AN EVALUATION OF ETHICAL CONCERNS OF AN INSTITUTIONAL RESEARCH ETHICS COMMITTEE IN GHANA, USING THE EMANUEL ET AL. (2004) PRINCIPLES AND BENCHMARKS

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Submitted in partial fulfilment of the requirements for the Masters of Social Science (Health Research Ethics) in the School of Applied Human Sciences, University of KwaZulu-Natal (Psychology), Pietermaritzburg, South Africa

30th August 2016

Acknowledgements

I am highly indebted to Professor Douglas Wassenaar, my academic supervisor, for his mentorship and meticulous supervision, guidance, and critical review of the project. I am grateful to Dr Bertha Garshong, for being my informal local site supervisor and providing oversight responsibility, ensuring that the conduct of research was carried out in accordance with the approved protocol. Special thanks are due to Dr Frances Ivy Osei who provided comments on the second draft of this thesis. Her detailed review and comments have shaped this thesis. Again, I thank Nita Coffie, Nana Abena-Kwaa, and Ignatius Dinituo, for their first, second, and third rating and coding of all the data, as well as Jane Amponsah and Ahmed Sauda for assisting me to design the computer screen for the data collection and data analyses. I am also thankful to the SARETI Administrator (Ms Carla Pettit) for her administrative support towards the realisation of this thesis. Finally, I thank the index REC and its responsible institution for allowing me to access their meeting minutes for the research. I am also grateful to Ms V O'Neill for editing assistance, kindly sponsored by SARETI.

Funding

This work was supported by Grant Number 4R25 TW001599-14 from the Fogarty International Center of the US National Institutes of Health. The grant PI is Prof D R Wassenaar but this thesis reflects the work and opinions of the author and not the NIH.

Declaration

I declare that this dissertation represents my own work, except for those where due acknowledgement is made, and that it has not been included in a thesis, dissertation or report submitted to this university or any other institution for a degree, diploma or other qualifications.

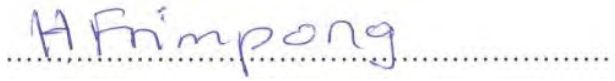
Signed 

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Table of contents

List of tables

List of figures

Abstract

Research Ethics Committees (RECs) are mandated to review and approve protocols of all proposed research projects, so as to ensure that all potential ethical risks associated with such projects are addressed appropriately before such projects are executed. This will ensure maximum protection for research participants. The eight-point framework of Emanuel et al. has been provided to be used as a universal tool by RECs for review of research protocols in many settings including developing countries. With the eight-points in place, RECs are encouraged to assess each research protocol to ensure that it has the following: (i) collaborative partnership; (ii) social value; (iii) scientific validity; (iv) fair participant selection; (v) favourable risk–benefit ratio; (vi) undergoes independent ethics review; (vii) informed consent; and (viii) will also demonstrate ongoing respect for participants in the project. What is not known is whether African research ethics committees' work is compatible or complies with the framework. Additionally, the lack of acceptable norms and critical analyses of the eight principles of the framework means that some RECs may raise diverse ethical concerns frequently than others during review of research protocols.

The purpose of this study was to identify and describe the pattern of ethical concerns and issues that were raised by the Ghanaian REC in their review of newly submitted research protocols, and to analyse the ethical issues and concerns in order of merit. The investigator used the eight principles of the Emanuel framework as a guide to assess the two-year minutes of the index REC, coded them, and ranked the most frequent ethical issues which were considered by members of the index REC during review of research protocols for the years 2012 to 2013. The study was based on content analysis of archived minutes of a Ghanaian institutional REC's review meetings for the period 2012-2013. Minutes of 153 newly submitted protocols were assessed.

In this study, scientific validity emerged as the issue that the index REC queried the most, followed (in descending order) by informed consent, respect for participants, favourable risk-benefit ratio, independent review, collaborative partnership, fair participant selection, and social value. Although the REC's comments conform with and were largely accommodated by the principles of the Emanuel et al. framework, there were some concerns raised by the REC that did not fit into the framework. These included storage and materials transfer agreements (MTA) for transportation of human biological materials, signed agreements between sponsors and investigators, and certificates of Good Clinical Practice (GCP). This study represents one of the first two attempts to analyse a Ghanaian institutional REC's minutes of review meetings. Applying the principles of the framework in this

study helped the researcher to describe and categorise the main business of the index REC during the protocol review.

Keywords: Ghana, assessment of ethics review, concerns of review ethics committee, health research ethics, research ethics committee meetings minutes, institutional review board, review of international collaborative research, ethical review committee, review framework, Emanuel framework, RECs.

