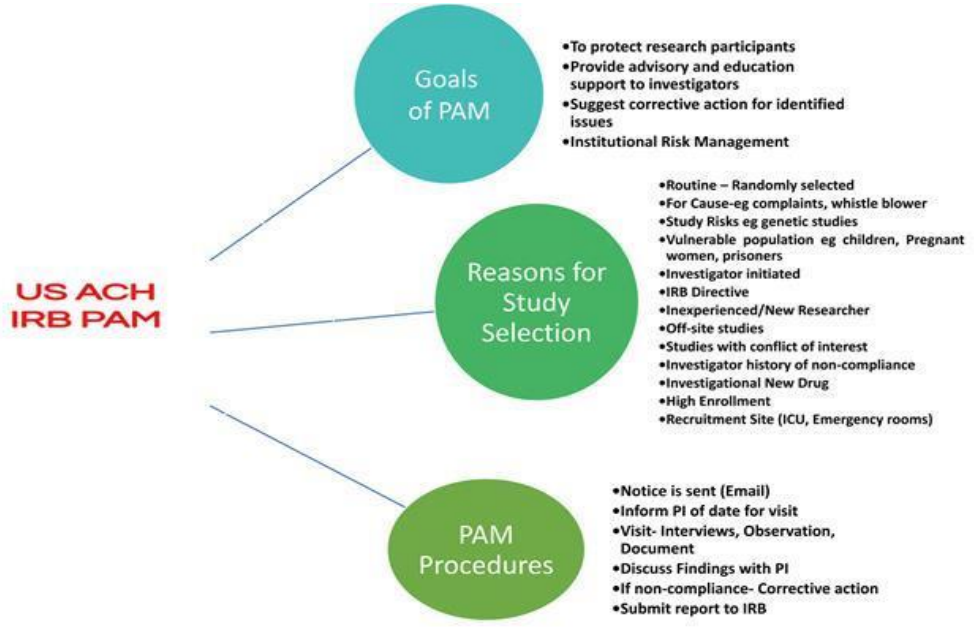

Figure 5.0 Thematic map for Paper III

The reviewed AHCs indicate that the overarching goal of the PAM program is to ensure compliance with IRB-approved protocols and to preserve research integrity. Other goals include 1) protecting research participants, 2) providing advisory and education support to investigators, 3) suggesting corrective action for identified issues, and 4) institutional risk management. There is consistency across all institutions regarding the expectations of the program. It could be interpreted that all other activities would be to achieve this primary objective. However, most emphasized giving advisory and educational support to researchers as an essential component of the program. The researcher may initiate this type of support when preparing for an audit by the US FDA or an external sponsor. If a researcher is new, the office may also facilitate training and conduct follow-up visits to verify compliance with the approved protocol. If the researcher has a history of non-compliance or a conflict of interest, the AHC may require additional monitoring. Although all IRB-approved protocols are subject to periodic review, there are situations when a complaint may prompt a visit. Exceptional circumstances include high-risk studies with vulnerable participants, high enrollment of participants, and where participant recruitment occurs in areas such as the Emergency room or the Intensive care Unit. During the visits, the PAM administrator/Monitor may review documents, conduct interviews, and observe informed consent processes. Identified non-compliance is discussed with the PI, and corrective measures are implemented. At the end of the visit, the PAM administrator generates a report and sends it to the PI. If necessary, the IRB chair or research compliance/integrity sub-committee would be informed for further guidance or action.

5.4 PART II: SYNTHESIS OF THE PAPERS

The findings were synthesized using the adopted role theory frame and reported in a structured narrative format in the Results chapter. The first table is organized based on excerpts from the three papers on the role expectation modalities of inscriptions, enunciations, and conceptions. The second table outlines the challenges or barriers identified across the various papers.

Table 6.0 Synthesis of Role Expectations using role theory schema

Role Expectations- Papers I-III		
Paper I	**Inscriptions (Rule, Representation)**	
	Continuing review, protocol amendments, adverse event reports, monitoring, terminate trial/withdraw a favourable opinion	
DoH	The committee, must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions	
GCP	The IRB/IEC should conduct continuing review of each ongoing trial at intervals appropriate to the degree of risk to human subjects, but at least once per year.	
EU	No change to the protocol may be made without consideration and approval by the ethics committee". EU Directive 2001/20/EC specifies that this should apply to substantial amendments. Research projects should be re-examined if this is justified in the light of scientific developments or events arising in the course of the research.	
USA	An IRB shall conduct continuing review of research covered by these regulations at intervals appropriate to the degree of risk, but not less than once per year, and shall have authority to observe or have a third party observe the consent process and the research	
	changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the human subjects	
	If the IRB determines that a research activity no longer meets the criteria for approval under 21 CFR 56.111, the IRB is not permitted to reapprove it, but may either disapprove it or require modifications in order to secure re-approval	

Paper II Enunciations (Demand, Assertion)

Annual reports are sent to the secretaries. They are not shared with the full committee unless there areserious adverse events (Participant #11- Ethics Chair).

So we say that we do not, do this continuing review, we only want to know if there is something that is substantial that would change the project. So no, we do not require yearly reports unless-, we have the opportunity to ask for it in special cases, if there's something specific with the project. But that's very, very seldom in my experience (Participant #12- REC secretariat).

The Ethics Committees get information from the pharmaceutical companies for any adverse incidents. Those come on a regular basis, and the Chairperson normally looks at those. If there are any major ones, that's brought to the Committee. (Participant #9-REC Vice- Chair)

Our state agency of medicine... they have the officer of clinical drug trials and this officer is the officer who monitors the drug trials ..... and they share the information with us if they find something related to ethical questions (Participant #3- REC Chair).

If we speak about monitoring, then I will say that the state drug agency is monitoring research. They visit the sites, they do inspections, and they see if there are any violations. It is also quite rare. It is not very often they do it .... In an ideal world, I would say that Ethics Committees should do independent monitoring, independent from State drug agencies, which would mean real contact with researchers, real visits on sites, or real contact with research participants, etc. But it is not happening (Participant #10, REC Vice-Chair).

Papers II & III Conceptions (norms, preference, belief)

We do not go unto sites and stuff like that. We only do a review based on information provided by the project manager, the research institution responsible for the research, and from regulatory authorities. So, we do not do any hands-on evaluation of that sort. But we review what kind of processes they have in place for those kinds of monitoring. So most clinical trials normally will report that they have an independent monitoring committee that will do that kind of work but we do not go into detail about that. I would say the system is based on a lot of trust, trusting that they will follow the law (Participant # 12- REC secretariat).

A Post-Approval Monitoring (PAM) program functions as the most significant quality assurance and improvement component of the Human Research Protection Program (HRPP) (Charlotte University)

The PAM program functions to maximize the safety of research participants and ensure data integrity by confirming that research is implemented in a manner consistent with the IRB approved protocol and in compliance with applicable regulations and institutional policies (University of Wisconsin).

I believe that some kind of monitoring of the running study is a good approach. But this should be done in a way that there is still a partnership of ethics committee and the researchers. We do not want to be considered just as a body who does government work. I think this brings distance into the system and this does not help to have good relationship between researchers and ethics committee (Participant #18, Head of REC secretariat).

Table 7.0 Factors contributing to divergent views on role expectations identified in the three papers

Factors contributing to divergent views on role expectations
1. Different Legislative authority across jurisdictions
Continuing review & Monitoring
IRB approvals in the USA are time restricted. Therefore, sponsors/investigators are encouraged to ensure that the research conforms to standards and submit research updates for continuing review before the expiration of the initial approval. FDA guidance on continuing review notes:
"A lapse in IRB approval of research occurs whenever an investigator has failed to provide continuing review information to the IRB or the IRB has not conducted continuing review and re-approved the research by the expiration date of IRB approval. In such circumstances, all research activities involving human subjects must stop. Enrollment of new subjects cannot occur after the expiration of IRB approval" **(Paper I)**
The 21 CFR 56 authorizes REC/IRBS "to observe the informed consent process or have a third party observe the consent process". A similar clause is not reported in the documents related to the EU **(Paper 1)**
Post approval monitoring forms part of compliance mechanism for the Federal Wide Assurance (FWA) terms for institutions that receive federal funding. **(Paper III)**
Sanctions
EU RECs/IRBs may withdraw favourable opinions or issue negative opinions but are not authorized to issue sanctions for protocol violations or stop the trials directly. **(Paper I)**
Due to federal oversight of IRBs in the USA, the FDA notes that IRBs have the right during the continuing review process to approve, approve with modifications/conditions or disapprove a study in progress. **(Paper I)**

Table 7.0 contd.

Factors contributing to divergent views on role expectations
2. Inconsistent meanings/interpretation of clinical trial nomenclature The US laws use phrases such as "authorized to approve/suspend/terminate" while the EU Directives and subsequent regulations use terms such as the "issuance of favorable opinion, withdrawal of opinion, and suspension or termination". From this, it could also be inferred that the EU views REC/IRBs more in an advisory capacity while the USA assigns more legal empowerment through its federal regulatory authority. The US federal system has more autonomy to issue stricter governance regulations than the EU due to the complexity of how the EU is structured on a regional level for harmonization without too much interference with member countries' independent rights to structure the ethics review process as they choose **(Paper I)** Although continuing review is identified in a majority of normative documents as what ought to be the main post-approval activities of RECs, this study reveals that within Europe, continuing review is considered part of the inspection remit of RAs. There are a few exceptions, such as Denmark and Estonia, where representatives of RECs have the right to verify that a clinical trials protocol are effected as approved. The lack of consistency could be that the ICH: GCP and the EU Regulation 536/2014, the main normative guidance documents for clinical studies, do not delineate the roles and responsibilities of the RECs and RAs in this regard. There appear to be overlaps and consequent gaps due to a lack of clarity on areas such as continuing review and post-approval monitoring. **(Paper II)**
3. Inconsistent reporting/response requirements The DoH notes that Ethics Committees ought to receive a final report of the trials' results regardless of the outcomes. The guidelines from CIOMS and the Council of Europe support submitting the final report to the REC/IRB. However, both the ICH-GCP and the WHO-GCP guidelines state that the final report should be sent to the regulatory authorities (Paper I) The expectation for REC continuing review is a form of passive monitoring and includes the adhoc receipt and review of annual progress reports for ongoing trials and a final report when the trial is complete. The participants opined that undertaking post-approval activities, such as active monitoring, is more work than RECs can handle. The submission of annual and adverse events reports to RECs is also not mandatory. In situations where the PI chooses to submit these reports, the REC chair or a designated person working with the REC, usually an administrative staff, may review the reports and then file them without any REC assessment. When a discrepancy or a breach is identified, and further guidance is required, the Chair decides if the matter should be brought before the full committee (Paper II). the status quo of RECs regarding post-approval activities of clinical trials in Europe as presented by the participants' responses is predominantly that of review of protocol amendments and receipt of end of trial reports**.** Although continuing review is identified in a majority of normative documents as what ought to be the main post-approval activities of RECs, this study reveals that within Europe, continuing review is considered part of the inspection remit of RAs**.** There are a few exceptions, such as Denmark and Estonia, where representatives of RECs have a right to verify that a protocol is being effected as approved. The lack of consistency could be that the ICH: GCP, the main normative guidance for clinical studies, does not clearly delineate the roles and responsibilities of the RECs and RAs in this

regard. There appears to be overlaps and consequent gaps due to a lack of clarity on areas such as continuing review and post-approval monitoring. **(Paper II)**

4. Availability/allocation of resource (Time, human, financial)

We do not have **resources** in ethics committees to really monitor research… that kind of resource is allocated to **competent authority.** They can do inspections and they have the right to withdraw the permission and things like that. In that sense, it is evident that they have the resources also. But the way ethics committees work, how we are organized, these members are taking part in the committee work on a voluntary basis, they have their actual work and business somewhere else than in this committee. **(Paper II)**

OHRP's FWAs, terms 4 and 5 require IRBs to have written procedures and institutional support (staff and space) for conducting the review, identifying non-compliance, and prompt reporting when necessary. **(Paper III)**

These AHCs appear to operationalize an organizational model in line with one of several models proposed by Charles Weijer for Ethics Committee monitoring. He proposed that research misconduct and better compliance could be addressed if ethics monitoring is organized to 307 conduct both passive and active monitoring of approved protocols. **(Paper III)**

The compliance unit performs various post-approval monitoring and directed review activities primarily to ensure the rights and welfare of research participants are protected. **(Paper III)**

CHAPTER SIX

DISCUSSION

The secret of change is to focus all of your energy not on fighting the old but on building the new (Socrates)

6.0 Overview

Research ethics and, consequently, research governance, has been undergoing a paradigm shift. Over the past decade, changes have occurred to ensure that the clinical research enterprise remains relevant, efficient, and effective. This thesis aims to contribute to this discourse by examining RECs/IRB through the lens of role theory and teleology. The aim is to strictly discuss the role of REC/IRBs in the context of expected behaviours, responsibilities and functions. This thesis does not intend to explore the quality and effectiveness of RECs/IRBs. However, the protocol violations of ethical relevance identified at the end of clinical trials implicitly signals a breakdown in the ethical oversight during clinical trials. In the introductory chapter, I highlighted some literature from various scholars who have published on the prospective role/activities of RECs/IRBs. There is seemingly a gap in the literature on REC/IRB's post-approval role towards the protection of research participants. This establishes the basis for this project's examination of RECs/IRBs post-approval role. The central goal is to explore REC/IRB post-approval expected behaviours and align these expectations with what ought to be done to mitigate against/address ethical issues identified during clinical trials. This is building on earlier research that identified that post-trial protocol violations remain unaddressed by Regulatory authorities. Whether RECs/IRBs could or should address these ethical violations required an inquiry into the role expectations of RECs/IRBs. To this end, in an attempt to set a foundation of understanding of the clinical research enterprise and how it functions, the earlier chapters expounded on the following:

1) the evolution of the clinical research enterprise-its past and current challenges,
2) the acknowledgement of the research enterprise as a social institution of various stakeholders,
3) the relevant theoretical frameworks and concepts that guide the investigation and analysis of RECs/IRBs, and
4) the methods and results from empirical research on the post-approval role of RECs/IRBs.

In this chapter, I will reflect on the results from the papers and discuss the results of the various papers in the context of some key role concepts and teleology. The main concepts to be explored in the discussion are role expectations, role identity, and behaviour based on the outlined objectives of the project.

6.1 Main REC/IRB post-approval activities to be examined in this chapter

The first step in understanding the post-approval role of RECs/IRBs was to explore and understand role expectations , i.e., what is said explicitly about RECs/IRBs in legislation and guidelines (inscriptions-Paper I) and by REC representatives (enunciations-Paper II), and conceptions (norms-Paper III). The analysis of international and regional normative

documents revealed a consensus (agreement) that REC/IRBs have various responsibilities after they approve clinical trials. The main expectations are that RECs/IRBs should have procedures for the follow-up of approved research, especially concerning the review and issuance of an opinion/approval for significant protocol amendments and receipt of notifications of serious adverse events. All three papers note that these activities were generally expected of RECs/IRBs regardless of region or country.

Post-approval follow-up activities by RECs/IRBs for protecting the rights, interests, and welfare of research participants range from passive review of reports from investigators/sponsors to active verification of trial procedures including observation and audit strategies. In Paper I, an outline of expected general activities of RECs/IRBs for countries in Europe as and the USA was presented (see figure 4.0 in the Results Chapter). However, the implementation of these activities vary according to regions and individual countries. It is therefore not the intent of this thesis to discuss REC/IRB activities at the micro level due to the variability in structures, processes, resources, legislative framework, and organizational/institutional culture of individual REC/IRB practices from country to country. Nevertheless, as mentioned earlier, Paper I reported the various post-approval activities that could be categorized as required, recommended or desirable based on how the activities are described in the examined normative texts. However, this interpretation is highly subjective and will only be categorized for ease of elucidating to the reader how the various post-approval activities are considered in the next two chapters. For example, wherever both the EU Regulations and the USA Code of Federal Regulations have published role expectations, those activities will be treated as required. However whenever there is a more lax approach and the role expectation is noted in a non-binding albeit influential normative document, those activities will be treated as recommended or desirable. Examples of strictly required post-approval activities across regions are the reporting of 1) significant protocol modifications, and 2) serious unanticipated adverse events such as those causing disability or death.

Other post-approval activities such as continuing review or receipt of annual progress reports is required in the USA but there are inconsistent expectations regarding this activity in the surveyed European countries. Activities that may be considered desirable are active post-approval monitoring and the review of final or end-of the trial report. Each of these activities have different proximate objectives and as such will be considered and discussed equally. The consideration is that the joint cumulative effect of each proximate goal enables the research to achieve its ultimate goal of protecting the participant. Table 0 summarizes the various activity, their corresponding objective and what is considered required, recommended and desirable.

Post-approval REC/IRB activities	Type	Corresponding Objective	Normative Consideration in Papers
Notification of protocol modifications/deviations/ violations	Passive	To identify if the study still meets the initial standards for ethical clearance	Required in Europe and the USA-**Papers I and II**
Continuing Review/Annual Reports	Passive	To evaluate the progress of the trial and review new information	Required in the USA-**Paper I**
Serious Unanticipated Adverse events reports	Passive	To identify if the trial should be suspended or stopped to avoid harm to enrolled and potential subjects	Required in the USA and Europe-**Papers I and II**
Active Monitoring	Active	To independently verify that the trial is being conducted as approved	Desirable but not mandated. Undertaken at the documented USA AHCs - **Papers I, II and III**
Suspend/Stop clinical trials	Active	To suspend or stop approved trials for a breach (non-compliance) or when new information indicate that the risk to enrolled participants is high.	Required in the USA and some EU countries– **Paper I**
End of the trial/Final Report	Passive	To facilitate comparative analysis and reflection on challenges that arose that were not foreseen that could be useful in future evaluations	Desirable –**Paper I**

Table 8.0 Summary of post-approval activities, corresponding objectives and normative considerations

6.1.1 Protocol Modifications/Deviations

The findings in Papers I (normative documents) and II (interviews) report that all major modifications must be sent to the RECs/IRBs for a new opinion/approval. RECs/IRBs are expected to reassess significant protocol changes to identify whether the protocol still met the original standards met at the initial evaluation and approval. This expectation is required regardless of region (USA/EU).