List of abbreviations

CIOMS	-	Council for International Organizations of Medical Sciences
COI	-	Conflict of Interest
FDA	-	Food and Drug Administration
IRB	-	Institutional Review Board
MSocSc	-	Masters in Social Science
NIH	-	National Institutes of Health
NMIMR	-	Noguchi Memorial Institute for Medical Research
REC	-	Research Ethics Committee
RECMM	-	Research Ethics Committee Meeting Minutes
SA	-	South Africa
SARETI	-	Southern African Research Ethics Training Initiative
SOP	-	Standard Operating Procedure
UKZN	-	University of KwaZulu-Natal
WMA	-	World Medical Association
WHO	-	World Health Organization

CHAPTER 1: INTRODUCTION

1.1 Overview and background information

This chapter provides background to this research. This was a qualitative study which formed part of an international collaborative study involving five University of KwaZulu-Natal SARETI Masters students (of whom the investigator is one) from four African countries (Ghana, Nigeria, Malawi, and Zimbabwe). The study sought to evaluate the contents of meeting minutes for two years (2012-2013) of an institutional research ethics review committee (REC) in Ghana, to ascertain the main issues of concern raised by the REC during research protocol review.

It is reported that "RECs are designed to provide independent review, hopefully minimising conflict of interest" (Kass et al., 2007, p. 26). The review process helps to protect the welfare of research participants through attention to risks, benefits and informed consent, and hopefully reduces or avoids exploitation of vulnerable individuals and populations (Kass et al., 2007). However, it is not known how well these RECs fulfil their task of third-party review (Kass et al., 2007). Many international studies have found that different RECs reach different conclusions when reviewing the same research protocols, and existing ethical guidelines may be interpreted in different ways and are sometimes contradictory (Kass et al., 2007).

Literature also reveals that, in the past, several international and local ethics guidelines have been developed, resulting in some confusion over which to use (Tsoka-Gwegweni & Wassenaar, 2014). In response to this, Emanuel and colleagues analysed major international guidance documents and developed a framework consisting of eight principles and benchmarks to guide ethics review of biomedical research" (Tsoka-Gwegweni & Wassenaar, 2014). The framework requires RECs to assess each protocol to ensure that the proposed research has i) collaborative partnership; ii) social value; iii) scientific validity; iv) fair participant selection; v) a favourable risk-benefits ratio; vi) independent review; vii) informed consent; and viii) on-going respect for study participants (Tsoka-Gwegweni & Wassenaar, 2014) .

The issue at stake here is that, although RECs provide a mechanism to ensure that studies adhere to the highest scientific and ethical standards, there is little empirical research into the actual decision-making process and outcomes regarding issues of concern raised by RECs in developing countries during research protocol review. It is against this background that this research was carried out to evaluate recorded meeting minutes. In this research, data was extracted from two years of meeting

minutes of a particular institutional REC in Ghana, using the principles and benchmark of the framework as tool.

This research hopefully contributes new findings to the existing literature on RECs activities in developing countries, and provides recommendations to improve research study protocols review processes in Africa, particularly in Ghana, to ensure maximum protection for research participants and communities. Particularly, this study attempts to replicate the Tsoka-Gwegweni and Wassenaar (2014) study which is reviewed more fully in Chapter Two.

CHAPTER 2: REVIEW OF LITERATURE

2.1 Importance of research ethics review

Kirigia, Wambeba and Baba-Moussa (2005) say that in the present era of increasingly globalised biomedical research, "good ethics stewardship demands that every country, irrespective of its level of economic development, should have in place a functional research ethics review system in order to protect the dignity, integrity and safety of its citizens who participate in research" (Kirigia, Wambeba & Baba-Moussa, 2005, p. 1). Unfortunately, it is said that "over 50 years after the Nuremberg trials and the Nuremberg code, unethical (bio)medical research on humans continues to exist, even in highly developed countries" (Kirigia et al., 2005, p. 1). According to Kirigia and colleagues, "biomedical research involves research on pharmaceuticals, medical devices, medical radiation and imaging, surgical procedures, medical records, and biomedical samples, as well as epidemiological, social, and psychological investigations" (Kirigia et al., 2005, p. 2). This often "involves collection, analysis, and interpretation of information obtained from human beings" (Kirigia et al., 2005, p. 2). Therefore research must be conducted according to accepted ethical standards so as to ensure maximum protection of the dignity, integrity, and safety of all actual and prospective participants in research (Kirigia et al., 2005).

Further, it is said that since World War II, a number of guidelines have provided "ethical and scientific standards for the conduct of biomedical research with humans" (Kirigia et al., 2005). These include the Nuremberg Code, the Declaration of Helsinki, the International Covenant on Civil and Political Rights, the International Code of Medical Ethics of the World Medical Association, the CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects, and the ICH Guidelines for Good Clinical Practice (Kirigia et al., 2005). However, in spite of the differences in scope and emphasis of these international instruments on the ethics of research, it is important to have justification and scientific validity of research which should include aspects such as:

> ethical review; informed consent; vulnerability of individuals, groups, communities and populations; women as research subjects; equity regarding burdens and benefits; choice of control in clinical trials; confidentiality; compensation for injury; strengthening of national or local capacity for ethical review; and obligations of sponsors to provide health care (Kirigia et al., 2005, p. 2)

Kirigia and colleagues maintain that it is essential for every country to have a functional REC. This is because of the growing volume of and potential for exploitation in "collaborative biomedical studies involving national, multinational and trans-national partners developing various interventions targeted against health conditions such as HIV/AIDS, malaria, tuberculosis, childhood illnesses, and causes of maternal morbidity and mortality contained in the Millennium Development Goals" (Kirigia et al., 2005, p. 2). They point out that "the purpose of an international REC is to contribute independently,

competently, and efficiently to safeguard the dignity, rights, safety, and well-being of all research participants" (Kirigia et al., 2005, p. 2). This is to ensure "the highest attainable quality in the science and ethics of biomedical research in the country" (Kirigia et al., 2005, p. 2).

Literature reveals that as part of an effort to develop research ethics capacity for the conduct of multinational collaborative research, a group of "researchers and others involved in the research enterprise from 12 African countries met with those working in ethics and oversight in the United States, to develop research ethics capacity" (Sugarman & Participants, 2007, p. 84). Participants in the workshop identified five important ethical issues for discussions. According to Sugarman and colleagues, "there is now a considerable volume of multinational research conducted in many African countries with collaborators from other parts of the world" (Sugarman & Participants, 2007, p. 84). Again, "while this research is ideally aimed at addressing some of the enormous burdens of disease that can be exacerbated by poverty", a variety of concerns such as: (i) Role of investigators; (ii) Standard of care; (iii) Vulnerability; (iv) Biological materials; and (v) Conflict of interest "have been raised about the ethics of this research in medical journals, the popular press, and popular culture" (Sugarman & Participants, 2007, p. 84). Drawing on their enormous experience, the participants of the meeting discussed the concerns enumerated above and recommended the following for those who are charged with the conduct of multinational collaborative research to address prior to implementation of such research (Sugarman & Participants, 2007). These are:

(i) that investigators of research should '"build 'true' research teams where members of the team are meaningfully involved in decisions regarding the research protocol and its implementation" (Sugarman & Participants, 2007, p. 85);

(ii) that there should be explicit discussion about the standards of care "at the outset of project planning that includes clarification of the terminology that is being used" (Sugarman & Participants, 2007, p. 85);

(iii) that while internationally collaborative research may involve populations that have inherent vulnerabilities, "it is important to recognise the limitations of host country solutions (such as elaborated consent processes), and look for means to negotiate appropriate protections for those willing to participate" (Sugarman & Participants, 2007, p. 86);

(iv) that in conducting research involving biological materials "it would be prudent to develop material transfer agreements at the outset of the study to clarify expectations and, to minimise the likelihood of harm" (Sugarman & Participants, 2007, p. 86); and

(v) that those engaged in international collaborative research need to be alert to the potential conflict of interests of hosts country ethics committees during the approval process and "to take measures to manage them if they indeed exist"(Sugarman & Participants, 2007, p. 86).

Kass and colleagues report that a case study on the ethical review process in several African countries identified inadequate training, inconsistent funding, and disproportionate focus on science in the review process, constraints in budget, multiple responsibilities of REC members, and "the tendency of some RECs to 'rubber stamp' approvals in order to secure international funding", as the major challenges (Kass et al., 2007, p. 29).

According to Nyika and colleagues (Nyika, Kilama, Tangwa et al., 2009), over the past decades, there has been an unprecedented expansion in health research in both the developed and developing world. They maintain that although the increasing trend of collaborative research in Africa is good news, RECs in African countries will have to review more research protocols than anticipated (Nyika, Kilama, Tangwa et al., 2009). In addition, studies conducted in some African countries reveal that some African RECs/IRBs lack the capacity and strength to review collaborative studies in the sub-region (Nyika, Kilama, Tangwa et al., 2009). This is also due to factors such as: (i) complexity of collaborative research studies, (ii) new technology development, (iii) emergence of new diseases, (iv) the shift from local research projects to international collaborative projects that involve participants and collaborating researchers drawn from different countries with diverse cultural and socio-economic backgrounds, (v) international funding issues, (vi) lack of expertise and technology to perform some of the more complicated research procedures, (vii) shipment of samples to high-tech laboratories in developed countries because collaborating institutions in developing countries generally have inadequate expertise and technology, and (viii) RECs in developing countries have had to grapple with controversial issues (e.g. genetic manipulation of human embryos) that were unheard of a few decades ago in Africa (Nyika, Kilama, Tangwa et al., 2009).

Amdur and Bankert (2011) report that the value of research depends upon the integrity of the study results. One of the ethical justifications for research involving human subjects is the social value of advancing scientific understanding and promoting human welfare by improving health care (Amdur & Bankert, 2011). However, if a research study is so methodologically flawed that little or no reliable information will result, it is unethical to put subjects at risk or even to inconvenience them through participation in such a study (Amdur & Bankert, 2011). Therefore, every REC should ask how much it is their responsibility to review the underlying science of the proposed research, as poor science is clearly not ethical (Amdur & Bankert, 2011). However, the federal regulations, under which

Institutional Review Boards (IRBs) in the USA operate do not clearly call for IRBs to review the scientific validity of the research design (Amdur & Bankert, 1993). However, they do require that IRBs determine how reasonable the risks to subjects are in relation to the importance of the knowledge that the study hopes to achieve; if the underlying science is flawed, then it is unlikely that useful or important knowledge will emerge (Amdur & Bankert, 2011).