6.1.2 Serious Unanticipated Adverse Event Reports

All serious unanticipated adverse events such as causing death and disability are required to be reported. This reporting is required from the Sponsor/PI only. The DMC/DSMB plays a crucial role in identifying adverse events that may be considered serious and statistically significant and is usually the Committee to report events of this type to the sponsor. However, none of the three papers identified in normative documents or interviews that RECs/IRBs are mandated to receive reports directly from the DMC (DSMB). Earlier in Chapter two, it was noted that EMA guidance documents regarding DMC/DSMB note that this committee reports directly to the sponsor. There is no stringent requirement for reporting to the REC nor RA. Conversely, the US FDA note in their Guidance documents regarding DSMB recommends that sponsors/investigators ought to send these reports directly to the IRB citing legislative support for this type of reporting (U.S. Food and Drug Administration, 2006). However, it is still a DMC/DSMB - sponsor -IRB chain of reporting and not a direct from DMC/DSMB reporting directly to the IRB. It could therefore be inferred that receiving DMC/DSMB reports directly by REC/IRBs is not required but recommended in the USA (US FDA) and is expressed as desirable in other jurisdictions based on some publications on the subject. Direct reporting is noted as desirable if there is an incident of significance especially in light of an obvious conflict of interest when sent only to the Sponsor organization.

6.1.3 Continuing review/Annual Progress Report

Post-approval activities such as passive continuing review (annual progress reports) and active verification of trial procedures are supported by legislation in the USA (Office for Human Research Protections, 2010). Continuing review was not identified as explicitly required commonplace in the EU Directives nor Regulations. Paper II reports that annual reporting is not mandated in European countries based on the lack of awareness of REC members on whether their respective RECs in the surveyed countries received such reports (Paper II). Mention of continuing review or annual reports are in guidance documents such as the adopted version of the EU's ICH: GCP and the WHO operational guidance for RECs. It may also be important to note that although continuing review is legislated in the USA, publications highlight that US IRBs sometimes do not receive these reports. US FDA and other quality audit reports indicate IRB non-compliance in relation to receiving annual continuing review reports (Shetty & Saiyed, 2015; Bramstedt, & Kassimatis, 2004). It could be inferred therefore that although passive continuing review in the form of annual reports is either required or recommended across regions, but not always strictly enforced.

6.1.4 Active Post-Approval Monitoring

Paper III describes Active IRB post-approval monitoring (PAM) as a quality strategy of individual Academic Health Centres within the USA. Active post-approval monitoring is not noted as a norm among EU RECs (Paper III). Therefore, REC/IRB actively monitoring research in the form of physical verification of trial procedures or observation and audits by REC/IRB representatives may be considered desirable but not required. This assumption may be supported by the DoH, that only asserts a right to monitor approved research by RECs/IRBs (World Medical Association, 2013). The use of the term right to monitor instead of mandate may be interpreted to mean desirable but optional REC/IRB post-approval activity. The wording in the DoH implies that the clause may be conveniently applied if it is in tandem with an organization's goals and is feasible, i.e. if there are adequate resources (human and non-human) to enable active monitoring.

6.1.5 Suspend/Stop approved trials

The authority to suspend or stop a trial varies across jurisdictions. In the USA, IRBs are authorized in law to suspend or stop trials to protect the interests and welfare of research participants. However, authority to suspend or terminate varies among European countries. REC/IRB initiated suspensions or terminations may be considered required or desirable. EU REC representatives indicate that this authority is usually the remit of the RA.

6.1.6 Final or End-of Trail Report

The final or end of trial report is identified as a valuable source for comparative analysis between what was proposed to what actually transpired during the course of the trial. The final report also has the results of the clinical trial which can inform the REC/IRB of potential or not previously considered issues when evaluating similar studies. This type of reflection is described as retrospective review (Dawson, 2019). This type of post-approval activity may be considered desirable.

In summary, passive reporting of significant protocol modifications and serious unanticipated adverse events are required post-approval activities across jurisdictions. Passive reporting that forms part of an annual continuing review or progress is both required and recommended

depending on jurisdiction. Active post-approval monitoring and review of the end of trial or final report may be considered desirable, especially for quality assurance purposes. Acknowledging the highlighted difference across jurisdictions in REC/IRB expectations and behaviours and the joint interconnectedness of actions within a social institution towards the achievement of institutional goals, the discussion and recommendation chapters will examine all post-approval activities equally. The underlying assumption is that although each activity and its proximate objective, it is the cumulative effect of all activities that enables the ultimate goal of protecting research participants. If all activities before a trail is considered prospective ethics review, the activities in the middle or during the trial considered – continuing review, and the activities at the end of the trial considered retrospective review then the combined activities may be described as end to end ethics review.

6.2 Post-approval review activities - Divergent views

There is inter-regional (Europe: US) and intercountry (within Europe) dissensus on whether RECs/IRBs should conduct continuing review, receive and review safety and final reports. There was dissensus on whether REC/IRBs should be notified of protocol deviations and violations. There was also dissensus on whether RECs/IRBs have the authority to stop/terminate clinical trials.

Consensus was assessed by identifying whether most normative documents had themes coded under the various sub-headings. Dissensus was identified when comparing regions (USA vs EU) and variations in responses from the different EU representatives (Cox et al., 2022). Additionally, the responses of the REC representatives in Paper II and the content analysis findings in paper III were considered. Normative laws and guidelines within the USA explicitly described the post-approval expectations of IRBs outlining IRB responsibilities such as continuing review, verification of informed consent processes, receipt of unanticipated adverse events reports, and authorizing IRBs to stop trials. Paper I outlined these findings, supported by paper III. While paper I reported on the expectations in the normative documents, paper three reported the activities of US Academic Health Centers (AHCs) post- approval monitoring programs.

Contrariwise, within the EU, although Paper I indicates various expected activities of RECs guided by the EU Regulations, Paper II revealed a disconnect between the written expectations in normative documents and the enunciations of EU REC representatives. Many REC representatives were unaware or were not of the opinion that their RECs undertook activities such as continuing reviews in the form of annual reports or any form of active follow-up (Cox et al., 2022). They shared various challenges that would prevent them from undertaking these activities. Nevertheless, there was consensus among EU REC members that all significant protocol amendments should be sent to RECs for approvals and serious adverse events must be reported (Cox et al., 2022). However, some REC members were disinclined to receive and review annual safety reports, although this is a requirement in both EU regulations and ICH: GCP guidelines (Cox et al., 2022). There was also dissensus on active monitoring or follow-up of clinical trials among REC representatives (Cox et al., 2022).

Biddle notes that consensus and dissensus are usually detected when examining different modalities of expectations (Biddle, 1979). He states, “consensus may exist among norms, beliefs, or preferences or may be noted among enunciated expectations—likewise, dissensus (Biddle, 1979). The findings in the three papers are consistent with these observations, as

REC representatives in the EU shared divergent views during interviews on role expectations (Cox et al., 2022). Some role expectations noted in normative documents were not the enunciated expectations among European REC representatives. One could argue that the EU consists of many countries, and inter-country variability is an important consideration, especially given European countries' cultural and governance differences. A few countries, such as Denmark and Switzerland, note legal mandates to follow up on approved research by RECs (Cox et al., 2022). However, some participants emphasized a culture of trust between RECs and researchers. An interesting observation is that although Scandinavia is generally known for a trust culture, Denmark and Norway – two Scandinavian countries- had different approaches to post-approval follow-up (Dahlen & Skirbekk, 2021). Norway did not require this activity, while Denmark mandates this in law (Cox et al., 2022).

There was consensus on suspected unexpected serious adverse reactions (SUSARs) (European Medicines Agency,2017). The EMA notes that SUSARs are to be reported to Eudravigilance effective January2022 (European Medicines Agency, 2017). The EMA says that some countries may require that sponsors report to the Ethics Committees (European Medicine Agency, 2017). The emphasis within the EU is on the safety of the medicinal product, and the responsibility is delegated to the RA and sponsors to review and assess safety considerations of investigational new drugs (European Medicine Agency, 2017). On the contrary, annual reporting (continuing review) in the US emphasizes the research itself and a broader scope within the reports (Office for Human Research Protections, 2010; US Food and Drug Administration, 2017). It is, of course, important to highlight that we did not examine governance documents for individual countries within the EU. The main points of consideration that ought to be clarified were 1) whether it is the remit of RECs in the EU to conduct follow-up of approved protocols and 2) to what extent RECs would do such a follow-up. In paper II, it was noted by some participants that their RECs do not require annual safety reports. They note resource challenges such as 1) lack of capacity, 2) time and 3) trained staff. They also note that requiring this type of oversight may have a negative effect on research and researchers (Cox et al., 2022).

6.3 Inconsistent nomenclature and meanings

During the data analysis phase, one challenge was the inconsistent meanings of various terminology in the normative documents. Although clinical research is a global phenomenon, normative documents describe some activities that differ depending on the region. Nomenclature such as:

- continuing review and annual safety reports,
- periodic review and monitoring,
- sponsor monitoring and REC/IRB monitoring,
- End-of-the trial declaration/Final report

<u>Continuing review and annual safety reports</u>

The term continuing review is prominent in the US and the ICH: GCP guidelines (International Conference on Harmonisation, 2018; Office of Human Research Protections, 2010; US Food and Drug Administration, 2017). Continuing review in the US is a legal requirement for the continuity of approved research (Office of Human Research Protections, 2010; US Food and Drug Administration, 2017). According to the office for Human Research Protection, continuing review is conducted once annually and must have a majority

of IRB members present (Office of Human Research Protections, 2010). The main objective of continuing review is to examine whether the research is being conducted in compliance with the approved IRB protocol (Office of Human Research Protections, 2010; US Food and Drug Administration, 2017). The IRB will review reports on research progress, unanticipated problems with the research; sample informed consent form that was given to the research participants, subjects' enrollment/withdrawals, complaints, investigator/ institutional challenges, and any modifications to the original protocol. Since this is an annual federally mandated undertaking, the PI/Sponsor is subject to continued scrutiny throughout the life of the research (Office of Human Research Protections, 2010; US Food and Drug Administration, 2017).

Within the EU, annual safety reports seem to be most similar to what the US describes as continuing review (European Medicines Agency, 2017). According to the EU Regulations, a safety report on investigational medicinal products should be uploaded to the EU's clinical trials information systems (CTIS) annually (European Medicines Agency, 2017). The EMA notes that regulatory authorities and ethics committees may access the CTIS (European Medicines Agency, 2017; European Medicines Agency, 2020).
However, the RA is recognized as responsible for assessing the safety reports (European Medicines Agency, 2017).The findings in paper II corroborate this observation.

The term annual reports featured prominently during the interviews but not as a general requirement for all RECs (Cox et al., 2022). Some REC representatives note that the law mandates annual reports, but most representatives indicate that this report is optional (Cox et.al., 2022). It is unclear if the EMA's annual safety report is the EU's equivalent term for the continuing review mentioned in the GCP guidelines. Annual reports imply written submissions to be sent once each year to the responsible entity. The ICH: GCP guidelines outline what is considered continuing review in reference to the REC/IRB, not the RA:

> "The IRB/IEC should conduct continuing review of each ongoing trial at intervals appropriate to the degree of risk to human subjects, but at least once per year" (International Conference on Harmonisation, 2018).

Whether the EMA's annual safety report is equivalent to the continuing review mentioned in the GCP guidelines would be necessary for the EMA to clarify. Coincidentally, the US FDA also requires an "investigational new drug annual report" (US Food and Drug Administration, 2015). This report is different from what is described as the IRB continuing review. If both agencies are indeed harmonized, it would be reasonable to infer that the EMA annual safety report is similar to the US FDA's IND annual report. If we accept this interpretation, we could conclude that continuing review, as described in the GCP guidelines, is not a general role expectation in EU Member States.

Periodic review and monitoring

The ICH: GCP guidelines also have the term periodic review (ICH, 2018). This requires further explanation because of the various interpretations associated with another terminology, i.e., monitoring. Is periodic review synonymous with monitoring but occurs more frequently than annually?

The DoH refers to a right to monitor as an activity for RECs:

> "The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events" (World Medical Association, General Principles 23, 2008, para. 2).

However, the ICH: GCP refers to monitoring as an activity for the sponsor:

> "The sponsor should ensure that the trials are adequately monitored. The sponsor should determine the appropriate extent and nature of monitoring. The determination of the extent and nature of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the trial" (International Conference on Harmonisation, 2018).

During the data analysis for papers I and II, monitoring was not identified as a significant (theme) expectation for RECs/IRBs. However, based on the reworked strategy to conduct a preliminary literature search on post-approval activities in the US, the term monitoring was most significant in paper III. Examination of AHC webpages revealed that IRB monitoring was considered a separate activity from IRB continuing review. Post-IRB approval continuing review is primarily document review by the IRB itself. At the same time, post-approval IRB monitoring is an ongoing activity carried out by the staff employed by the AHC's IRB offices. Contrariwise, when the term monitoring was deliberated in paper II, some REC representatives expressed that monitoring was an activity for RA inspectors (Cox et al., 2022). The general view was regarding the legitimacy of such a role and the lack of or limited resources available to RECs for that type of activity (Cox et al., 2022).

As noted earlier, the DOH indicates a right of REC to monitor. While REC monitoring within the EU is not commonplace, monitoring occurs in different jurisdictions. Therefore, it would be necessary for the term monitoring to be properly defined in all normative research documents, distinguishing REC/IRB monitoring from sponsor monitoring. Policymakers could consider replacing the word monitoring with the term quality assurance as a descriptor for the sponsor, inspecting the RA, and relegating the word monitoring to the REC/IRB.

Alternatively, accepting that the term monitoring is already a well-established sponsor activity. In that case, the WMA could consider replacing the word monitor in the DoH with continuing or periodic review, explaining that continuing or periodic review includes a right to verify trial procedures. Currently, continuing or periodic review has the interpretation of document review. Of note, if the change is made in the DoH, it may still create challenges for a global interpretation of its meaning since continuing review is interpreted as a passive IRB process in the US, while monitoring is considered an active process. Additionally, a reasonable amount of literature uses the term monitoring as an activity of REC/IRBs across various jurisdictions (Bediako & Kaposy, 2020; Pickworth, 2000; Shafiq et al., 2020; Weijer et al., 1995). The description of monitoring by these scholars includes activities that are very interactive and not passive. Other words used to describe monitoring are the active follow-up of a trial or ongoing follow-up. Consistency is vital to achieving consensus on what monitoring entails and whose responsibility it ought to be.

End-of-the-trial and final report

Another term is the use of "end-of-the-trial and final report. Some normative documents refer to a final report, while others note a declaration of the end of the trial (Cox et al., 2021a). A final report implies a comprehensive report on the trial's findings. At the same time, a declaration of the end of the trial is a one-page document intended to communicate that the trial is complete.

Inconsistent terminology, dissensus, and divergence of views on REC/IRB post-approval role expectations signal challenges to role identity. The application of role identity in this thesis is regarding how REC/IRB members perceive or come to understand their roles. Having shared the various challenges with understanding role expectations and the divergent views of REC members, one can examine how this may influence the identity salience, authority, and legitimacy of RECs/IRBs, particularly within the EU. John Balmer highlights a lack of consensus on terminology as a contributory factor in creating what he describes as a fog in business' (organization's) identity (Balmer, 2001). Ezekiel Emanuel notes this as a challenge in his critical reflection on the 50th anniversary of the DoH- it uses "multiple and poor phrasings" (Emanuel, 2013, p. 1532). Frewer et al. also called on the EU to better define terms and concepts in clinical trial governance documents (Frewers, 2010). Transparency International UK notes that weak legislative and regulatory frameworks in the pharmaceutical industry contribute to a "lack of oversight" and "the inability to produce a universal anti-corruption response, which consequently limits uniformity between jurisdictions (Kohler et al., 2016, p. 28). They further note:

> "Attempts at international frameworks are also hampered by the need for state sovereignty acceptance. Nationally, the regulatory framework is often decentralised and key decision-points are self-regulated, which increases corruption risks" (Kohler et al., 2016, p. 28).

Papers I and II provide insight into the simple yet practically significant inconsistencies in role expectations in normative documents and enunciations of REC representatives. Inconsistencies and confusing nomenclature lead to inconsistent interpretations and subsequently inconsistent behaviours (Cox et al., 2021, 2022).

6.4 Role Identity

The divergent views on role expectations and inconsistent meanings of terms used to describe role expectations may contribute to dissonance in identity. A previous chapter shared that role identity is about internalized meanings and expectations associated with a role (Stryker & Burke, 2000, p. 289). This role concept was most explored in paper II, where representatives from 19EU countries shared their experiences and reflection on the post-approval activities of their RECs. Some of the EU REC representatives expressed that they did not wish to assume the role of regulators. Some expectations, in their opinion, were regulatory and not a matter for ethics committees (Cox et al., 2022). They also note that the REC members were volunteers and not employees. Although AHCs indicated on their web pages that their IRBs were within their rights to perform some of the exact role expectations that EU representatives considered regulatory, it was emphasized that the intention was not to "catch" researchers but to give support to their work. The AHCs note that their authority to perform many functions was based on legislative instruments that govern clinical research.

Similarly, the REC representatives who enunciated role expectations such as monitoring and reviewing safety reports also note that they derived this authority from the legislation. Therefore, it could be inferred that some role expectations will not be accepted as legitimate without being explicitly written in statutory instruments. Fear of being challenged by researchers may be a reasonable consideration for this way of thinking and subsequent behaviours.

Emma Pickworth, in her article on the prospect of REC monitoring in the UK, articulates the sentiments shared by EU representatives that a shift to monitor approved research may be perceived as "policing" of researchers (Pickworth, 2000). RECs/IRBs are already characterized with negative connotations such as "ethics police" and "IRB hyper compliance" for exhibiting what may be construed as behaviours outside the remit of an Ethics Committee (Babb, 2020; R. Klitzman, 2011). Although there appears to be compliance with IRB authorities within the US, this should not be interpreted that practices such as IRB post-approval monitoring are considered a legitimate role for IRBs. The legitimacy of this type of monitoring by Ethics Committees has been challenged. Emma Pickworth makes the critical observation that many institutions that engage in this practice have interests beyond the IRB (Pickworth, 2000). She notes that these institutions invest resources and have the structure to enable this oversight (Pickworth, 2000).

Additionally, she expresses concern that the voluntary independent nature of these IRBs may be compromised as they have to conform to more significant institutional obligations (Pickworth, 2000). Sarah Babb supports this intimation when she highlights the shift from proximate compliance to hyper-compliance due to punitive measures such as withholding federal funding from institutions where researchers breached HRPP guidelines (Babb, 2020). These considerations raise important considerations for how REC/IRB members perceive a post-approval role. Authority and legitimacy of REC post-approval activities would be very relevant for increased identity salience, i.e., increased commitment to post-approval role expectations (Biddle, 1979; Stryker & Burke, 2000).

6.5 Role Behaviours

This project did not aim to examine the actual behaviour of REC/IRBs. However, we managed to extrapolate from papers II and III some practices based on secondhand accounts, i.e., from the enunciations of REC participants and webpages of AHCs. The post-approval behaviours seem to be predominantly the review of various documents. These documents include protocol amendments, continuing review submissions, serious adverse events reports, final reports, and end-of-trial notifications. Continuing review submissions are a federally mandated requirement in the USA. However, annual report submissions within the EU vary from country to country. These reports may only be reviewed by the REC Chair or REC secretariat, not the full committee. Active monitoring is not a predominant activity in Europe but is part of the institutional research programs at Academic institutions in the USA. In Europe, the review of protocol violations is not regarded as a REC activity but the remit of the Regulatory Authorities. Further exploration of this role concept through empirical research using direct observations and appraisals may prove beneficial.

6.6 Justification for a post-approval role-Telos and neglected prima facie duties

6.6.1 The Neglected Prima facie duties - arguments for complementing the Belmontprinciples

Having reflected on the post-approval expectations, identity challenges, and perceived behaviours of REC/IRBs within the US and Europe, it invites one to consider the arguments proffered about the telos (REC/IRBs) of institutional role actors within the clinical research enterprise. It is generally accepted that clinical research should have social value. In that case, the aim is not simply to generate knowledge but achieve a collective good, ensuring the rights of all –involved in generating and benefiting from this collective good- are protected. However, the aforementioned is only considering intentions and ends, not the many nuances that arise during the process of clinical research. Emanuel, Wendler, and Grady outlined the following as fundamental to evaluating clinical research as ethical: respect for potential and enrolled subjects, informed consent, independent review, favourable risk-benefit ratio, fair subject selection, scientific validity, and social or scientific value (Emanuel et al., 2000). REC/IRBs play a critical role during prospective review by considering these fundamental values. It is now the accepted norm within research ethics and the evaluation of research proposals. The main ethical principles underpinning the evaluation criteria have been based on the Belmont Report's – respect for persons, non-maleficence, beneficence and justice (Brothers et al., 2019; Friesen et al., 2017; US Department of Health and Human Services, 1979). Several scholars have critiqued the principles as obsolete and insufficient to address modern ethical issues adequately. Some have argued for additional principles, while others focus on the areas in which the principles were lacking (Brothers et al., 2019; Friesen et al., 2017). It is also claimed that RECs/IRBs focus primarily on respect for persons and avoidance of harm and less on justice (Edwards & Kirchin, 2004; London, 2020). I will not attempt to elucidate the various arguments regarding the Belmont principles but support the claim that there needs to be a "rethinking" of the way forward.

I reflected on some of William Ross's prima facie duties in the theoretical chapter. I will now attempt to argue that they can complement current Belmont ethical principles and be more broadly appropriate for purpose-driven research governance. The Belmont report acknowledges the duties of beneficence, non-maleficence, and justice. However, there are some of Ross' prima facie duties that I would like to classify as neglected but complementary duties. These are fidelity, gratitude, reparation, and self-improvement. I will discuss these neglected duties by adopting a frame (Figure 6.0) that organizes Ross' prima facie duties in the following categories; special relationships, Non-maleficence, and promoting the good (A defense and extension of W. D. Ross' ethics of prima facie duties, 2017).[1] I will now discuss the neglected duties in relation to the post-approval role of REC/IRBs below.

[1] The diagram was obtained from an online philosophy forum identified during literature search on Ross' prima facie duties. Additional search was conducted to identify the original source document but was unsuccessful. It was decided to acknowledge the source of the diagram without using the general information from the blog.

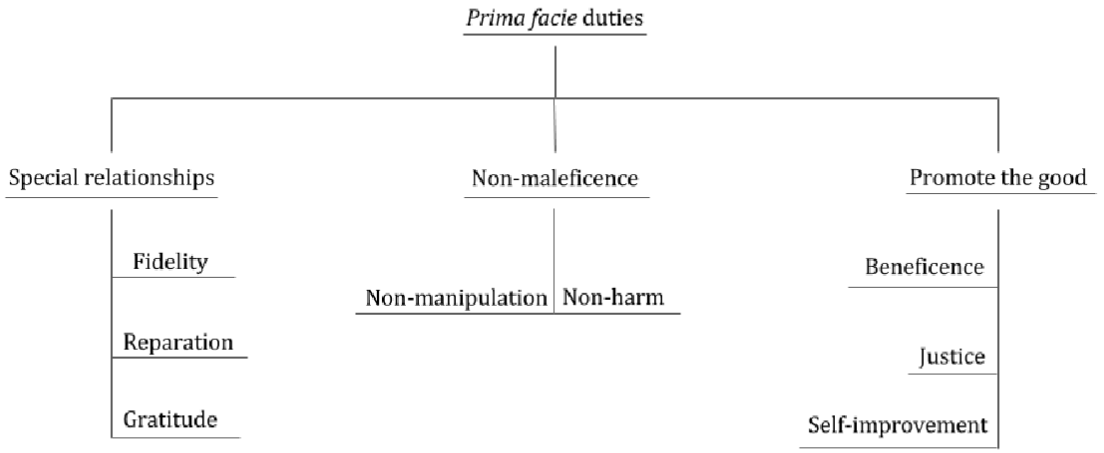

Figure 6.0 Categorization of William D. Ross' prima facie duties (A defense and extension of W. D. Ross' ethics of prima facie duties, 2017)

Fidelity

Earlier I applied the prima facie duty of fidelity by noting that RECs/IRBs have a duty to keep their promise, i.e. the commitment it makes to its stakeholders, primarily the research participants, that approved clinical research is ethical. However, I would like to accentuate further the relationship between the REC/IRB and other stakeholders, not just the keeping of promises. While the general role expectation of REC/IRB within the current model of clinical research is that approved research is assessed prospectively as ethical, the main stakeholder of focus is the research participant. If this expectation goes beyond prospective review to continuing and retrospective review, it would require examining the REC/IRB relationship with all stakeholders within the clinical research enterprise. Stakeholders would need first to accept that RECs/IRBs are responsible for ethics throughout the life of the clinical trial and cooperate with RECs/IRBs to meet this role expectation. With stakeholder acceptance and cooperation, the potential is significant. What is most fundamental about RECs/IRBs is the purported independence.

Assertions that REC/IRB monitoring may negatively affect the relationship with researchers are reasonable but do not rule out the possibility of positive outcomes if done judiciously. One reason for making this claim is the observation made earlier in the discussion that the bane of researchers with RECs/IRBs is bureaucratic inefficiencies and inconsistent decisions in multicentre trials during the prospective review, not continuing review. Another observation is that many of the arguments noting disagreement with REC/IRB continuing and retrospective review are centred on resource issues (Paper II). Although further exploration is

necessary to verify general researchers' attitudes to REC/IRB post-approval monitoring, we note that PI-initiated visits are typical in some US institutions (Paper III).

Should RECs/IRBs concede fidelity as a prima facie duty with all, not only research participants, the relationship between RECs/IRBs and its most disgruntled stakeholders (researchers) may improve? Certainly, fidelity to other stakeholders, such as sponsors/PIs, ought to be considered secondary to the fidelity to the research participants. An acknowledgement of a duty of fidelity to other stakeholders should be understood as part of the discharge of the commitment made to the research participant. Supporting sponsors/PIs by being available to them to address ethical queries would be the de facto protection of research participants. Cultivating a positive open-door culture for researchers would be contingent on RECs/IRBs addressing bureaucratic inefficiencies/inconsistencies and making ethics support readily available.

Addressing bureaucratic inefficiencies by examining and reinventing the organizational features of REC/IRBs does not diminish its core purpose. Over the past decade, regulatory agencies made changes to address bureaucratic inefficiencies across the examined jurisdictions. The EU has sought to address the issue of timelines by implementing a single portal and centralized reporting in the new Regulations (European Medicines Agency, 2020). The US has recently changed its Common Rule to exempt some studies from IRB review (DeRenzo et al., 2019; Dove, 2019). The EU streamlining its processes is similar to the US NIH's enforcement of the single IRB approval system for multi-centre trials in 2017. A model copied from the UK (Dove, 2019). Sarah Babb has coined the phrase compliance with efficiency as the ideal REC/ IRB-researcher environment (Babb, 2020). Babb notes that compliance with efficiency was facilitated by streamlining prospective IRB review through employing qualified staff and implementing efficient systems (Babb, 2020). However, she also expounds on some challenges with the requirements of the Common Rule and IRB review processes (Babb, 2020). She notes that the revised Common Rule is the era of compliance with flexibility (Babb, 2020). Important features of compliance with efficiency and with flexibility were expedited review, trained IRB staff, education of researchers, provision of ongoing ethics support, and quality audits (Babb, 2020).

Paper III highlights that IRB monitoring includes consultations, quality improvement audits, site visits, provision of educational resources, and suggesting corrective measures (Paper III).The US AHCs note that one of the reasons for study selection may be inexperienced researchers or researchers with a history of non-compliance (Paper III). If the emphasis is on relationship building (fidelity), trust will become a key value for improving stakeholder relationships. To the sponsor/PI/RA/patient organizations, the REC/IRB would be a partner/resource for ethical guidance. To the research participant, the REC/IRB would maintain its protectionist mandate.

Gratitude

It is well-established in scholarly ethics literature that the principal value of clinical studies research is that society should reap the benefit from research (Delden & Graaf, 2021; Habets et al., 2014). One form of demonstrating gratitude to research participants is to guarantee post-trial access to the benefits of research (Iunes et al., 2019; Usharani & Naqvi, 2013). Post-trial obligations are emphasised in the DoH (Usharani & Naqvi, 2013; World Medical Association, 2013). Another form of gratitude would be to recognise vulnerable participants and special communities. Friesen et al. and Schroeder et al. highlight that indigenous

communities and LMIC countries do not usually reap the benefits of research conducted in their communities/countries (Friesen et al., 2017; Schroeder, 2021). According to the CIOMS guidelines, REC/IRB should prospectively assess the social value of research:

> "Although scientific and social value are the fundamental justification for undertaking research, researchers, sponsors, research ethics committees and health authorities have a moral obligation to ensure that all research is carried out in ways that uphold human rights, and respect, protect, and are fair to study participants and the communities in which the research is conducted". (Council for International Organisations of Medical Sciences, Guideline 1, 2016, para. 2).

However, it is unclear if there is any follow-up during or after the trial to assess whether these obligations are honoured. Any contribution of social value to research participants could be elucidated in the final report noted in normative documents (Cox et al., 2021). This could form part of the retrospective review process proffered by Dawson et al. and inform future research (Dawson et al., 2019).

Gratitude to other stakeholders, such as research sponsors, would also include recognising them as essential to research and development. The EU's response by making legislative (EU Regulations) and process changes through the CTIS could be construed as recognition and gratitude by addressing sponsors' concerns. Additionally, many businesses now include corporate social responsibility as part of their business model (Nussbaum, 2009). Portraying an image of being an ethical stakeholder that gives back and contributes to the social well-being and development of future generations augers positively for public perception and trust. An accompanying obligation could be ensuring that research sponsors explicitly indicate in their protocols the societal benefits of their research, not just in product development but any contribution to a community or a particular research group. The REC/IRB could prospectively review and note the commitments to research participants. Then retrospectively, evaluate whether these commitments were fulfilled.

Reparation

The third neglected duty is reparation. One of the issues addressed implicitly in some research governance frameworks is mandating insurance for trial participants. However, in jurisdictions where insurance is not required, persons may become permanently disabled or die without any means for redress (Avilés, 2014; Minacori et al., 2012). High-risk studies or studies that are difficult to predict, for example, gene therapy or more complex technological interventions such as brain implants are examples of scenarios where research participants may be left worse off and without compensation. The duty of reparation would be a relevant consideration for the disabled participant or family. Ghooi notes that a lack of consistency in requiring insurance for trial participants creates confusion (Ghooi, 2022). European countries generally require insurance. However, this requirement's associated costs deter sponsors who may be inclined to go elsewhere to conduct trials (Avilés, 2014; Ghooi, 2022; Ghooi & Divekar, 2014). Insurance should not be optional as risks and uncertainty increase for research participants due to more complex technological interventions. I would further agree with Ghooi that RECs/IRBs ought to "read the documents carefully before approving them", i.e. the insurance sections of the research protocol (Ghooi, 2022). However, relevant to post-approval obligations would be for RECs/IRBs to play a part during continuing review on behalf of participants by checking on the number and type of harm experienced by participants. The RECs could follow up with the sponsor/PI on actions taken to address the

harm to participants. This is especially important in jurisdictions where insurance is not mandatory.

Self-improvement

If the purpose of RECs/IRBs were only to protect research participants from harm and exploitation, then the current Belmont principles would be sufficient. The principles of respect for persons and non-maleficence adequately address these areas. However, having applied Miller's teleological account, the clinical research enterprise is in fact a multi-stakeholder social institution with joint interconnected actions yielding both proximate and ultimate ends. Ideally, it is convenient to focus on the ultimate end, the generation of knowledge that is ethically appropriate and scientifically sound; however, it is imperative that we take into consideration the proximate ends of each stakeholder. Irrefutably, the proximate ends of stakeholders influence the conduct of research because of the interconnectedness of the institution. For example, the pharmaceutical industry's proximate end is to generate a profitable product. Therefore, it is not strange that the industry has been accused of and has faced sanctions for inappropriate conduct allegedly motivated by this proximate end. There is significant scholarship that the industry is rife with accusations of corruption. The call for rethinking relevant Belmont principles and re-examining the foundations of research ethics, the duty to improve is pragmatic. Recognizing these special stakeholder relationships, accepting the duty to avoid harm, and promoting the good, REC/IRBs must continuously improve its role activities to be better equipped to identify and respond to unethical practices.

Going forward, an important self-improvement strategy for RECs/IRB is the adoption of technology in the entire process of ethics review. Not only does incorporating technology help with bureaucratic inefficiencies, it can also help fight against corruption in the industry. Transparency International notes the following:

> "The need for "gatekeepers" and unregulated discretion for processes along the pharmaceutical value chain can be reduced by government agencies utilising technology. While it is impossible to completely eliminate face-to-face interactions between actors in the pharmaceutical sector, technology can help reduce or completely eliminate the role of human agents and avenues for opportunistic behaviour by digitalising routine procedures" (Kohler et al., 2016, p. 39).

Some European ethicists have criticized the new EU Regulations, labelling it a missed opportunity. However, EU RECs are acknowledged as key stakeholders with access to the CTIS (European Medicines Agency, 2020). If RECs embrace the implementation and make recommendations for its improvement, the possibilities for ethics oversight may be better than before. I will discuss this further under practical implications.

6.7 Promoting the Common Good-Relevance of Role Theory

The REC/IRB remains the principal institutional actor responsible for ensuring this protection. According to Savulescu, Chalmers, and Blunt:

> "Research ethics committees (RECs) are uniquely important institutions for at least two reasons. Firstly, they are the only regulatory point through which all proposed clinical research is likely to pass. Secondly, unlike other players who influence the

> research industry, they are unlikely to have strong vested interests in seeing particular results from research" (Savulescu et al., 1996, p. 1392).

The telos of REC/IRBs is that clinical research is conducted ethically, thus protecting the rights of research participants. The interest of these Committees ought to be motivated only by the good (summum bonum) for the research participants, science, and society. It is for this reason that REC/IRBs conduct a prospective review. There is consensus across jurisdictions and over time on these principles despite varying interpretations and subsequent applications. Although there is a plethora of criticisms meted out to REC/IRBs, those criticisms have been directed at bureaucratic inefficiencies, not the purpose. The protectionist role of REC/IRBs remains a well-respected one. An important consideration is how to address the role perceptions in the minds of researchers because of bureaucratic inefficiencies. There may be a need for a new approach to ethics education and implementation. As London outlines, a new way of thinking would mean examining the foundations of research ethics and subsequent governance. The examination would require critical reflection toward change. A role theory teleological approach enables one to visualize the main expectations, understand identity challenges, and recognize the steps necessary to achieve the telos of RECs/IRBs, i.e., the protection of research participants.

Many examples of unethical conduct in ethics scholarship are usually historical. However, mainstream media and current journal publications constantly highlight ethical concerns. During the COVID-19 pandemic, there were several publications on the role of research ethics during epidemics and pandemics, especially for the most vulnerable and when faced with high risks and uncertainty (Chappell & Singer, 2020; Solbakk et al., 2021). Many of the challenges outlined in the literature review chapter indicate that research ethics and governance are still under threat despite the laws, guidelines, and associated sanctions. Trust is diminishing in scientists, the pharmaceutical industry, and regulatory authorities (Parikh, 2021). Trust became a predominant consideration for the clinical research enterprise. Pharmaceutical companies and Drug Regulators are increasingly scrutinized and challenged by the public. The growing distrust of the pharmaceutical industry is justification for a paternalistic role. Alex London argues that this sustained protectionist role for REC/IRBs is essential. If the telos of research is to generate a collective end, which is a collective good. In that case, it is imperative that the one entity entrusted with this task be enhanced and expanded in its prominence and scope in the public's eye rather than diminished based on the singular interest of researchers being put off by bureaucracy.