The World Health Organization (WHO), 2011 standard and operational guidance for ethics review on health-related research with human participants indicates that "in some countries review may occur only at the institutional level, while in other countries review occurs at both national and institutional levels, and in still others at a regional level" (WHO, 2011, p. 3). It is asserted that about 25% of health-related studies in developing countries were not subjected to some form of ethics review by an international review board, national ethics board, or ministry/department of health, which is worrisome (WHO, 2011). In line with this, "countries are required to take into account the volume of research conducted by various entities in the country" when designing systems for research ethics review (WHO, 2011, p. 3). The guidance maintains that "having a good systems approach and clear rules of how the various RECs within a country interact with each other can greatly facilitate the ethical conduct of international health research (WHO, 2011, p. 3). The WHO guidance further explains that adherence to these guidelines helps to promote the ethical conduct of research, and enhances and protects the rights and well-being of research participants and communities (WHO, 2011).

Again, the WHO guidance maintains that "a core component of all contemporary research ethics guidelines is that research should be subject to prior ethical review by an independent competent REC" (WHO, 2011, p. xi). And, that "such review is intended to ensure that the ethical principles and practices put forward in the guidelines will be followed in the proposed research" (WHO, 2011, p. xi). In this context, the establishment of RECs in many countries has faced several constraints. These include uncertainties about which guidelines to follow, who to appoint as members, what procedures to follow and how to train members (Kass et al., 2007). In addition, the work of RECs in Africa has been fraught with challenges. For instance, it is said that "in 2000, the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) published *Operational guidelines for ethics committees that review biomedical research*, in response to requests from collaborating researchers throughout the world" (WHO, 2011, p. xi).

It is reported that WHO guidelines "have been developed for individuals and organisations involved in health-related research with human participants, including biomedical, behavioural, social science, and epidemiological research (throughout this document, the term 'research' is meant to include, and

refers to, all of these domains" (WHO, 2011, p. xi). Particularly, the document referred to in the previous paragraph was intended to provide guidance to the RECs, on which organisations rely to review and oversee the ethical aspects of research, as well as to the researchers who design and carry out health research studies (WHO, 2011). According to the document, "ethics guidance for research involving human participants has been developed and disseminated by numerous organisations and agencies at international, national and regional levels over the past 50 years" (WHO, 2011, p. xi). The document indicates that "adherence to the guidelines helps to promote the ethical conduct of research, enhances, and protects the rights and well-being of research participants and communities" (WHO, 2011, p. xi).

It is said that the guidelines were also "reviewed by multiple experts, stakeholders, researchers, and organisations, including officials of the African Malaria Vaccine Testing Network, the Council of Europe, the National Institutes of Health (USA), ... and the World Medical Association" (WHO, 2011, p. xi). It is reported that an earlier (2000) version of the WHO guidelines was translated into more than 25 languages, widely disseminated, and used by RECs in more than 100 countries' research (WHO, 2011).

Additionally, "in 2006 the WHO Commission on Intellectual Property Rights, Innovation and Public Health (CIPIH) recognised the need for raising capacity for ethical review of research" (WHO, 2011, p. xi). The commission also noted that "Further efforts should be made to strengthen the clinical trials and regulatory infrastructure in developing countries, in particular in sub-Saharan Africa, including the improvement of ethical review standards" (WHO, 2011, p. xi). Then again, the commission noted that the World Health Organization (WHO) has a pivotal role to play in the improvement of ethical review standards (WHO, 2011). Also, under resolution 61.21 in 2008, and 63.21 in 2010, "whilst endorsing the Research Strategy for Health, Member States were encouraged by the World Health Assembly to put in place governance mechanisms for the conduct of health research"; this was to "ensure maximum application of good research norms and standards, including protection for human subjects who get involved in research" (WHO, 2011, p. xi). It was in this regard that the "Director-General of WHO was requested to provide support for Member States to strengthen mechanisms for ethical review of research, especially in developing countries" (WHO, 2011, p. xi).

It is also mentioned that "in November 2009, a consultation meeting was organised in Geneva by WHO" (WHO, 2011, p. xii) The meeting brought together key international experts, including researchers, ethicists, members and chairs of RECs, as well as representatives of international organisations, to further deliberate on whether additional guidance, if any, was needed by RECs globally - given the observation of the CIPIH that RECs continue to be quite variable in terms of their

experience, training, capacity, institutional support, human and financial resources, and expertise (WHO, 2011). Thereafter, “based on their experiences and expertise, the participants agreed that the 2000 WHO publication, that is the operational guidelines for ethics committees that review biomedical research, has been an invaluable resource but should be updated and strengthened” (WHO, 2011, p. xii). Again, participants in the meeting were also of the view that it was about time member states put in place a set of global standards for high quality decision-making to enable RECs measure their own performance (WHO, 2011). Further, “participants in the meeting decided that WHO should put in an effort to draft standards for RECs and to revise the 2000 Operational guidelines to describe specific procedures that would meet the standards” (WHO, 2011, p. xii).

In addition, it is said that “the second edition of the 2000 operational guidelines were developed as a result of global developments which consisted of a compilation of ten standards that are applicable to the ethics review of health related research with human participants” (WHO, 2011, p. xii). Also in the guidelines, the term ‘standards’ is used to delineate general principles and norms that all research ethics systems are expected to follow” (WHO, 2011, p. xii). It is explained that “the set of standards is meant to help RECs achieve high quality performance, and not to make a very strong position as to how specific ethical dilemmas should be resolved” (WHO, 2011, p. xiii). Furthermore, “there are series of operational guidance points accompanying the WHO (2011) standards which reflect the commonly used strategies for implementing and fulfilling each of the standards” (WHO, 2011 p. xiii). “Apart from listing the research ethics system standards, three other changes were made in the 2011 edition” (WHO, 2011, p. xiii). In the first of these, “the title was revised to reflect the purpose of the document”; in the second, “the research ethics approach which was alluded to the 2000 edition of the book was further elaborated, and expanded to include the role of national governments and relevant legal and regulatory authorities” (WHO, 2011, p. xiii). Thirdly, “the scope of the document was modified and extended to include all health-related research ethics committees, irrespective of what they review, whether biomedical, social science, epidemiological, operational, or health systems research” (WHO, 2011, p. xiii).

Again, it is explained that “the operational guidance is not intended to take precedence over existing laws, regulations, and practices. Rather, they complement them and that RECs can use them as a guide to develop their own standard operational procedures for their specific practices” (WHO, 2011, p. xiii). Also, the document is not intended to “replace countries’ national and local guidelines for the ethical review of research involving human participants, neither does it supersede national laws and regulations” (WHO, 2011, p. xiii). Instead, the guidelines “will help authorities put in charge to draft national, local, and institutional regulations, and policies, to improve the quality of RECs’ work worldwide" (WHO, 2011, p. xiii). Also, with the WHO guidance in place, relevant authorities are encouraged to ensure that “ethics review of health-related research is supported by an adequate legal

framework that conforms to standard guidelines" (WHO, 2011, p. xiii). In addition, they should ensure that RECs "are capable of providing independent review of all health-related research; and that there exist at the national, subnational, and/or institutional (public or private) levels, appropriate and sustainable system to monitor the quality and effectiveness of research ethics review" in their respective countries and institutions (WHO, 2011, p. xiii).

In a study conducted by Lidz and colleagues, it was mentioned that "despite the importance of IRBs in human subjects research, relatively very little is known about how they function" (Lidz et al., 2012, p. 969). The results from the study by Lidz and colleagues showed that several studies dating to the 1970s, including surveys of the composition, staffing, and workload of IRBs, and the types of protocols, found that IRBs focused principally on consent forms (Lidz et al., 2012). According to Lidz and colleagues, other studies also looked at the variation of decisions when IRBs at different sites reviewed the same protocol and found substantial differences between IRB decisions, calling into question the reliability of such determination (Lidz et al., 2012). "However, the existing research has not examined exactly what RECs/IRBs discuss when they review a protocol. What is known on this subject stems largely from surveys of IRB members" (Lidz et al., 2012, p. 969). For example, "in the 1970s, Gray and Cooke examined the performance of a single IRB by reviewing its meeting minutes" (Lidz et al., 2012, p. 969). "More recently, there have been several ethnographic descriptions of one or two IRB panels. One of the most important questions that remains unanswered is the degree to which IRB deliberations address the primary elements of human subject protection regulations" (Lidz et al., 2012, p. 969).

"The International compilation of human research standards (2016) enumerates over 1,000 laws, regulations, and guidelines that govern human subjects' research in 120 countries, as well as the standards from a number of international and regional organisations" (Office for Human Research Protections (OHRP), 2016, p. 1). In addition, "the Compilation was developed for use by researchers, IRBs/RECs, sponsors, and others who are involved in human subjects' research around the world. However, these guidelines have resulted in challenges with interpretation and application, particularly for research in developing countries" (OHRP, 2016, p. 1).

2.2 Creation of research regulations for research involving human subjects

2.2.1 Tracing the roots of research ethics regulations

It is reported that "most of the laws, regulations, and guidance documents in place today are a result of World War II" (Richeson, 2014). According to Richeson (2014), although the first US law related to control over drug development was passed early in the twentieth century, it was only after the

Nuremberg trials, “that the world really sat up and took note” (Richeson, 2014). In these war crime trials held after World War II, a number of German physicians and camp administrators were charged with “conducting medical experiments on prisoners in concentration camps that resulted in the crippling and/or death of most of the test subjects” (Richeson, 2014). As these atrocities came to light, countries globally were horrified and, shortly thereafter, in 1948, the Nuremberg Code (described in detail in section 2.2.3.1) was established to protect participants in medical experiments (Richeson, 2014).