Anglin, Kincaid, and Allen note that role theory "[…] provides a valuable tool to understand how expectations are tied to broadly held social roles,….influence important outcomes for individuals and place emphasis on how individuals interpret their in-role and extra-role experiences and treat roles as flexible and negotiated" (Anglin et al., 2022, p.1471). They clarify the main differences and value of applying the structural-functional application of role theory and the symbolic interactionist perspectives in empirical research (Anglin et al., 2022).They note that while some role expectations is "rooted in the macro-oriented structural- functional perspective in sociology that views society as structured according to a set of interconnected rules and laws that bring order to society," the symbolic-interactionist perspective "adopts a micro-oriented approach to studying the subjective meanings that humans impose on objects, behaviours, and events" (Anglin et al., 2022, p.1742). The application of role theory to the empirical study of RECs/IRBs incorporates both the macro and the micro perspectives yielding data that facilitate an understanding of the role expectations and some of the possible reasons there is a lack of conformity. Our initial analysis indicates the expected roles according to various normative documents. However,

the stakeholder analysis identified deviation from some of the expected behaviours. The identified differences are essential for the consideration of a way forward. When we align role expectations with the purpose (telos) of Recs/IRBs, we can suggest factors that could be further explored.

6.8 Practical Implications - Opportunity for RECs in the EU

Bernabe et al. raised the question of responsible persons/entities for the enforcement of regulatory sanctions in papers addressing post-approval protocol violations that are ethically relevant (Bernabe et al., 2019a, 2019b). They alluded to the fact that regulators and, to a lesser but still significant extent, the pharmaceutical company may have this responsibility. However, having ethics clearance by RECs/IRBs is a fundamental part of determining that a research protocol is ethically acceptable. For this reason, this project aimed to identify whether and to what extent RECs/IRBs have a role in addressing post-approval violations of ethical relevance. Our findings did not explicitly indicate a role expectation for RECs/IRBs concerning sanctions for post-approval clinical trial violations of ethical relevance identified by GCP inspectors. A possible reason for this lacuna is the lack of consensus and inconsistent interpretations on the legitimacy of RECs/IRBs doing what is perceived as a regulatory role. However, if one is to explore how RECs/IRBs could address this issue, the most probable medium could be the role expectation requiring RECs/IRBs to receive a final report. Suppose this final report has the sponsor's/PI's overview of the research and copies of inspection and sponsor monitor reports citing protocol violations. In that case, there is an opportunity for the REC/IRB to assess the findings and issue informed opinions on whether the trial was completed satisfactorily. This would be a form of passive follow-up activity as it would entail a report submitted to the REC. This type of reporting would need to be mandated explicitly in law to ensure consistency across all countries.

Although working together to address protocol violations could prove beneficial for science and society, there may be resistance. Bernabe et al. propose a four-step approach for addressing protocol violations. The steps are 1) identification, 2) analysis, 3) evaluation of possible courses of action, and 4) decision (Bernabe et al., 2019). Since GCP inspectors and regulators may not be the most competent in analyzing ethical issues, the first two parts of this proposed approach could be delegated to the REC/IRB, i.e., the identification and analysis of GCP inspection reports. The REC/IRB grading (gravity and magnitude) of the violation would inform an opinion on possible courses of action and, ultimately, the decision of the RAs.

Dawson et al. note that stakeholders may not embrace retrospective review due to perceived additional bureaucracy, inadequate support and funding, and fear of repercussions (Dawson et al., 2019a). However, the new EU CTIS may provide a medium to enable this kind of interaction between RAs and RECs. The single portal is accessible by EU sponsors/PIs, RAs, and RECs. The RA and the responsible REC could be alerted once sponsors submit their annual and final reports to the system. This would prevent additional paperwork and extended timelines.

Another strategy would be for RECs to reorganize their administrative structure to facilitate the employment of expert staff who are sufficiently competent in identifying and analyzing protocols for issues of ethical relevance not just as the end but during the life cycle of a

clinical trial. Certainly this type of ongoing review would require allocating more funding to RECs for office space, employment of competent staff, and requisite information technology equipment.

Additionally, expert staff could assist in a pre-screening process to assist researchers in identifying issues that may prevent their protocols from being rejected by RECs before the protocol is sent to the full Committee. This type of pre-screening, ongoing and end-of-process analysis would be resource-intensive. As noted by a participant, addressing resource issues may inadvertently cause an increase in fees. Still, the potential savings and revenue that would be an indirect benefit of the improved systems may be an incentive for sponsors. They have paid significant amounts to CROs and private IRBs in the USA to provide efficiency.

If ethics support begins with a prospective review and continues to the end of the trial with a stakeholder-inclusive approach that is efficient, the fear of repercussions could be dispelled. Researchers may welcome these types of ethics support. That is, unless the researcher has a blatant disregard for ethical standards. Dawson et al. note that

> […] it must be acknowledged that some identified problems could lead to criticism or even negative consequences for researchers. At the same time, If problems are identified, these need to be addressed. If researchers must face consequences for serious ethical violations, then retrospective review will have served a role in ensuring these are noticed and receive a response. An unwillingness to conduct retrospective review because it may bring ethical violations to light should lead to questions about the ethics and integrity of such research" (Dawson et al., 2019, p. 6).

The fear of repercussions ought not to be the compelling reason for failure to act if we consider that the purpose of ethics review is to ensure that research is ethical. Suppose RECs/IRBs conduct a retrospective review. In that case, this will fulfil the prima facie duty of keeping its promise that the approved research was conducted as promised, i.e., without infringing or exploiting the rights of the research participants. However, stakeholder support is key to attaining the paradigm shift in research governance from purely paternalistic to collaborative (A. London, 2020). Dawson et al. further argue that:

> "Retrospective review, if conducted openly and honestly, could promote greater transparency and fairness in assessment of research and this may help identify common values, different priorities, and potential disagreements between stakeholders and help consider how these might be resolved" (Dawson et al., 2019, p. 5).

However, while touting arguments for retrospective review, the authors do not strongly support continuing review, citing resource constraints (Dawson et al., 2019).

Nevertheless, other scholars have indicated that continuing review is a valuable resource for addressing ethical issues in research (Asghari & Ghalandarpoorattar, 2013; Shafiq et al., 2020; Weijer et al., 1995). What I am asserting is the argument that the primary purpose of RECs/IRBs within the clinical research enterprise is to ensure research is ethical, and achieving this requires a continuum for ethics review. This would enable an end-to-end approach to ethics oversight. This is especially important with new and emerging technologies fraught with uncertainties and unpredictable risks (Hermerén, 2009; Hirsch et al., 2019). Traditional risk models used by DMCs may not be feasible for new technologies

(Hermerén, 2009; Hirsch et al., 2019). RECs/IRBs continued involvement and oversight would enable a collaborative approach to ensure continued ethics oversight with a retrospective opinion.

Practical implications of this would be a culmination of the benefits proffered by the various scholarship on prospective, continuing, and retrospective review, i.e., the protection of research participants and in the context of the common good and justice- facilitating a research ethics environment that is supportive to researchers and beneficial to society. An end-to-end ethics oversight would fulfil prima facie duties of fidelity and justice. End-to-end is a commonly used term in business and technology. According to the Cambridge Dictionary, end-to-end is "from the very beginning of a process to the very end" or "including all the stages of a process" (Cambridge Dictionary, 2023). What is being proposed is not a new way of doing an ethics review but adopting a term that could facilitate a new way of thinking about ethics review. The various post-approval activities that have been described previously are activities that are currently undertaken by RECs/IRBs in multiple jurisdictions. The challenge, however, is the divergent view on what activities RECs /IRBs must undertake compared to what are optional activities. Also, as discussed earlier, inconsistent nomenclatures and interpretations/understandings of normative documents contribute to divergent views and behaviours. Accepting end-to-end ethics review as an overarching term to cover prospective, continuing and retrospective review may be a concept worth exploring. Figure 7.0 illustrates the end-to-end concept, while Figure 8.0 is a proposed process flow for how the RECs within the EU could efficiently conduct prospective, continuing, and retrospective reviews.

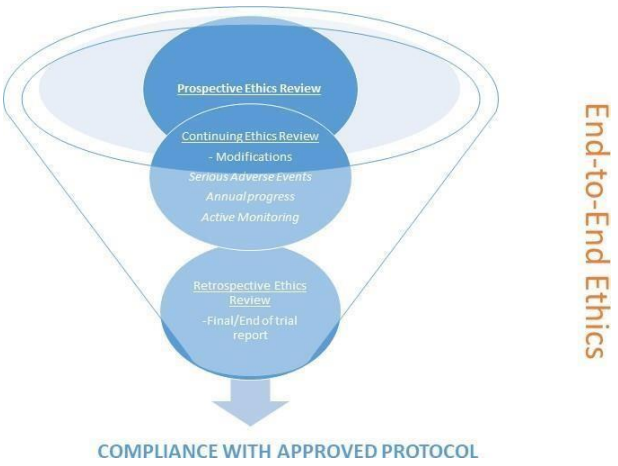

Figure 8.0 End-to-End Ethics Review

The new EU CTIS presents a unique opportunity for European RECs. This system enables various stakeholders to access information about a clinical trial simultaneously. If RECs employ expert staff to support the multiple tasks, the REC would be free to focus on the significant review processes and issue an opinion. The expert staff would facilitate efficient and comprehensive review processes by doing prior vetting of submitted protocols, ongoing assessment of sponsor safety, and GCP inspection reports. They could also review complaints from research participants. The single online portal combined with expert staff would enable

reduced paperwork and timelines. The DMC and CTSC could also directly submit their reports to the portal, removing the long-discussed conflict of interest issue. With expert staff conducting an initial assessment of protocols before submission to RECs during the various stages of the review process, they could engage the researchers and make suggestions to the sponsor/PI on red flags that could elicit negative responses from the RECs. In the US, these are called corrective actions. Should the sponsor/PI cooperate, would the REC only be involved when there is a blatant disregard for the proposed corrective actions? The REC (volunteers/appointees) would spend less time sifting through paperwork and more time deliberating the key ethical issues and issuing opinions.

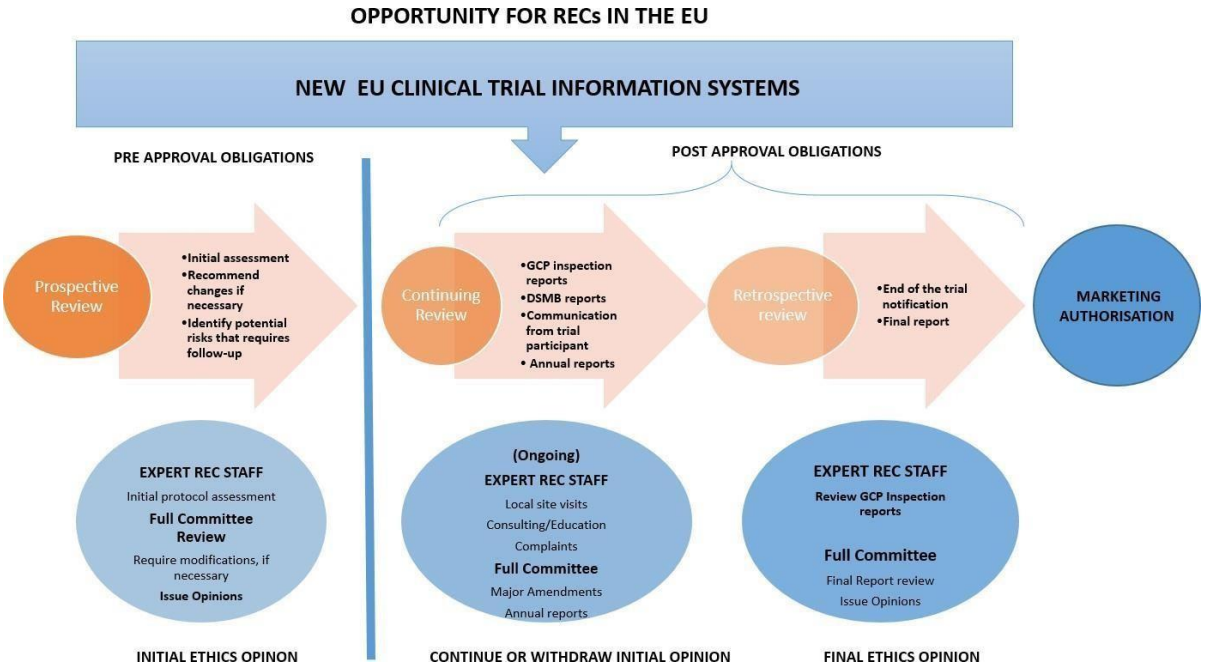

Figure 8.0 Diagram representing how EU RECs could utilize the new CTIS for ongoing ethics review

6.7.2 Quality and Effectiveness of REC/IRB review in protecting the interests, and welfare of research participants

Having discussed extensively on the post-approval role of RECs/IRBs within the clinical research enterprise in both the European and US contexts, then presenting suggestions for how the EU could enhance their current research oversight, I will now explore the topic of REC/IRB quality and effectiveness. Here, the discussion goes beyond considering what REC/IRB role expectations are but in the direction of how one can know that RECs/IRBs are meeting these individual normative expectations and their overarching goal of protecting the welfare and interests of research participants. How can quality and effectiveness be measured? Although an empirical examination of quality and effectiveness was not within the scope of this thesis, the emphasis on REC/IRBs having a role in mitigating against or addressing identified ethical violations at the end of a clinical trial begs the question of how best to measure the RECs/IRBs effectiveness in this capacity. Fortuitously, the topic of IRB quality and effectiveness is an ongoing debate in scholarships, both from empirical studies

conducted mainly in the USA and inter-disciplinary reflections from various academicians exploring the topic.

Three things are clear from a review of the literature on measuring REC/IRB quality and effectiveness, 1) there is agreement that an effective REC/IRB achieves the outcome of protecting research participants, 2) there is a lack of consensus on what research participant protection means, and 3) what is the best approach to measure quality and effectiveness (Abbott and Grady, 2011; Nicholls et al., 2012, Lynch et al., 2022; Tsan, 2022; US General Accounting Office, 2023). Notwithstanding, multiple scholarly responses are proffering different approaches to measuring quality and effectiveness and a significant number or tools. The various approaches to assessing this protection have been mainly what is described as surrogate measures or performance metrics focused on evaluating REC/IRB structure and processes, stakeholder experiences, regulatory compliance, and participant outcomes. A surrogate measure uses an "indicator that effectively represents another indicator that is intended to be measured" (Abdul et al., 2020, p.13).

Three systematic/scoping reviews of literature examining REC/IRB various quality assessment approaches and tools were published in 2011, 2015 and 2020 by Abbott and Grady, Nicholls et al., and Lynch et al., respectively. After examining 43 publications, Abbott and Grady identified inconsistencies in measuring quality across IRBs. They reported that empirical research examining REC/IRB quality was predominantly surrogate measures focused on the IRB structures, processes, and to a lesser extent, outcomes. They concluded that although there was a lack of consensus on how quality IRB review could or should be measured, the surrogate measures employed can be useful to a certain extent. Consequently, they made several recommendations. These are: 1) further research employing methods such as ethnographic approaches to observing IRB deliberations, 2) assessment of how changes to protocols influence outcomes, and 3) assessment of how changes to consent forms impact how well research participants understood research risks (Abbot and Grady, 2011).

Similarly, Nicholls et al's scoping review of 198 publications reported inconsistencies and a lack of consensus on appropriate assessment criteria for RECs/IRBs (Nicholls et al., 2015). Some of the quality measures they noted were 1) assessment of structural elements such as member compositions and expertise, 2) assessment of processes such as the number of protocols rejected or approved and timelines, and 3) assessment of procedural-interactional justice through the IRB researcher assessment tool. They observed that the predominant stakeholders in the reviewed literature were REC/IRB members, researchers, and non-research healthcare workers. Only 4% presented participant perspectives on REC/IRBs (Nicholls et al., 2015).

Some scholars have argued for the need to move away from using structure and process measures in assessing the quality and effectiveness of RECs/IRBs and to go in the direction of examining the participant's perspective. Coleman and Bouësseau drew attention to this challenge in their publication "How do we know that research ethics committees are really working? The neglected role of outcomes assessment in research ethics review." They argued for measures that consider research participants to be foremost in IRB quality outcomes assessments. They raised the following considerations: 1) "RECs should be able to identify what prospective research participants and their communities hope to get out of the ethics

review process" and 2) "whether REC review actually affects participants' subjective experiences in studies or their attitudes about research" (Coleman and Bouësseau, 2008, p. 5). Of note is that they centred their examples around participants' experiences with the consent process and how this influenced their decisions (Coleman and Bouësseau, 2008).

Lynch et al. systematically reviewed ten (10) evaluation tools used for measuring IRBs/RECs internationally. The following are the ten included tools:

> *"AAHRPP Tool: Association for the Accreditation of Human Research Protection Programs Evaluation Instrument for Accreditation*
>
> *FDA Tool: U.S. Food and Drug Administration and Office for Human Research Protections Guidance for Institutions and IRBs: IRB Written Procedures Checklist*
>
> *IRBRAT: Institutional Review Board Research Assessment Tool*
>
> *OHRP Tool: U.S. Office for Human Research Protections Self-Assessment Tool*
>
> *Orion Tool: Orion Accreditation Standards and Requirements*
>
> *RECAT: Research Ethics Committee Assessment Toolkit*
>
> *RECQASAT: Research Ethics Committee Quality Assurance Self-Assessment Tool*
>
> *SIDCER Tool: Forum for Ethical Review Committees in the Asian and Western Pacific Region Strategic Initiative for Developing Capacity in Ethical Review*
>
> *VA Tool: Quality Indicators for Assessing Human Research Protection Programs in the Department of Veterans Affairs*
>
> *WHO Tool: World Health Organization Standards and Operational Guidance for Ethics Review of Health-Related Research with Human Participants"* (Lynch et al., 2020, p. 210)

The tools varied in their focus from assessing IRB programmes for accreditation and regulatory compliance purposes to assessing researcher experiences, international best practices, and internal quality assurances/improvement measures. The authors organised the evaluation tools into three categories, namely; 1) REC structure, 2) review process and standards, and 3) post-approval outcomes. Tools that evaluated REC structure examined "their organization, allocation of resources and workload, and mission; the expertise and conflicts of committee members; and the training and educational resources they offer". (Lynch et al., 2020, p. 210). Tools that evaluated processes and standards examined "how they carry out their review and oversight of research, such as the processes for protocol submission, approach to reviewing research in different categories, continuing review, timeliness of reviews, approach to investigator complaints, and documentation and record keeping". (Lynch et al., 2020, p. 210). Finally, tools that examined post-approval outcomes focused on "what participants experience in research and how their complaints and questions are considered." (Lynch et al., 2020, p. 210). The authors noted that there was a dominance of assessment of REC/IRB structure and processes and less focus on participant outcomes.