2.2.2 History of suffering of research participants that led to health research regulation

Literature suggests that “research ethics in its broadest definition encompasses the principles, standards, norms and guidelines that regulate scientific inquiry” (Ajuwon & Kass, 2008). These authors maintain that “the primary role of ethics in health research is to protect the rights, integrity, and safety of research participants”. As suggested in the previous section, the present ethical guidelines were developed in response to public awareness of abuses to human research participants. These included “the horrific human experiments of the Second World War in Germany and the Tuskegee syphilis study in America” which led to “the formulation of several ethical guidelines including the Nuremberg Code, the Declaration of Helsinki, and the Council for International Organizations for Medical Sciences (CIOMS) guidelines” (Ajuwon & Kass, 2008). However “despite the availability of these relations and guidelines, violations of the rights of research participants continue to occur in both higher and lower income countries” (Ajuwon & Kass, 2008).

Again, Ajuwon and Kass (2008) report that African study participants may be “more susceptible than their counterparts in developed countries to exploitation because of high levels of poverty, low literacy rates, severely limited access to basic health care and inadequate local regulation of biomedical research” (Ajuwon & Kass, 2008). In addition, there have been specific research ethics controversies in Africa, which “include the Pfizer drug trials of *trovan* in Nigeria and *tenofovir* in Cameroon that have again highlighted the need for African professionals to have sophistication in research ethics in order to be able to participate in the debates locally” (Ajuwon & Kass, 2008). Therefore “one of the strategies for addressing this situation is the initial and continuing education in the ethics and science of biomedical, as well as behavioural, research for investigators, members of the Institutional Review Boards (IRBs), and sponsors of research” (Ajuwon & Kass, 2008).

According to Amdur and Bankert (2011) in the 1950s, a series of studies was done to understand issues related to the transmission of the hepatitis virus in retarded children who were residents in the Willowbrook state school, an extended care facility in New York. Because many of the residents contracted hepatitis during their time at Willowbrook, it was important to try to understand more

about the mode of transmission of the hepatitis virus in the study population (Amdur & Bankert, 2011). However, the study generated a lot of debate in both the national professional journals because the study was designed to intentionally infect healthy children with hepatitis by feeding them a solution made from the faeces of children with active hepatitis (Amdur & Bankert, 2011). Furthermore, the parents of the children were told that Willowbrook would not take care of their children, if they did not take part in the study, thereby applying coercion (Amdur & Bankert, 2011).

Wassenaar (2006, p. 61) reports that "most accounts of the history of research ethics attributes the growth of research, to the aftermath of the atrocities committed by Nazi medical researchers in Germany during World War II". It is also reported that research ethics codes emphasise the "importance of individual informed consent in all research with humans in order to prevent the recurrence of abuses by scientists in the name of research" (Wassenaar, 2006, p. 61). However "the Nuremberg Code is rather restrictive regarding persons who could not consent to research, and that the World Medical Association published the more detailed Declaration of Helsinki in 1964, last revised in 2000" (Wassenaar, 2006, p. 61), and subsequently revised in 2013. In addition, "numerous other guidelines and ethical codes for researchers have been published since World War II, and most of these codes focus on biomedical research" (Wassenaar, 2006, pp. 61-62). However, other social science disciplines (including psychology, sociology, anthropology, history, and nursing) have developed different other codes of ethical conduct (Wassenaar, 2006).

Further, research explains that "the abuse of human subjects in biomedical research is as old as humankind" (Wekesa, 2015, p. S26). For example, a look at history shows that people have often been used as 'guinea pigs' by people with power. An example of this is that "when the French King Louis XIV was sick, and the royal surgeon was allowed to operate on as many patients with similar symptoms until he gained sufficient experience to operate on the King, successfully" (Wekesa, 2015, p. S26).

Beauchamp and colleague report a longstanding distinction between clinical ethics and research ethics (Beauchamp & Childress, 2013). The difference between clinical research and clinical practice required different regulations and guidance documents. They argue that research has become heavily regulated because it has the potential to place subjects at risk for the benefit of others (Beauchamp & Childress (2013). In contrast to this medical practice is less regulated because it focuses only on the patient and relies on scientifically proven interventions with reasonable risks (Beauchamp & Childress, 2013).

Beauchamp and Childress explain that this distinction between research and practice determines which activities must undergo committee review for the protection of human subjects of research. In general, components of research that introduce risk require independent ethics review to protect prospective participants (Beauchamp & Childress, 2013). Nothing comparable exists at the national level in most countries for medical practice. But the question is, are these sharp distinctions between research and practice, as well as the parallel differences in ethics and regulations, truly warranted? Why, morally, should practice be treated so differently from research when it comes to the protection of patients? (Beauchamp & Childress, 2013). These authors believe that the common view has been that research lacks a focus on personalised care in that its specific objective is scientifically designed testing of a hypothesis aimed at producing a social good – i.e., generalisable knowledge (Beauchamp & Childress, 2013).