Furthermore, that outcome measures such as risk and injury to participants and privacy and confidentiality were infrequently assessed (Lynch et al., 2020). The participant outcome measure that was most frequent identified in the evaluation tools was informed consent. However, it was still represented in only five of the ten tools. Lynch et al. argued that participant outcome measures were more relevant to REC quality assessment than turnaround times (a process measure), and suggested more focus on participant experiences (an outcome measure). However, others have questioned whether the assessment of participant experiences is a good indicator of REC/IRB quality or effectiveness as participant experience, like researcher experiences, may vary and are highly subjective. Instead, metrics that examine regulatory compliance have been proposed as more feasible (Tsan 2022).

Tsan and colleagues, in a series of publications published between 2010 and 2019 on quality assessment of Human Research protection programs (HRPP) at various Veteran Affairs (VA) IRBs, argued for measures to address IRB effectiveness, some of which have been accepted and challenged by other scholars (Tsan et al., 2010, 2013,2019a, 2019b). Tsan and his co-authors' publications on the VA program support regulatory compliance as an important factor for consideration when reviewing IRBs. Compliance measures employed in the VA audit process include auditing the number of approvals, suspensions, continuing review, and sanctions. Nevertheless, although he highlighted improvements in applying these types of quality metrics at the VA institutions, he noted that improved compliance with regulations does not mean research has achieved its ultimate goal. In a 2019 publication, Tsan, proposed the need for a consortium of IRB to deliberate and identify clear quality and performance metrics to know if IRBs do fulfil the goal of protecting research participants. In addition, he emphasised the need to distinguish between IRB quality and IRB quality reviews. However, his article stirred several commentaries regarding the emphasis on compliance metrics (Tsan, 2019a, 2019b). Holly Lynch, Eriksen, and Clapp responded to Tsan, noting that other metrics, such as research facilitation and participant protection, would be more critical. They noted that stakeholder interviews identified these metrics as key in assessing outcomes and concluded the following:

> "[…] we found that compliance and efficiency, not participant protection or careful deliberation, were at the core of how those in the trenches – directors leading IRBs and HRPPs at major research centers – reported their institution's visions of IRB quality. Given that other stakeholders prioritized thoughtful review and participant protection, a critical next step is to work on re-centering the entire IRB enterprise on its primary purpose. A reckoning is needed in which regulators, institutions, IRBs and the offices that administer them, research ethicists, researchers, and research participants collectively ask what is truly in service of participants, what types of IRB requirements and oversight will best achieve those goals without unduly inhibiting research, and what can be stripped away from the audit culture that has become so entrenched in this realm. Whereas our study asked how to define and measure IRB quality, further empirical research could productively focus on how best to move from compliance to meaningful protection, and more specifically, what meaningful protection – without overprotection or over-auditing – should look like" (Lynch,Eriksen, & Clapp, 2022, p. 9).

Tsan responded to his critics by giving examples of how regulatory compliance metrics have historically played a key role in improving HRPP and IRB effectiveness. He cited examples of Jesse Gelsinger and Ellen Roche, and described how the subsequent sanctions on the affected IRBs influenced the entire human research protection ecosystem in the USA (Tsan, 2019b).

Furthermore, he noted that despite the constant call for quality and effectiveness metrics beyond compliance, the proponents of this argument have yet to present these measures (Tsan, 2019b). Despite the negative feedback from Tsan, Lynch and colleagues have taken up the challenge to answer the question of what ought to be considered appropriate measures for assessing IRB quality and effectiveness. Their response is the establishment of a consortium aptly named the Consortium to Advance Effective Research Ethics Oversight (AEREO) (Lynch, Eriksen, & Clapp, 2022).

In addition to the ongoing dialogue among academics, the US Government Accountability office (US GOA) has embarked on its own examination of the topic. The US GOA recently published its findings after examining federal laws and conducting stakeholder consultations, concluded that:

> "[…] the HHS and FDA conduct annual risk assessments to determine if the agencies are routinely inspecting an adequate number of IRBs and to optimize the use of inspections in the oversight of IRBs and protection of research participants, and examine and implement approaches for measuring IRB effectiveness" (US General Accounting Office 2023, p. 60).

Not surprisingly, the US GOA focused on regulatory compliance metrics as a measure for evaluating IRB compliance but acknowledged simultaneously that compliance does not mean effective. They acknowledged that neither the OHRP nor the FDA has been able to "overcome the challenge of determining the best approach" to assess the effectiveness of IRBs in fulfilling the goal of protecting research participants. In addition, they noted the following:

> "An IRB is only one component of a larger framework charged with protecting human subjects, thus it is difficult to isolate its specific contribution relative to the actions of the sponsor, the institution, the investigator, or the research staff.
> There is lack of clarity about how IRBs and IRB reviews contribute to protecting human subjects" (US General Accounting Office, 2023, p. 60).

Having expounded on the challenges of identifying appropriate or the best metrics for assessing REC/IRB quality and effectiveness in the USA, it may be worthwhile to note at this time that this challenge would be significantly more difficult in Europe because of inter-country differences in how RECs are structured and their respective legislative and policy frameworks. Considering the various approaches and after examining the various tools and reflections, the measures that seem most suitable for assessing REC post-approval activities emphasised in this thesis may be regulatory compliance and, to a lesser extent, participant outcomes. The very basis of this thesis is the findings in the GCP inspectors' reports that revealed unaddressed protocol violations of ethical relevance. These are compliance concerns. However, none of the scholarship here reviewed asserts that regulatory compliance was not a significant indicator but should not be the main indicator. Despite the lack of global consensus on effectively measuring ethical oversight by IRBs to know whether they were achieving their goals, adopting some form of measure is imperative. Holly Taylor noted that:

> "A measure of whether the oversight process is achieving the ethical goals of research oversight will allow institutions to monitor their human subjects' protection programs or to guide the investment of funds to improve performance to guide the investment of

> funds to improve performance. Institutions or social scientists can use the measure to assess the efficacy of interventions implemented to enhance the ethical quality of research (Taylor, 2007 p. 13).

Furthermore, she said that while lack of regulatory compliance has been a measure of assessment of IRBs' effectiveness, there ought to be a shift to examine IRBs beyond compliance measures. The phrase beyond compliance indicates outcome measures that consider key stakeholders, particularly the research participant.

There appear to be three main categories (surrogate and direct) for examining the effectiveness of REC/IRBs. The first is the well-established audits of RECs/IRBs by regulatory and accreditation agencies with a focus on the structures and processes of RECs/IRBs in relation to regulatory compliance. This measure would be appropriate for assessing the time after receipt to respond to reports for protocol modifications, annual progress reports, and the end of the trial report. Additionally, whether actions are taken when serious unanticipated adverse events reports are submitted. The second is the assessment of the efficiency of RECs and the impact on the researcher experience by employing tools such as IRB-RAT. The consideration in this type of experience is the number of protocols approved in a timely manner and support during the research process. The third is stakeholder focused, most importantly, the research participant and their experiences with the undertaken research. The focus on research participants would be to examine informed consent procedures, adverse effects, and knowledge and awareness of how RECs respond to complaints and actions taken when violations occur.

Earlier in this thesis, the suggestion was made that the EU and its CTIS portal offer a unique opportunity for EU RECs to review reports from sponsors/investigators (researchers), regulatory agencies (sanctions and inspection reports) and patient complaints. Presently, the emphasis on using the CTIS is for improved timelines by having a single communication channel. However, this channel provides opportunities for increased follow-up (albeit passive) by RECs and RAs within the EU. Over time, using the CTIS to review reports by trained qualified REC representatives may allow individual RECs to be more aware of challenges that arise in clinical trials, implement active monitoring as needed and provide the necessary guidance to researchers. However, should RECs incorporate these suggestions, there would need to be some form of measure to identify if the follow-up makes a difference. The on-going dialogue within the US can present a starting point for organisations such as EUREC to explore this topic among EU Member States through its network. EUREC, in collaboration with the European Medicines Agency, may host a consensus forum with regional and international experts to identify the most suitable approach or tool for assessing REC quality.

Additionally, they can build alliances with consortiums such as AEREO (Advancing Effective Research Oversight), a US-based group led by Holly Lynch (The Trustees of the University of Pennsylvania, 2023). AEREO has published several recommendations for evaluating REC/IRB effectiveness (The Trustees of the University of Pennsylvania, 2023). Some of the recommendations include developing tools that focus on 1) regulatory compliance while minimising audit culture, 2) prioritizing participant protection outcomes, 3) assessment of processes and standards likely to promote participant protection, 4) ensuring reliance on prior decisions to promote consistency, and 5) adopt quality assessments that incorporate feedback from stakeholders (The Trustees of the University of Pennsylvania, 2023).

By forging an alliance with AEREO, EUREC may subsequently, learning from their work examining various evaluation tools and approaches, adopt or develop a unique REC quality assessment tool tailored to the European context. It is beyond the scope of this thesis to suggest the essential components that ought to be considered for appropriately measuring the effectiveness of EU REC prospective or post-approval activities. However, in relation to the specific activities outlined earlier in the thesis, regulatory compliance and stakeholder (researcher/participant) outcome measures would be necessary. Hence, the recommendation for this type of assessment is to be a joint undertaking of EUREC and the EMA.

In summary, although the question of how REC/IRB effectiveness can or ought to be measured is still lacking expert consensus, there are various surrogate measures such as audits to assess regulatory compliance, increased stakeholder (research and participant) feedback can provide information that helps to identify where improvements are needed. As emphasized by Tsan, we cannot wait another 50 years to identify the most ideal outcome metrics beyond compliance. In the meantime, given that regulatory compliance is an important measure that has worked as proffered by Tsan with supporting evidence from decades of work with the VA system, the aspiration should be to have compliance with efficiency and one that satisfactorily considers all stakeholders.

6.7.3 The way forward – changing role perceptions by the rebranding of ethics review

One important first step towards achieving an end-to-end ethics review would be to address the perception that ethics review is predominantly prospective. Relevant stakeholders would need to be sensitized and engaged in discussing how ethics review could be accepted as a continuum beneficial to all involved. Organizations responsible for issuing normative documents, such as the WMA, the WHO, and the ICH, should deliberate on whether the nomenclature in their normative guidelines could be harmonized to facilitate the uniform interpretation and application of role expectations across the jurisdiction. One approach would be to incorporate a rebranding exercise.

Rebranding is a common practice approach in organizational development. It is a “continuing process whereby an organization responds to the dynamics in its business environment by changing its self-identity to survive and thrive” (Tevi & Otubanjo, 2013, p. 89). This process includes reconnecting to the organization's original mandate, identifying the challenges in negative perception, addressing these challenges, and re-engaging stakeholders to communicate the new brand identity (Balmer, 2001; Tevi & Otubanjo, 2013). It would be of paramount importance to stress the concept of compliance with efficiency proffered in Babb’s account of what took place in the USA. Compliance with efficiency/flexibility requires reorganizing the ethics review system to be responsive to the PI/Sponsor without compromising the protection of participants. A rebranded REC/IRB would require a comprehensive review of organizational structure, hiring competent staff, incorporating technology to reduce paperwork, and verifying standardized processes by an accreditation body. Additionally, there should be more ethics consults with researchers to offer ongoing ethics support. Therefore, standardised training of REC members in the EU by an agency such as EUREC could prove beneficial.

CHAPTER SEVEN

CONCLUSIONS AND RECOMMENDATIONS

The overarching post-approval role of RECs/IRBs is to conduct activities that would ensure the protection of research participants. This role begins at prospective review and continues throughout the clinical trial. Depending on the jurisdiction, REC/IRB role expectations are to examine and issue opinions, approve significant protocol amendments, and receive notification of serious unexpected adverse events. RECs/IRBs should also receive notifications of the end-of-the-trial or a final report. In the US, IRBs are mandated to conduct continuing reviews of approved research at least once annually. However, this is not the norm for RECs within most EU and affiliate countries. Although the ICH: GCP guidelines should provide harmonized regulations for clinical research across different jurisdictions, inconsistencies exist in the interpretation and implementation of the guidelines. The EU Regulations require an annual safety report that may or may not be reviewed by the REC/IRB but is unequivocally the remit of the RA.

7.0 Recommendations

The following recommendations are considerations on the way forward to facilitate harmonized post-approval role expectations and end-to-end ethics oversight:

1. Evaluate the continuing review and post-approval programmes in the USA to assess implementation and effectiveness in detecting and addressing protocol deviations and violations.
2. Harmonize meanings of clinical trial nomenclature in various normative documents such as the ICH: GCP and the DoH guidelines.
3. Forge alliance between European and US ethics and regulatory experts to attain consensus on how to define and measure quality and effectiveness of RECs/IRBs towards the protection of human research participants.
4. Create supplementary guidelines within the EU for REC prospective, continuing review and retrospective review of clinical trials using the CTIS portal
5. Implement sensitisation training of RECs across the EU in post-approval monitoring and continuing review of approved protocols.
6. Encourage EU countries to allocate more funds to RECs to enable organisational restructuring and employment of qualified staff to engage researchers throughout the research process.
7. Address bureaucratic challenges that contribute to negative perception of RECs by reducing timelines for prospective review while placing more emphasis on continuing and retrospective review.
8. Rebranding process to change stakeholder perception of REC/IRBs from a bureaucratic prospective review model of REC to an ongoing engagement entity that facilitates training and support researchers.

Additionally, the EMA should mandate that RECs/IRBs have access to DMC reports when the safety of the research participant is compromised or at risk. If there is perceived harm to participants, RECs in the EU should be authorised in law to withdraw their previously issued opinion or make recommendations for sanctions appropriate to the violation. The EU has the unique opportunity to facilitate efficient oversight with the CTIS by enabling all stakeholders to access submitted reports. If done correctly, this system would allow countries within (and allied to) the EU to achieve the shared objective of harmonising standards and reducing

bureaucracy without additional paperwork. These measures would be essential steps in the REC/IRB maintaining its telos within the clinical research enterprise towards society and fulfilling the prima facie duties to research participants. A role theory perspective is vital to explore role expectations, identity, and behaviours within institutions to help with identifying, restructuring/reorganizing, and rebranding to achieve their mandate efficiently.

Scholarship on the role of REC/IRBs has been predominantly on prospective review while continuing review and monitoring have been discussed to a lesser extent. Retrospective review is perhaps the least explored concept. The unique contribution of this thesis to the literature on the role of RECs/IRBs is an in-depth examination of their post-approval role expectations, identity, and behaviours. In summary, the findings and arguments presented in this thesis support more involvement of REC/IRBs by treating ethics oversight as an end-to-end process. In fact, it could be opined that ethical clearance should actually be at the end of a trial by issuing an opinion on the final report rather than approving a proposal.

7.1 CHALLENGES & LIMITATIONS

One of the project's objectives is to conduct a scoping review of the literature on the post-approval role of RECs/IRBs. The literature search and data analysis was completed. However, time constraints did not permit drafting the results to be included in this thesis. This part of the research will be continued and submitted for publication.

The COVID-19 pandemic influenced our ability to engage more stakeholders. There was a global work-from-home mandate. Low responses to invitation letters from targeted stakeholders in regulatory agencies, sponsors, and patient organizations forced us to only focus on RECs in Europe. We began interviews with representatives from one patient and two sponsor organizations. The perspective of these stakeholders could prove fruitful and possibly enhance the scope of the discussion. Still, we did not include the transcripts in our write-up of the data in paper III data due to the low representativeness of the population.

The qualitative nature of the research restricts the generalisability of the research findings. In paper I, some interpretations of latent meanings could be flawed and influenced by the researchers' biases and preunderstandings. Reflexivity was paramount to reducing these biases. The selected normative documents were limited to those in the English Language. In paper II, only one representative (albeit an expert) was interviewed from each country. It would be ideal to conduct further research and improve representativeness to assess intra-country variations in responses. However, since the aim was to conduct a lay-of-the-land empirical study, we did not go beyond the target sample size. We also did not verify the responses against legislative and policy documents in each country. We reported the information only based on what was disclosed during the interviews. Nevertheless, the applicability/transferability of the findings are trustworthy based on quality measures implemented throughout the project period.

7.2 FURTHER RESEARCH

The application of role theory to empirically explore REC/IRB post-approval expectations and behaviours requires further exploration. Additional stakeholder engagement is necessary to gain a comprehensive understanding of role expectations. The empirical study of the viewpoints of sponsors, regulators and patient organizations may provide unique insights. Additionally, research on the post-approval monitoring activities of US IRBs could provide a valuable understanding of the effectiveness of this type of follow-up. The employment of hermeneutic content analysis enabled us to identify challenges with the interpretation of nomenclature in normative documents that can contribute to varied responses in role expectations. Additional research could be done on this sub-topic to strengthen recommendations for clarification of terms in normative guidelines and legislation. I also believe that the model for ethics oversight using the CTIS could be implemented in a pilot study to identify whether such a model could work. This type of implementation study could inform future policies for RECs across the EU.

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PAPERS I-III

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Current Medical Research and Opinion

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/icmo20

Institutional Review Boards and post-approval monitoring (PAM) of human research: content analysis of select university (academic health center) web pages across the USA

Shereen Cox, Jan Helge Solbakk, Frederick Luthardt Jr & Rosemarie DLC Bernabe

To cite this article: Shereen Cox, Jan Helge Solbakk, Frederick Luthardt Jr & Rosemarie DLC Bernabe (2023) Institutional Review Boards and post-approval monitoring (PAM) of human research: content analysis of select university (academic health center) web pages across the USA, Current Medical Research and Opinion, 39:3, 341-350, DOI: 10.1080/03007995.2023.2175999

To link to this article: https://doi.org/10.1080/03007995.2023.2175999

Published online: 14 Feb 2023.

CURRENT MEDICAL RESEARCH AND OPINION
2023, VOL. 39, NO. 3, 341–350
https://doi.org/10.1080/03007995.2023.2175999
Article ST-0806.R1/2175999

Taylor & Francis
Taylor & Francis Group

RESEARCH ARTICLE

Institutional Review Boards and post-approval monitoring (PAM) of human research: content analysis of select university (academic health center) web pages across the USA

Shereen Cox[a], Jan Helge Solbakk[a], Frederick Luthardt Jr[c] and Rosemarie DLC Bernabe[a,b]

[a]Centre for Medical Ethics, Institute of Health and Society, Faculty of Medicine, University of Oslo, Oslo, Norway; [b]The Faculty of Health and Social Sciences, University of Southeastern Norway, Kongsberg, Norway; [c]OHSR Compliance Monitoring Program, Johns Hopkins University School of Medicine, Baltimore, MD, USA

ABSTRACT

Objective: To conduct a content analysis of IRB webpages of select universities (academic health centers) in the USA that describe post IRB- approval monitoring activities.

Method: This was a qualitative study. Thematic analysis was the method to review the webpage content of selected academic health centers (AHC) within the USA.

Results: Some US academic health "centers" IRB administrative or research compliance offices conduct post- approval monitoring (PAM) of human subjects' research including clinical trials. The goals of these PAM programmes are to (a) ensure compliance to approved protocols, (b) preserve research integrity, (c) manage institutional risks, d) provide advisory/educational support to researchers, (e) recommend corrective actions for identified issues, and most importantly, (f) to protect the safety, rights, and well-being of research participants. Although not a requirement by law, the PAM program has legislative support in the US Code of Federal Regulations as part of the US Office for Human Research Protection's (OHRP) Federal Wide Assurance (FWA). This is especially for institutions that conduct studies funded by the Federal government. PAM on-site checks reveal various incidents of protocol deviations and violations. This includes issues with recruitment processes, informed consent discrepancies, and incidents of non-compliance. When a study protocol is identified as non-compliant, the principal investigator works with the PAM monitor to develop a corrective action plan that would allow the study to become compliant and avoid sanctions from the IRB or the regulatory authority.

Conclusions: REC/IRB post-approval monitoring of clinical trials is a valuable mechanism of protection for research participants while giving educational and quality assurance support to researchers. The program enables early detection and resolution of non-compliance to approved protocols. The impact of the program in the USA requires further exploration.

ARTICLE HISTORY
Received 28 October 2022
Revised 24 January 2023
Accepted 31 January 2023

KEYWORDS
Clinical trials; compliance; Institutional Review Boards; research ethics committees; post-approval monitoring; protection; role

1. Introduction

The balancing act between advancing scientific knowledge while protecting research participants has been challenging. In the modern era, many historical incidents of unethical conduct in research with humans include instances of exploitation, deceit, scientific misconduct, and cruelty. In response to these troubling and sometimes tragic events, research ethics has emerged as a means to define and articulate the ethical principles necessary to protect and establish as values the rights, well-being, and best interests of research participants. Along with ethics, human "subjects" research regulations have been created to promote and safeguard these values. The development of this field of ethics includes normative guidelines, enforcement institutions, and compliance measures to facilitate prior vetting of research to ensure integrity in research while protecting the most vulnerable from the passionate pursuits of scientists[1]. The Research Ethics Committee (REC) is one of the main developments during this period. Savulescu, Chalmers and Blunt notes that

> Research Ethics Committees (RECs) are uniquely important institutions for at least two reasons: Firstly, they are the only regulatory point through which all proposed clinical research is likely to pass. Secondly, unlike other players who influence the research industry, they are unlikely to have strong vested interests in seeing particular results from research.[2]

However, RECs are not without their critics. On the one hand, there are complaints of excess oversight of clinical research, particularly for the initial review and approval of the protocols by Ethics Committees. On the other hand, there are outcries

CONTACT Shereen Cox shereen.cox@medisin.uio.no, coxshereen@gmail.com Centre for Medical Ethics, Institute of Health and Society, Faculty of Medicine, University of Oslo, Box 1130, Blindern, Oslo 0318, Norway

This article has been corrected with minor changes. These changes do not impact the academic content of the article.

regarding unethical practices and scientific misconduct. Successful clinical research outcomes contribute positively to public health. However, unethical research significantly impacts trust. Without trust, the entire research enterprise is compromised. Therefore the fundamental goal of clinical research is not merely to generate a safe product/intervention but to ensure the scientific and ethical integrity of the process. There are many approaches to achieving this goal, one of which is post-approval monitoring by Ethics Committees[3,4].

Research ethics Committees (RECs) or Institutional Review Boards (IRBs) are integral to research oversight. The US National Institute of Health first established an Ethics Committee for the prior approval of research in the 1950s. This became a legal obligation in the US by the subsequent promulgation of the National Health Research Act of 1974[5]. International and regional normative documents outline what ought to be the activities of ethics committees after the approval of clinical trial protocols in the EU and the USA[6]. A review of normative documents reveals that RECs are expected to (1) conduct continuing review, (2) receive notification of adverse events, (3) review and approve protocol amendments, (4) receive notifications of protocol deviations and violations, (5) suspend or terminate trials if necessary, and (6) withdraw favorable opinion or stop trials[6]. The authors highlight a difference in the legislative support for an active post-approval role for REC/IRBs in the USA compared to the European Union's (EU) regulatory documents for clinical research. A study of the experiences of REC representatives in Europe indicates that post-approval activities are mainly limited to the review of protocol amendments and receipt of end-of-the-trial reports. Active or passive monitoring of research is considered the remit of the National Regulatory authorities or Medicine Agencies[7]. Although European REC representatives acknowledge the possible benefits of post-approval monitoring, they note challenges with a lack of legislative support, organizational structure, and financial/human resources[7]. Brown et al. have also raised similar concerns regarding post approval monitoring in resource constrained countries conducting US initiated studies. Ethics post-approval monitoring seems to be an established practice within the US[8].

Anecdotal web and literature search on US IRB post-approval activities reveals that some research institutions, particularly academic health centers (AHCs), have implemented what is known as post-approval monitoring (PAM). These programs may be part of the institution's wider human research protection program (HRPP), which encompasses audit and research integrity activities, or may be directly connected to the IRB administrative offices. IRB administrative office support includes the prior review and approval of research and compliance monitoring of IRB-approved research[i]. Brown et al. and Melinda Young offers insight into the approaches to PAM. These include (1) administrative check-ins, (2) full on-site assessments, (3) self-assessments, (4) consent process review, (5) consent process observation, and (6) project team review[8–10]. The program's on-site or direct review assessment includes (1) observation of the research activity, (2) assistance to and education of the principal investigators (PI) in identifying deviations from the approved protocol, (3) implementation of any required changes, and (4) documentation of the findings of the PAM assessment[9,10]. Young's paper provides a basis for further exploration to identify the extent to which US institutions have implemented PAM and related programs and to assess its impact. This explorative study seeks to identify the post-approval activities of Institutional Review Boards (IRBs) within the US.[ii] However, it seeks only to provide a descriptive content analysis on select US academic health centers (AHC)[iii,11] based on the publicly available content on their websites. The focus of the paper is on post-approval activities that are connected to the IRB offices and the IRB itself. It may not address all the elements of the more comprehensive aspects of HRPP programs.

2. Method

2.1. Research question and scope

This study was guided by the research question, "What are the activities of IRBs after the approval of clinical research on humans in the USA?" It is part of a project with the overarching theme: Ethics and compliance post clinical trial approval: the role of Research Ethics Committees. The project's scope covers Europe and the USA, however, this paper only reflects on findings in the USA.

2.2. Data sources and search strategy

This study was a review of content on webpages of select AHCs in the USA. The Office for Human Research Protection (OHRP) database for Registered IORGs and IRBs was searched to identify the number of active IRBs in the USA. Of the 2598 registered university and hospital based IRBs, 1581 were active. To prevent duplication, only IRBs with designate IRB#1 for universities with multiple IRBs listed was selected. The final number for analysis was 235 (see Figure 1). Further screening of content is described under Section 2.4.

2.3. Eligibility criteria

Webpages of AHCs were eligible for inclusion if they broadly described post approval monitoring as a heading and/or note post-approval activities that were related to compliance checks of IRB approved protocols. Web pages that described quality assurance or quality improvement as an institutional audit function or risk management function but did not have content referring to IRB-approved protocols and compliance with these protocols were excluded. The focus on AHCs is based on an initial google search to identify which US IRBs mentioned PAM on their webpages. We then tailored our inclusion/exclusion criteria towards these institutions.

2.4. Title and content relevance screening

First author did a search of the selected webpages to identify post-approval activities listed on the webpages under the title of post approval "monitoring." This search was limited to human subject research. Of the 235 IRB

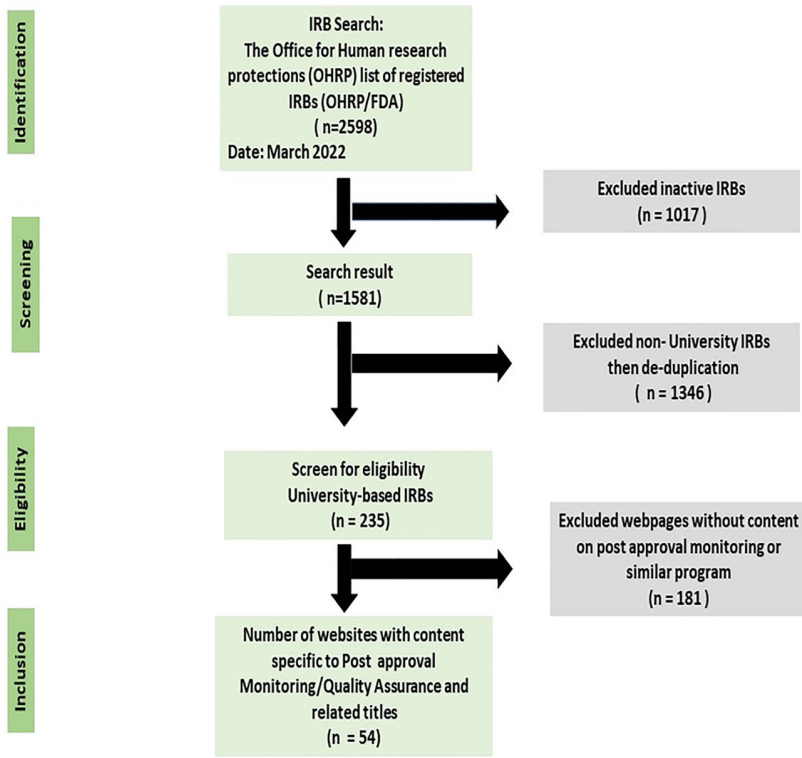

Figure 1. PRISMA flowchart of the selection process.

Table 1. States (30) and names of selected institutions (54).

	States	Institutions
1	Alabama	University of Alabama, University of Southern Alabama
2	California	Chapman University, University of California, University of Southern California
3	Carolina	Charlotte University, Duke University, East Carolina, University of North Carolina, Wake Forest
4	Colorado	University of Denver
5	Connecticut	University of Connecticut, Yale
6	Delaware	University of Delaware
7	Florida	Florida State University, Nova Southeastern University, University of South Florida
8	Georgia	University of Georgia
9	Hawaii	University of Hawaii
10	Illinois	Northwestern University, University of Illinois
11	Indiana	Indiana University, Purdue University
12	Louisiana	Tulane University
13	Maryland	John Hopkins University, University of Maryland
14	Massachusetts	Boston University, University of Massachusetts
15	Michigan	Michigan State University, University of Michigan, Wayne State University
16	Missouri	St Louis University, University of Missouri
17	Nebraska	Creighton University
18	New Jersey	Princeton
19	New Mexico	University of New Mexico
20	New York	Albany University, Binghamton University, University of Rochester
21	Nevada	University of Nevada
22	Ohio	Case Western University, Ohio State University
23	Pennsylvania	Penn State University, Thomas Jefferson University
24	Virginia	Virginia Tech University
25	Rhode Island	Brown University , University of Virginia
26	Washington	Washington State University
27	Wisconsin	University of Wisconsin
28	Tennessee	University of Tennessee at Chattanooga
29	Texas	Texas A&M University, Texas Tech, University of Houston, University of Texas
30	Utah	University of Utah

websites selected for analysis, 24 explicitly used the title Post approval monitoring (PAM) or noted the term in the general web content. Additionally, other programs under headings such as: quality improvement, quality assurance, routine monitoring, research congruency, audits, research or compliance monitoring program were identified as relevant to the study. After deliberation, the authors agreed to narrow the focus to webpages that outlined post approval monitoring activities despite variations in headings. After several readings of webpages designated for

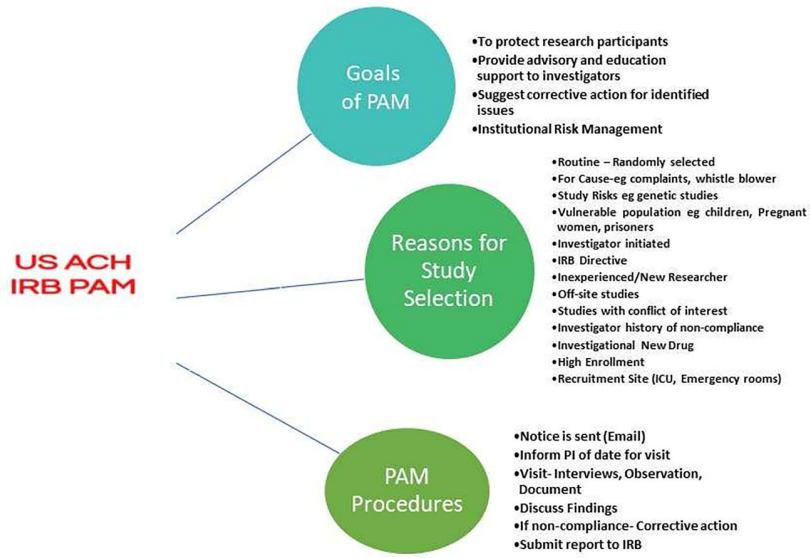

Figure 2. Final thematic map showing main themes and explanations.

screening, a total of fifty-four (54) active University IRB webpages from 30 States were selected and the content extracted for analysis (Table 1).

2.5. Data summary and synthesis

A spreadsheet was created of the active registered OHRP/FDA University-based IRBs and imported into Microsoft Excel 2016. A list of the webpages that met the eligibility criteria was generated. The relevant content for selected webpages was copied into Microsoft word and uploaded to NVIVO 12 Pro for analysis and coding.

2.6. Data analysis

Thematic analysis was used to identify themes according to Braun and Clarke's six-step procedure for qualitative data analysis[12,13]. The extracted data from the IRB websites in the USA was read several times to identify patterns and themes. The phase of familiarization enabled initial code creation and subsequent organization of these codes into categories. After several discussions and revisions, the final themes are reported in the research findings below. Braun and Clarke's method was appropriate because the inductive process and codes were not predefined.

2.7. Researcher characteristics and reflexivity

The researchers are a PhD research fellow, one attorney-at-law and two ethicists. The researchers have experience in pharmacy, research ethics, health law, and research governance/compliance. This study is part of a larger ongoing project on the topic of post-approval activities of research ethics committees. The preunderstanding of the research topic influenced the interpretation of data and subsequently the themes. However, the process was inductive. All themes were generated from the data.

2.8. Ethics approval and process

The Norwegian Centre for Research data reviewed and approved the research project *Incorporation of ethics in Pharmaceutical Authorization Regulatory Procedures (REGULATORY ETHICS): Ethics and compliance post clinical trial approval- the role of Research Ethics Committees*. Reference number 360856. According to Norwegian law governing research, the study is excluded from review by a research ethics committee as its focus is not considered health research.

3. Findings

3.1. Search results

A total of fifty-four (54) active AHC IRB webpages from 30 States were identified and the content extracted for analysis (see Figure 1).

3.2. AHC-IRB PAM "programs" thematic groupings and explanations

The main themes from content analysis of IRB websites in the USA regarding the role of the PAM programs are organized into three main thematic categories with sub-themes. The main categories are (1) Goals of PAM, (2) Reasons for study selection, and (3) PAM procedures. The sub-themes are discussed under the main thematic categories (see Figure 2).

3.2.1. Goals of PAM

The reviewed AHCs indicate that the overarching goal of the PAM program is to ensure compliance with IRB-approved protocols and to preserve research integrity. Other goals include (1) to protect research participants, (2) to provide advisory and educational support to investigators, (3) to suggest corrective action for identified issues, and (4) institutional risk management. There is consistency across all institutions regarding the expectations of the program.

Table 2. Thematic examples of reasons for PAM.

Themes	Examples
Ensuring compliance and preserving research integrity	The PAM Program functions to maximize the safety of research participants and ensure data integrity by confirming that research is implemented in a manner consistent with the IRB approved protocol and in compliance with applicable regulations and institutional policies (University of Wisconsin)
Protection of research participants	The compliance unit performs various post-approval monitoring and directed review activities primarily to ensure the rights and welfare of research participants are protected (Northwestern University)
Advisory/Educational support	The program aims to ensure research staff have the educational resources and guidance necessary to successfully conduct research and provide the research community the study support tools and other resources needed to perform compliant research (Northwestern University).
Suggest corrective actions for identified issues	The final visit report will list actionable findings, as well as areas in which deficiencies were identified. In cases where problems are noted, the investigator has the opportunity to respond to recommendations of the monitor or to provide clarifications or to develop a plan of corrective action to eliminate the potential for future problems(John Hopkins University)
Institutional risk management	The PAM program also aims to provide researchers with education and tools to fulfill their role as principal investigators (PI) and reduce institutional risk (University of Wisconsin.)

3.2.1.1. Theme 1: Ensuring compliance and preserving research integrity. All institutions indicate that the objective of the PAM program is to confirm compliance with IRB-approved protocols. However, as emphasized on the webpage of the University of Binghamton,

> PAM visits are not designed to "catch" individuals. Rather, they are conducted to verify that research is being carried out as approved. The IRB recognizes that if noncompliance is detected, it may be a result of a lack of understanding or inadequate training (Binghamton University).

In addition to compliance, the verification of data integrity is integral to the validity of the results

> The PAM program functions to maximize the safety of research participants and ensure data integrity by confirming that research is implemented in a manner consistent with the IRB approved protocol and in compliance with applicable regulations and institutional policies (University of Wisconsin).

Compliance checks are usually routine (not for cause). There are also for-cause reviews which may be prompted by complaints or IRB-directed reviews due to questionable observations during the annual review (continuing review). Examples of non-compliance include (1) modifications of protocols without IRB approval, (2) failure to report unanticipated serious adverse events, (3) deficient documentation for eligibility assessments, and (4) incomplete or missing informed consent forms (see Table 2). Compliance checks may include document reviews, interviews, and observations. Document review may include informed consent forms, participant records, lab and dispensing records, and approved protocols. Interviews are usually done with research teams and/or participants. Observations are usually of the informed consent and research processes.