2.2.3 Existing international health research ethics codes, rules and regulations

2.2.3.1 Nuremberg Code

According to Amdur and Bankert, the Nuremberg trials were conducted at the end of World War II to bring justice to Nazi leaders who had committed crimes against humanity in their treatment of civilian prisoners under their control (Amdur & Bankert, 2011). It is said that "a major portion of the trials was devoted to the case of Nazi physicians who had forced prisoners to undergo horrifying procedures for research purposes" (Amdur & Bankert, 2011, p. 10). They maintain that, in order to "make the case of crimes against humanities, the prosecutors had to argue that the Nazi defendants conducted research in ways that violated the fundamental ethical standard of civilised society" (Amdur & Bankert, 2011, p. 10). Also, "as part of the proceedings at Nuremberg, the prosecution issued what is now referred to as the Nuremberg Code – a document which articulated the basic requirements for conducting research in a way that respects the fundamental rights of research subjects" (Amdur & Bankert, 2011, p. 10). The Code explains ethical standards that have been incorporated into most subsequent ethical codes – such as the Declaration of Helsinki – and in federal research regulations (Amdur & Bankert, 2011). The basic elements of the Nuremberg Code include: i) voluntary and informed consent; ii) favourable risk/benefit analysis; and iii) the right to withdraw without penalty (Amdur & Bankert, 2011, p. 10).

The Nuremberg Code was the first step towards the Good Clinical Trial Practice (GCP) that many follow today, all designed to protect the right, health and safety of clinical trial participants. On the flip side, there are also regulations designed to protect the right, health and safety of the general public from drugs available on the market. It is reported that these regulations can be traced back to the tragic event that took place in early 1960s (Richeson, 2014)

2.2.3.2 Kefauver Amendment – the Thalidomide experience

According to Amdur and Bankert (2011), in the late 1950s, a drug called thalidomide was approved as a sedative in Europe; however, it was not approved by the United States Food and Drug Administration (FDA). “Thalidomide is a drug that doctors used in the 1950s to treat a variety of unpleasant symptoms associated with pregnancy” (Amdur & Bankert, 2011, p. 12). This drug was prescribed to control sleep and nausea throughout pregnancy. At that time, it was not standard practice to inform patients when their doctors were recommending an investigational medication (Amdur & Bankert, 2011). However, after treating large numbers of pregnant women with thalidomide, it became clear that taking this drug during pregnancy caused severe deformities in the infants who were exposed to thalidomide (Amdur & Bankert, 2011). According to Amdur and Bankert (2011, p. 12), “public outrage over the situation led to an amendment to Drug, and Cosmetic Act that required investigators to obtain informed consent from potential subjects before administering investigational medications” (Amdur & Bankert, 2011, p. 12). Amdur and Bankert (2011, p. 9) explain that this legislation was “a milestone in the history of research regulations” because it was the first time that Federal agency regulations were used to establish specific ethical standards for the conduct of research.

2.2.3.3 Declaration of Helsinki

Amdur and Bankert (2011, p. 13) report that “in 1964, the World Medical Association met in Helsinki, Finland, to draft the Declaration of Helsinki, a document that would build on the Nuremberg Code of 1947to describe the standards of ethical research involving human subjects”. They report that since then, the Association has met many times to revise the declaration (Amdur & Bankert, 2011). The Declaration has since been revised in 1975, 1983, 1996, 2000, 2002, 2004, 2008, with the latest version revised in 2013 and it is the basis for Good Clinical Practices used today. The general principles discussed in the latest version of the Declaration of Helsinki (World Medical Association (WMA), 2013) are described below. The revision binds physicians with the following statement: “The health of my patient will be my first consideration” (WMA, 2013, p. 2191).

The International Code of Medical Ethics also declares, amongst others (WMA, 2013, pp. 2191-2192):

> i) That a physician shall act in the patient’s best interest when providing medical care.
>
> ii) That it is the duty of the physician to promote and safeguard the health, well-being, and rights of patients, including those who are involved in medical research. The physician’s knowledge and conscience shall be dedicated to the fulfilment of this duty.

iii) That medical progress is based on research that ultimately must include studies involving human subjects.

iv) That the primary purpose of medical research involving human subjects is to understand the causes, development and effects of disease and improve preventive diagnostic and therapeutic interventions (methods, procedures and treatment), even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

v) That medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

vi) That while the primary purpose of medical research is to generate new knowledge, this goal cannot take precedence over the rights and interests of individual research subjects.

vii) That it is the duty of the physicians who are involved in medical research to protect life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. Thus, the responsibility for the protection of research subjects must always rest with the physicians or other health care professionals and never with the research subjects, even though they have given consent.

viii) That physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international, ethical, legal or regulatory requirements should reduce or eliminate any of the protection for research subjects set for in this declaration.

ix) That medical research should be conducted in a manner that minimises possible harm to the environment.