3.2.1.2. Theme 2: Protection of research participants. The institutions explicitly state that the protection of research participants is the ultimate purpose of their programs. Therefore, it is emphasized that while balancing the role of educating researchers, the monitors after identifying non-compliance issues in the research records, they would notify the PI, IRB Chair, and any other relevant department for reporting and reconciliation purposes.

> The compliance unit performs various post-approval monitoring and directed review activities primarily to ensure the rights and welfare of research participants are protected (Northwestern University)

> The aim of the Program is to ensure maximum protection of human participants involved in research activities and promotion of best practices in the conduct of human research. (East Carolina University)

3.2.1.3. Theme 3: Educational and advisory support. Educational and advisory support is a significant part of PAM. As noted by Northwestern University

> the program aims to ensure research staff have the educational resources and guidance necessary to successfully conduct research and provide the research community the study support tools, and other resources needed to perform compliant research (Northwestern University).

Educational support is distinguished from advisory support in that the former emphasize formal didactic courses/seminars/training while the latter is the provision of ongoing guidance on issues that may arise throughout the study. The didactic component may include training on Good Clinical practice, national and local regulations governing clinical research, and institutional best practices. Boston University notes the following:

> reviews are intended to be educational and consultative in nature. The educational component involves providing the study staff with up-to-date information on best practices based in Good Clinical Practice (GCP). The consultative aspect is to find and help correct potential problems in study conduct, documentation, or process, including problems arising from IRB noncompliance (Boston University)

3.2.1.4. Theme 4: Recommend corrective actions for identified issues. Whenever the PAM monitor identifies non-compliance, a report is written and corrective actions recommended. Corrective actions enable researchers to avoid sanctions by regulatory authorities or unfavorable reports by sponsor monitors. However, if a researcher fails to comply or obey the directives of the PAM monitor, and continues to have clear protocol violations, then the matter is reported to the research compliance office director or a sub-committee and then, if necessary, reported to the IRB. Several of the AHCs note that it is the IRB that has the authority to suspend or terminate previously approved

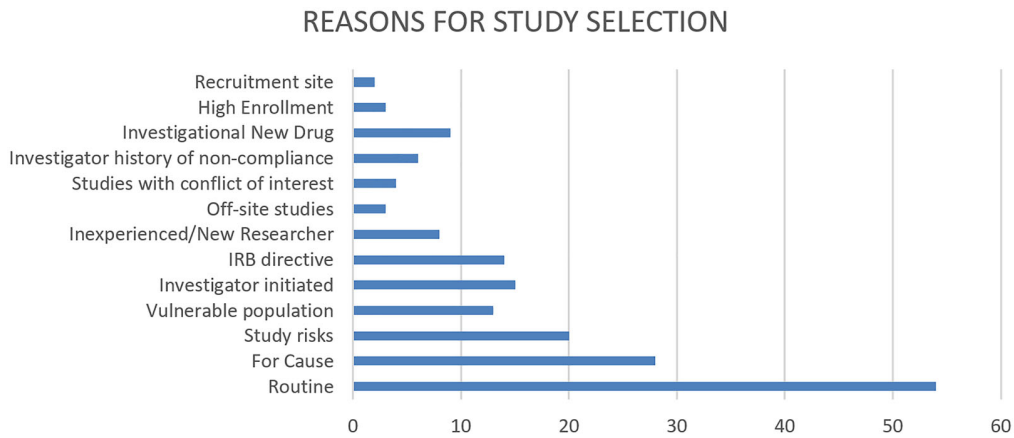

Figure 3. Descriptors identified as reasons for study selection. The diagram is intended to provide insight into some of the listed reasons for study selection. It should not be interpreted to mean that some AHCs do not include these reasons in their programs. The data analyzed is from webpages and as such is limited. AHCs may have internal practice, policies and procedures that are not reflected on the webpages. This is a limitation of this type of study.

protocols. We do not interpret this to mean that it is only the IRB that may have this authority within an institution.

> The IRB monitoring representative will observe the research activities, prepare reports, provide recommendations for maintaining compliance, provide training, if needed, and, if appropriate, assist in the execution of corrective and/or preventative actions. (Binghamton University)

> The final visit report will list actionable findings, as well as areas in which deficiencies were identified. In cases where problems are noted, the investigator has the opportunity to respond to recommendations of the monitor or to provide clarifications or to develop a plan of corrective action to eliminate the potential for future problems. (John Hopkins University)

> PAM staff will generate a draft report of findings outlining the concern/allegations that prompted the monitoring visit, the findings of the monitoring visit, any required corrective actions and the time frame within which the corrective actions should be addressed, and recommendations for best practices. (East Carolina University)

3.2.1.5. Theme 5: Institutional risk management. Several of the institutions indicate that PAM form part of their institutional risk management policy. Institutional risk management is an essential mechanism for Universities to achieve organizational objectives through strategic risk identification and mitigation. This is especially important for federal and externally funded projects and to protect the reputation of the institution. Some AHCs note the benefits of PAM as part of its overall institutional risk strategy:

> A Post-Approval Monitoring (PAM) program functions as the most significant quality assurance and improvement component of the Human Research Protection Program (HRPP) (Charlotte University)

> A quality assurance program provides many benefits to the University and its research program. It is imperative that research programs can assure adherence to federal research compliance mandates in order to protect the operation and reputation of the University, its human research program, and researchers (St Louis University)

3.2.2. Reasons for study selection

Thirteen descriptors were identified and coded as reasons for study selection (see Figure 3). Routine or periodic review and for cause visits were the most listed reasons on the web pages for a monitoring visit. Routine reviews are randomly selected IRB-approved protocols for monitoring. Routine monitoring may be annual or more frequently if non-compliance is identified. For cause reviews are the second highest noted reason for study selection. These may be initiated by a participant or employee complaint, IRB suspension/termination, allegation of non-compliance, or a whistleblower. Studies with Investigational new drugs, high risk and involving vulnerable participants are also regularly reviewed. A few AHCs note genetic studies may be selected for PAM, but many of the webpages only list but did not define or describe high risk. The IRB may also direct the PAM monitor to review a study that it is of the opinion requires more monitoring than annually. Some AHCs also note that PAM visits may be initiated by the PIs to solicit assistance in resolving concerns, prepare for external audits, or for educational purposes. This kind of assistance is also given if the principal investigator (PI) is new, a student, or has a history of non-compliance. Other reasons include studies with high enrollment of research participants, located off-site research, and studies with conflicts of interest. A few AHCs specifically highlighted recruitment site as important. Examples of flagged recruitment sites are emergency rooms and intensive care units.

3.3.3. Pam procedures and findings

The process includes a notice, usually *via* electronic mail, informing the principal investigator of the date for a PAM monitor/compliance officer's visit. Visits include interviews, observation of procedures, and document reviews. The monitor reviews the documents relevant to the IRB-approved protocol. At the end of the visit, the PAM monitor will discuss the findings with the principal investigators. If non-compliance is identified, a corrective action plan is discussed

Table 3. Documents reviewed by PAM monitors and commonly identified non-compliance issues.

Documents reviewed by IRB PAM monitor	Non-compliance identified
1. Regulatory documents	1. Issues regarding consent process or forms
2. Approved protocols	2. Unapproved modifications to the informed consent document (i.e. a change made to the consent document by the investigator) without the approval of the IRB
3. Consents and authorizations	3. Lost or missing consent forms
4. Recruitment materials	4. Consent forms signed after the implementation of research procedures
5. Survey instruments	5. No informed consent obtained prior to study procedures
6. IRB correspondence related to the study	6. The informed consent document on file is not complete (i.e. only the page containing the signature is on file).
7. Data security methods	7. The IRB-approved version of the informed consent or assent document was not used.
8. Adverse event and unexpected occurrence records	8. Dates on informed consent document for participant and researcher are not the same.
9. Pharmacy Dispensing logs	9. Collaborative IRB Training Initiative (CITI) training for study personnel is expired or is not on file.
10. Lab records	10. Study personnel do not have a current conflict of interest disclosure on file
11. Training and licensing documents	11. Study documents not stored as indicated in the approved protocol OR stored with linking list.
12. Advertisements for study	12. Modifications to the protocol (i.e. a change in study procedure) without the approval of the IRB
	13. Failure to report events or de*via*tions
	14. Deficient documentation of eligibility assessment
	15. Adverse events and unexpected occurrence

Table 4. Legislative and policy support for HRPP in the USA.

USA Legislation	Policies
45 CFR 46.103(b)(5) 45CFR46.109(e) FDA 21CFR56.108(b) 21CFR56.109 (f)	Association for the Accreditation of Human Research Protection Programmes I.5.A, I.5.B OHRP Federalwide Assurance (FWA) for the Protection of Human Subjects (4) (5)

and implemented. Table 3 gives an overview of some of the documents reviewed during a PAM visit and commonly detected non-compliance issues. The PAM monitor usually submits the report of the visit to the IRB or research compliance office director who may directly communicate with the IRB chair or a sub-committee established by the IRB.

4. Discussion

Ethicists across various jurisdictions have argued the benefits of active monitoring of research by Ethics Committees[3,4,14–16]. Theoretically, the concept of REC/IRB monitoring seems very plausible. However, in some jurisdictions, such as the EU, there is skepticism about its practicality with suggestions regarding lack of legislative support, resource constraints, and negatively influencing trust between REC and researchers[7,14,17]. An examination of normative documents, such as the Declaration of Helsinki, identified various activities that RECs/IRBs are expected to undertake following the initial review and approval of research protocols.

4.1. Organizational model

This review of US AHCs webpages indicates the feasibility and practicality of Ethics post-approval monitoring. The AHCs note that PAM aims to:

1. confirm that clinical research complies with the approved protocol,
2. educate researchers/investigators,
3. ensure the well-being of research participants, and
4. assist investigators in preparing for external audits.

These AHCs appear to operationalize an organizational model in line with one of several models proposed by Charles Weijer for Ethics Committee monitoring. He proposed that research misconduct and better compliance could be addressed if ethics monitoring is organized to conduct both passive and active monitoring of approved protocols[3]. Passive monitoring of health research includes document review/self-assessment. In contrast, active monitoring is an in-person review of adherence to the approved protocols, assessment of study records and participant files, evaluation of other research activities, and/or an observation of the consent process) or both[4,14]. Passive monitoring would predominantly be the usual course of action of for the actual committee, while active monitoring is done by qualified administrative staff who submit reports to the committee.

4.2. Legislative support, OHRP Federal Wide Assurance and compliance oversight

The US OHRP outlines the legislative support (see Table 4) and the Federal Wide Assurance (FWA) terms for institutions that receive federal funding. Pursuant to their FWAs, human subject research in AHCs must be reviewed, approved, and overseen by an IRB. Particular emphasis would be on terms 4 and 5 of the FWA. Succinctly put, terms 4 and 5 require IRBs to have written procedures and institutional support (staff and space) for conducting the review, identifying non-compliance, and prompt reporting when necessary[18]. The outlined policies described by the AHCs PAM programs appear to conform to the terms. Many AHCs note that PAM programs form part of their OHRP FWA policies and procedures. The AHCs also indicate that PAM programs were facilitated by the administrative staff of the IRB or research compliance offices.

The administrative involvement of AHCs in bolstering IRB's compliance with OHRP requirements was in response to pressure placed on federally funded institutions following several scandals due to lax institutional oversight and overworked IRBs[19]. These occurred in the late 1990s to early 2000s. One case of notoriety is that of Jesse Gelsinger who participated in a clinical trial at University of Pennsylvania. Gelsinger should have been excluded based on the inclusion/exclusion criteria of the trial but due to lax oversight he was enrolled and died[20,21]. Another relevant case is that of 24-year-old Ellen Roche, a healthy volunteer, who died a few days after inhaling hexamethonium[22]. Federal funding of research at John Hopkins was suspended by the OHRP. Subsequently, the AHC admitted fault and sought to address their shortcomings. The OHRP noted that the AHC's IRB failed in its responsibility to protect research participants in both the initial review and the monitoring of the research. A third relevant case is that of Hoiyan Wan, another healthy volunteer, who died while participating in a clinical trial at the University of Rochester. Wan died due to a deviation from usual procedure where a higher than usual dose of lidocaine was administered. These deaths emphasized the importance of independent verification by AHC IRBs to ensure they are fulfilling their mandate[19]. The main strengths of the responses in the various cases were (1) the influence of the enforcement of the federal regulations *via* institutions such as OHRP, (2) the connection of FWA to funding of research, and (3) the public scrutiny and reputational damage to an institution when research participants are harmed. The financial sanctions and accompanying requirements forced many AHCs to implement stringent administrative measures to prevent fall out with the regulators.

Another very important institutional consideration is accreditation[19]. The Association for the Accreditation of Human Research Protection Programs (AAHRPP) plays an integral role by including compliance and quality auditing and monitoring as an element of their accreditation process. Specifically, AAHRPP evaluates an AHC's HRRP policies and procedures to assure the quality of their programme[19] AAHRPP is a private non-profit organization that is focused on setting standards sometimes considered even more rigorous than those of the regulators but without the punitive characteristic or consequence that the regulators may assert[19]. Sociologist Sarah Babb describes this period in her book –Regulating Human Research as the period of hyper-compliance that was replete with bureaucracy[23].

A relevant legislative area is that the US Code of Federal Regulations (CFR) permits IRBs or authorized third parties to observe informed consent processes[24,25]. IRBs are also authorized to suspend or terminate research when deemed necessary. Several AHCs note that violations may be related to a breakdown in the informed consent processes. AHCs receiving federal funding/support must conform to the OHRP's *Compliance Oversight Procedures for Evaluating Institutions*. Similar to what obtains in the PAM programs, the AHCs are subject to OHRP's "for cause" and "routine" compliance evaluations. If an institution is non-compliant, the OHRP may either restrict or attach conditions to its FWA until full compliance is achieved or suspend the institution and prohibit further funding[18] It may be for this reason that many AHCs, despite recent federal exemptions of some research from IRB continuing review, still require these studies to be reviewed under the PAM programs as part of their institutional risk strategy.

4.3. Compliance by means of cooperation, not coercion

A majority of the AHCs emphasize fostering an atmosphere of cooperation between the researcher and the PAM monitor/administrator. They note that PAM is not designed to "catch" bad researchers. The compelling strength of PAM is that the researcher considers it part of the institutional risk management strategy conducive to a pro-research environment and not external regulatory oversight rife with sanctions. The PAM program involves direct interactions between PIs and the IRB compliance or monitoring representative. It is important to distinguish between the roles of the IRB monitoring representative and the monitor mentioned in Good Clinical Practice (GCP) guidelines. The GCP monitor is usually a pharmaceutical industry sponsor or designated representative (an institution with overall responsibility for the trial) who checks whether a trial complies with laws and guidelines. The sponsor monitor reports directly to the sponsor. Despite the presence of sponsor monitors, non-compliance with protocols is still identified during and at the end of clinical trials by Regulatory Authority inspectors[26–28]. Shafiq et al. highlight this incongruity in their paper regarding a pilot IRB monitoring of research in India. They note that IRB monitors identified breaches at clinical trial sites even after the site was audited by sponsors[4]. They suggest that sponsor monitors might not have sufficient experience or clinical training to identify some violations. Although this observation is highly subjective, one could also argue that sponsor monitors have biased interests in the continuation of a study and may be less inclined to point out issues that an IRB may find relevant. The same argument could be advanced about GCP inspectors whose focus is more on the safety of the drug and less on ethical issues.

Sponsor and GCP representatives are important players in research compliance oversight, however, researchers may be intimidated by their presence and oversight due to the perceived risk to losing research funding or credibility. PI initiated PAM reviews was the 4th most reported reason for a study selection. These requests were in line with tentative audits or regulatory checks. When challenges occur, the researcher ought to be aware that he/she can receive the requisite support from the REC/IRBs. If researchers consider the PAM monitor as an advisor towards achieving their intended goals, they may be more willing to engage them for advice. A 1992 survey of Australian researchers on their views of monitoring by a REC revealed that researchers were supportive of an advisory/educational post-approval role. They also admitted to protocol deviations without REC approval and noted that monitoring by the REC ensured compliance with the approved protocol[16]. The concern that RECs/IRBS have assumed the role of "ethics police" – stifling

research and indirectly cultivating an environment for research misconduct may be changed if this approach to ethics monitoring is adopted globally[29]. Researchers and Ethics Committees should work together to achieve the common goal of scientifically and ethically sound research outcomes.

5. Limitations

This study was based on webpage content which is limited due to a lack of human validation. Our findings report only 54 AHCs with specific webpage content on PAM. However, we note that webpage content analysis has limitations as an AHC may have implemented PAM or a similar programme that is not published. Additionally, information on the extracted web pages may not be current. The primary objective of this study was to report what may be considered some post-approval activities of IRBs in the USA. Therefore, while it is our opinion that there are limits in terms of generalizability, content analysis of these AHC web pages is a valuable method for gaining insight into what organizations assert as part of their mandate. Although there is implicit positivity in our description of PAM, we acknowledge that inherent challenges may not be gleaned based on our selected method of analysis and data source. Further exploration using observation, in-depth interviews/surveys of relevant stakeholders such as IRB representatives, PAM monitors, researchers, participants, and evaluation of reports would provide greater insight into the programme.

6. Conclusions and recommendations

The surveyed US AHC-IRB PAM programs provide insight into the organizational structure, goals, and administrative models necessary to operationalize Ethics Committee's passive and active monitoring of human subjects research. The US PAM model asserts a cooperative research environment between IRB administrative staff and researchers. It is our opinion that this cooperative model of research oversight could yield scientifically sound and ethically responsible research, thereby bolstering trust and facilitating scientific pursuits. Supplementary research is recommended to identify whether there is a difference in the number of identified protocol non-compliance between AHCs with PAM compared to programs without. Consideration of this type of a REC PAM model could be given in future reviews of the Declaration of Helsinki, ICH: GCP, and similar international normative guidelines. However, the established US programs would require supplementary investigation to aptly conclude that this model achieves the overarching goal of protecting research participants through education, cooperation, and quality assurance. For this type of research governance model to be operationalized in other jurisdictions, government funding, legislative support, organizational restructuring, and hiring and training of competent staff are important first steps.

Notes

i. The PAM monitor throughout this paper is not referring to the compliance monitoring by pharmaceutical sponsor agencies which is described within the ICH: Good Clinical Practice guidelines.

ii. Throughout this paper, reference to REC/IRB is regarding REC/IRB or research compliance offices and administrative staff employed to the office and not the actual committee members. IRBs/RECs are usually supported by staff who carry out various functions on the Committee's behalf. PAM monitors/administrators may report their findings directly to the IRB chair or to other relevant institutional managerial staff such as research integrity office based on the organizational structure of that institution. A Human Research Protection program (HRPP) is an institutional compliance program that encompasses a wide range of quality assurance and institutional risk management systems which may include auditing the IRB itself. This paper does not intend to go into the range of activities within this program. The focus is on activities of the PAM monitor/administrator regarding IRB approved protocols only. However, a majority of the reviewed webpages note these activities are part of their institutional HRPP.

iii. Association of Academic Health Centers defines an academic health center as: "An academic health center encompasses all the health-related components of universities, including their health professions schools, patient care operations, and research enterprise" (29).

Transparency

Declaration of funding

This manuscript was developed as part of a project at the Centre for Medical Ethics, University of Oslo. There was no external funding.

Declaration of financial/other relationships

The authors are employees of the University of Oslo, Norway. The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Author contributions

All the authors were involved in the writing of this manuscript. First author, a PhD research fellow, is the main author and did most of the core research. There were regular meetings with 2nd and 4th authors throughout the research process who were involved in conceptualization, design, interviews, analysis, and interpretation. Third author's expertise in US Law and experience in research governance at a US AHC was important for the correct interpretation of regulatory terms and policy procedures. The manuscript was drafted by 1st author, while other authors were involved in the revision and final version to be published.

Acknowledgements

None.

ORCID

Shereen Cox http://orcid.org/0000-0002-9674-8544

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Appendix A

Invitation letter to participants and Consent form

Participant information sheet and consent form

Are you interested in taking part in the research project, ***Incorporation of Ethics in Pharmaceutical Authorization Regulatory Procedures (REGULATORY ETHICS)*****?**

This is an inquiry about participation in a research project where the main purpose is to ***explore the role of Research Ethics Committees after they have approved clinical trials on human subjects.***

In this letter we will give you information about the purpose of the project and what your participation will involve.

Purpose of the project

REGULATORY ETHICS is part of ongoing research at the Centre for Medical Ethics of the University of Oslo. I work as a PhD research fellow on this project.

You are invited to participate in this research project to ***explore the experiences and perspectives of Research Ethics Committee (REC) members on what the status quo is in terms of RECs regulating ongoing clinical trials, if this status quo could be improved, and, eventually, in what ways?***

Who is responsible for the research project?
I am the PhD fellow responsible for this project and Assoc. Prof. Rosemarie Bernabe and Prof. Jan Helge Solbakk of the Centre for Medical Ethics, University of Oslo are the supervisors.

Why are you being asked to participate?

You have been invited because you have been identified as a member of one of the stakeholder groups in this project, that is; a) a member of a Research Ethics Committee/IRB, b) a Sponsor company, or c) being member of a patient organisation. Your participation is voluntary, and you may choose to withdraw at any time.

What does participation involve for you?

Due to Covid-19 restrictions on in person meetings, the interview will be via zoom. There will be a trained interviewer and an observer present. The interview will last about 30-45 minutes and will be audio taped. The recorded conversation will be transcribed by the researchers. Only the researchers will have access to the audiotape. All information will be coded and anonymized. Once the transcript has been completed and checked by the interviewer for accuracy, the audiotape will be erased.

The data we collect will be used only for the purpose of this research; if data were to be used for future studies, further approval need to be sought.

Participation is voluntary
Participation in the project is voluntary. If you chose to participate, you can withdraw your consent at any time without giving any reason for your withdrawal. All information about you will then be made anonymous. There will be no negative consequences for you if you chose not to participate or later decide to withdraw.

Your personal privacy – how we will store and use your personal data
We will only use information and data obtained from you for the purpose specified in this information letter. We will process your personal data confidentially and in accordance with data protection legislation (the EU General Data Protection Regulation and the Norwegian Personal Data Act).

- Only the researcher and supervisors will have access to the data. All information will be coded and identifiable information de-identified.
- I will replace your name and contact details with a code. The list of names, contact details, and respective codes will be stored separately from the rest of the collected data. The information we have collected as paper copies will be stored under lock and key, while the electronic data can only be accessed with a secure password. Only the researcher and supervisors will have access to the data.
- The results of the study will be published in peer-reviewed journals and form part of the researcher's dissertation. A summary of the results will be sent to you. You will not be identified in any publication or presentation without seeking your consent. Direct quotes from the interviews may be used in publications; however, the quotes will be anonymised to ensure that you cannot be identified.

What will happen to your personal data at the end of the research project?
The project is scheduled to end September 2022. Personal identifiable data will be destroyed.

Your rights
So long as you can be identified in the collected data, you have the right to:

- access the personal data that is being processed about you
- request that your personal data is deleted
- request that incorrect personal data about you is corrected/rectified
- receive a copy of your personal data (data portability), and
- send a complaint to the Data Protection Officer of the University of Oslo or The Norwegian Data Protection Authority regarding the processing of your personal data.

What gives us the right to process your personal data?
We will process your personal data based on your consent.

Permission to collect and make use of such data has been obtained from the Norwegian Social Science Data Services (NSD). That is, NSD has assessed that the processing of personal data in this project is in accordance with data protection legislation.

Where can I find out more?
If you have questions about the project, or want to exercise your rights, contact:
Centre for Medical Ethics, University of Oslo via:

Professor Jan Helge Solbakk, Dr Rosemarie de la Cruz Bernabe, *or* Shereen Cox *(Phd candidate/researcher)*
Postal Address:
Centre for Medical Ethics, Institute of Health and Society
University of Oslo
Postboks 1130, Blindern 0318 Oslo
Email: shereen.cox@medisin.uio.no or r.de.l.c.bernabe@medisin.uio.no or j.h.solbakk@medisin.uio.no
Telephone: +47-22850624

- Our Data Protection Officer: Roger Markgraf-Bye personvernombud@uio.no
- NSD – The Norwegian Centre for Research Data AS, by email: (personverntjenester@nsd.no) or by telephone: +47 55 58 21 17.

Yours sincerely,

Project Leader
Rosemarie de La Cruz Bernabe
(Researcher/supervisor)

Shereen Cox (PhD Candidate)

Consent form

I have received and understood information about the project *Incorporation of Ethics in Pharmaceutical Authorization Regulatory Procedures (REGULATORY ETHICS)* and have been given the opportunity to ask questions. I give consent:

- ☐ to participate in interview/focus group discussion
- ☐ *for information about me/myself to be published in a way that I cannot be recognised*
- ☐ *for my personal data to be stored after the end of the project for follow-up studies*

I give consent for my personal data to be processed until the end date of the project, approximately September 2022.

(Signed by participant, date)

Appendix B: Interview Guide

Interview Schedule

Project: Incorporation of Ethics in Pharmaceutical Authorization Regulatory Procedures (REGULATORY ETHICS)

Research Topic: Ethics and compliance post clinical trial approval – The role of Research Ethics Committees (RECs)

INTERVIEW GUIDE FOR RECs

Date of interview

Region/Country

Stakeholder group ☐ European RECs

INTERVIEW QUESTIONS

The interview questions are based on Michael Patton's six categories of qualitative research questions in the social sciences (Patton, 2002):

1. Behavior or experience.
2. Opinion or belief.
3. Feelings.
4. Knowledge.
5. Sensory
6. Background or demographic.

DEMOGRAPHICS

1. Gender
2. Age
3. Occupation

BACKGROUND/EXPERIENCE

4. Tell me about yourself/What is your background?
5. What is your role/job on this Committee?
6. How long have you been on/in this Committee?

KNOWLEDGE

7. Can you tell me what your Committee does as it relates to Clinical research?
8. Does your Committee have Ethics training for the members?
9. If yes, how often and could you share your experience with training and how it contributed to your competence?
10. Is this training mandatory? If no, is this something you wish to have?
11. How often does your Committee meet?

(Do you wish to meet more?)

12. Does your REC evaluate, approve, monitor/review/audit (protocols for) clinical trials?
13. What has been your experience with evaluation/approval/review/audit (inspection) of clinical trial protocols?
14. Does your Committee/Group/Organization have guidelines or codes by which you evaluate, approve, review, audit clinical research protocols?
15. If yes, please name them and share your perspective on the applicability of these guidelines to your role?
16. If no, is this something you wish to have?
17. Please share your understanding/knowledge of the monitoring of clinical trials?
18. Explain the role of your Committee, if any, in the monitoring of clinical trials?
19. What is your opinion on how clinical trials should be monitored for compliance? Does your REC do continuing review of protocols that has been been approved? If yes, is this mandatory?
20. Is the post-approval reporting considered part of the process of initial approval?
21. What has been your experience with the feedback received on clinical trials post approval?
22. What is your experience with follow up of clinical trials post approval of protocols?
23. What has been your experience with clinical trial sponsor feedback to the REC?
24. During the time on the Committee, were you aware of any protocol violations by Clinical Trial sponsors and if yes, how were these addressed by your committee?
25. What are some ways you think the REC should or could manage protocol violations in clinical trials?”

OPINION/BELIEF

26. In your opinion, what should be the role of RECs in ensuring compliance post clinical trial approval?
27. What is your opinion on RECs having the right to access recorded research data directly?
28. What is your opinion on Data Monitoring Boards reporting directly to the RECs?
29. What do your think should happen when ethical violations are identified in clinical trials after an inspection audit?
30. Do you have anything else you would like to share from your experience or recommendations you would like to make?

The following questions were generated during the course of the interview process

- What happens when you get adverse events reports as well as the final report? Are they reviewed by the full committee or by one person in the office? What happens to those reports?
- In the US system, there is a program where the IRB office does post approval follow up of approved studies, do you think a similar program could be practical for your REC?
- The EU Regulations are to be effected within a year, what measures/changes has your country put in place in preparation for this deadline?

Appendix C: Approval from NSD

NSD NORSK SENTER FOR FORSKNINGSDATA

NSD sin vurdering

Prosjekttittel

ETHICS AND COMPLIANCE POST-CLINICAL TRIAL APPROVAL-THE ROLE OF RESEARCH ETHICS COMMITTEES

Referansenummer

360856

Registrert

01.11.2019 av Shereen Cox Née Dawkins - shereec@uio.no

Behandlingsansvarlig institusjon

Universitetet i Oslo / Det medisinske fakultet / Institutt for klinisk medisin

Prosjektansvarlig (vitenskapelig ansatt/veileder eller stipendiat)

Jan Helge Solbakk, j.h.solbakk@medisin.uio.no, tlf: 4722844641

Type prosjekt

Forskerprosjekt

Prosjektperiode

01.01.2020 - 31.12.2022

Status

26.11.2019 - Vurdert

Vurdering (1)

26.11.2019 - Vurdert

Our assessment is that the processing of personal data in this project will comply with data protection legislation, so long as it is carried out in accordance with what is documented in the Notification Form and attachments, dated 26.11.2019. Everything is in place for the processing to begin.

NOTIFY CHANGES
If you intend to make changes to the processing of personal data in this project it may be necessary to notify NSD. This is done by updating the Notification Form. On our website we explain which changes must be notified. Wait until you receive an answer from us before you carry out the changes.

TYPE OF DATA AND DURATION
The project will be processing special categories of personal data philosophical beliefs and general categories of personal data, until 31.12.2022.

LEGAL BASIS
The project will gain consent from data subjects to process their personal data. We find that consent will meet the necessary requirements under art. 4 (11) and 7, in that it will be a freely given, specific, informed and unambiguous statement or action, which will be documented and can be withdrawn.

The legal basis for processing special categories of personal data is therefore explicit consent given by the data subject, cf. the General Data Protection Regulation art. 6.1 a), cf. art. 9.2 a), cf. the Personal Data Act § 10, cf. § 9 (2).

PRINCIPLES RELATING TO PROCESSING PERSONAL DATA
NSD finds that the planned processing of personal data will be in accordance with the principles under the General Data Protection Regulation regarding:

- lawfulness, fairness and transparency (art. 5.1 a), in that data subjects will receive sufficient information about the processing and will give their consent
- purpose limitation (art. 5.1 b), in that personal data will be collected for specified, explicit and legitimate purposes, and will not be processed for new, incompatible purposes
- data minimisation (art. 5.1 c), in that only personal data which are adequate, relevant and necessary for the purpose of the project will be processed
- storage limitation (art. 5.1 e), in that personal data will not be stored for longer than is necessary to fulfil the project's purpose

THE RIGHTS OF DATA SUBJECTS
Data subjects will have the following rights in this project: transparency (art. 12), information (art. 13), access (art. 15), rectification (art. 16), erasure (art. 17), restriction of processing (art. 18), notification (art. 19), data portability (art. 20). These rights apply so long as the data subject can be identified in the collected data.

NSD finds that the information that will be given to data subjects about the processing of their personal data will meet the legal requirements for form and content, cf. art. 12.1 and art. 13.

We remind you that if a data subject contacts you about their rights, the data controller has a duty to reply within a month.

FOLLOW YOUR INSTITUTION'S GUIDELINES
NSD presupposes that the project will meet the requirements of accuracy (art. 5.1 d), integrity and confidentiality (art. 5.1 f) and security (art. 32) when processing personal data.

To ensure that these requirements are met you must follow your institution's internal guidelines and/or consult with your institution (i.e. the institution responsible for the project).

FOLLOW-UP OF THE PROJECT
NSD will follow up the progress of the project at the planned end date in order to determine whether the processing of personal data has been concluded.

Good luck with the project!

Contact person at NSD: Silje Fjelberg Opsvik
Data Protection Services for Research: +47 55 58 21 17 (press 1)

NSD NORSK SENTER FOR FORSKNINGSDATA

NSD sin vurdering

Prosjekttittel

ETHICS AND COMPLIANCE POST-CLINICAL TRIAL APPROVAL-THE ROLE OF RESEARCH ETHICS COMMITTEES

Referansenummer

360856

Registrert

01.11.2019 av Shereen Cox Née Dawkins - shereec@uio.no

Behandlingsansvarlig institusjon

Universitetet i Oslo / Det medisinske fakultet / Institutt for klinisk medisin

Prosjektansvarlig (vitenskapelig ansatt/veileder eller stipendiat)

Jan Helge Solbakk, j.h.solbakk@medisin.uio.no, tlf: 4722844641

Type prosjekt

Forskerprosjekt

Prosjektperiode

01.01.2020 - 31.12.2022

Status

26.11.2019 - Vurdert

Vurdering (1)

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COREQ (COnsolidated criteria for REporting Qualitative research) Checklist

A checklist of items that should be included in reports of qualitative research. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Topic	Item No.	Guide Questions/Description	Reported on Page No.
Domain 1: Research team and reflexivity			
Personal characteristics			
Interviewer/facilitator	1	Which author/s conducted the interview or focus group?	3
Credentials	2	What were the researcher's credentials? E.g. PhD, MD	1
Occupation	3	What was their occupation at the time of the study?	1
Gender	4	Was the researcher male or female?	1
Experience and training	5	What experience or training did the researcher have?	1
Relationship with participants			
Relationship established	6	Was a relationship established prior to study commencement?	2
Participant knowledge of the interviewer	7	What did the participants know about the researcher? e.g. personal goals, reasons for doing the research	pg 2,3
Interviewer characteristics	8	What characteristics were reported about the inter viewer/facilitator? e.g. Bias, assumptions, reasons and interests in the research topic	1
Domain 2: Study design			
Theoretical framework			
Methodological orientation and Theory	9	What methodological orientation was stated to underpin the study? e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis	Grounded ther
Participant selection			
Sampling	10	How were participants selected? e.g. purposive, convenience, consecutive, snowball	pg 2,3
Method of approach	11	How were participants approached? e.g. face-to-face, telephone, mail, email	Email, pg 2
Sample size	12	How many participants were in the study?	19
Non-participation	13	How many people refused to participate or dropped out? Reasons?	none refused
Setting			
Setting of data collection	14	Where was the data collected? e.g. home, clinic, workplace	Virtual, pg 3
Presence of non-participants	15	Was anyone else present besides the participants and researchers?	No
Description of sample	16	What are the important characteristics of the sample? e.g. demographic data, date	see pg 4
Data collection			
Interview guide	17	Were questions, prompts, guides provided by the authors? Was it pilot tested?	yes
Repeat interviews	18	Were repeat inter views carried out? If yes, how many?	Only emails
Audio/visual recording	19	Did the research use audio or visual recording to collect the data?	yes pg. 3
Field notes	20	Were field notes made during and/or after the inter view or focus group?	yes
Duration	21	What was the duration of the inter views or focus group?	pg 2
Data saturation	22	Was data saturation discussed?	yes
Transcripts returned	23	Were transcripts returned to participants for comment and/or	No

Topic	Item No.	Guide Questions/Description	Reported on Page No.
		correction?	
Domain 3: analysis and findings			
Data analysis			
Number of data coders	24	How many data coders coded the data?	2
Description of the coding tree	25	Did authors provide a description of the coding tree?	no
Derivation of themes	26	Were themes identified in advance or derived from the data?	From data
Software	27	What software, if applicable, was used to manage the data?	NVIVO 12 Pro
Participant checking	28	Did participants provide feedback on the findings?	yes, pg 4
Reporting			
Quotations presented	29	Were participant quotations presented to illustrate the themes/findings? Was each quotation identified? e.g. participant number	yes pg. 5-10
Data and findings consistent	30	Was there consistency between the data presented and the findings?	yes pg 12
Clarity of major themes	31	Were major themes clearly presented in the findings?	yes pg. 5-10
Clarity of minor themes	32	Is there a description of diverse cases or discussion of minor themes?	yes, pg.7-10

Developed from: Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *International Journal for Quality in Health Care*. 2007. Volume 19, Number 6: pp. 349 – 357

Once you have completed this checklist, please save a copy and upload it as part of your submission. DO NOT include this checklist as part of the main manuscript document. It must be uploaded as a separate file.