x) That medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications, and that research on patients or healthy volunteers requires the supervision of a competent and appropriate qualified physician or other health care professional.

xi) That groups that are underrepresented in medical research should be provided appropriate access to participation in research.

xii) That appropriate compensation and treatment for subjects who are harmed as a result of participating in research and must be ensured.

xiii) That in medical practice and in medical research, most interventions involve risks and burdens. Medical research may only be conducted if the importance of the objectives outweighs the risks and burdens to the research subjects.

xiv) That some groups and individual are particularly vulnerable and have an increased likelihood of being wronged and incurring additional harm. Therefore all vulnerable groups and individuals should receive specifically considered protection.

xv) That research protocols must be submitted for consideration, comments, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influences, and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but must not be allowed to reduce or eliminate the protections for research subjects set forth in this Declaration.

xvi) That the ethics 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.

2.2.3.4 The 'Wichita Jury Study'

Another milestone in the history of research regulation is the 'Wichita Jury Study'. In the early 1950s, "social science researchers at the University of Chicago directed a study to better understand the decision-making process of jurors in criminal trials" (Amdur & Bankert, 2011, p. 11). For Amdur and Bankert, what motivated this study was the showmanship on the part of trial attorneys that potentially had a major influence on jury verdicts (Amdur & Bankert, 2011). Amdur and Bankert (2011, p.11) explained that the "study involved audiotaping jury deliberations in criminal trials in Wichita, Kansas". However, the researchers did not want the jurors' behaviour to be changed by their being observed, hence they were not told that they were subjects of a research project or that their deliberations were being recorded (Amdur & Bankert, 2011). The investigators completed the study and presented the results in academic forums. However, the study found a hostile reception from the American public as the study methodology was criticised and became a topic of a national interest (Amdur & Bankert, 2011). The main focus of the criticism was how people were deceived for research purposes in a setting where privacy and confidentiality were critically important (Amdur & Bankert, 2011).

2.2.3.5 The radiation experimentation and human participant abuses

Claremont Graduate University (n.d.) report other examples of abuses of human participants during World War II and the early cold war when US officials studied the effects of radiation through

experiments on human patients, pregnant women, retarded children, and enlisted military personnel. It also came to light that while some of the participants of the experiments gave informed consent, most did not know that they were being exposed to radioactive materials (Claremont Graduate University, n.d.). Again, it is mentioned that the "Manhattan Project officer authorised the wartime experiments to establish health and safety standards for the thousands of workers in atomic bomb plants" (Claremont Graduate University, n.d.). Then, "after the war, as the cold war deepened, officials justified expanded study of the effects of radiation on the grounds of national security" (Claremont Graduate University, n.d.). These serious abuses of humans led to congressional investigations, numerous official reports, scholarly studies and lawsuits, such that in the 1990s, "the government offered apologies and financial compensation to some of the victims of human radiation testing" (Claremont Graduate University, n.d.).

2.2.3.6 The Tuskegee Syphilis Study (1932-1972)

According to Wassenaar (2006, p. 63), "in 1932, the US public health service funded a study to examine the effects of syphilis". At that time "there was no effective treatment for syphilis, and the long-term effects of the illness had not been clearly described" (Wassenaar, 2006, p. 63). It is reported that over 300 hundred male syphilis sufferers were "enrolled from an impoverished rural area in Alabama where the prevalence of syphilis was known to high" (Wassenaar, 2006, p. 63). There were also 200 uninfected controls. However, "it is uncertain whether the men knew that they were participating in a natural history study involving no treatment, and there is also no clear record of informed consent" (Wassenaar, 2006, p. 63). The men then "were subjected to various examinations and medical procedures" (Wassenaar, 2006, p. 63). Though, penicillin, an effective treatment for syphilis became available during the course of the study, the men in the study were not informed of this. Furthermore, the researchers did not provided treatment for the participants as it would have undermined the scientific purpose of the study (Wassenaar, 2006, p. 63). As a result, the participants' condition worsened and many of them died. The study was stopped in 1972 after public exposure and it led to the development of national research regulations in the USA in 1974 (Wassenaar, 2006, p. 63). Thereafter, "the survivors and families of the deceased men were awarded compensation" (Wassenaar, 2006, p. 63). Not only did US President Bill Clinton award the survivors and families of the deceased men, but he also issued a "formal presidential apology for the Tuskegee syphilis study on behalf of the US government in 1997" (Wassenaar, 2006, p. 63).

2.2.3.7 The Belmont Report

The Office for Human Research Protections of the US Department of Health explains that "the Belmont Report was written by the National Commission for the Protection of Human Services of

Biomedical and Behavioral Research" (Office of Research Integrity, 1979). This was prompted in part by problems arising from the Tuskegee Syphilis Study (1932–1972) and based on the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1974–1978). Later, the Department of Health, Education and Welfare (HEW) revised and expanded its regulations for the protection of human subjects 45 CFR part 46 in the late 1970s and early 1980s (Office of Research Integrity, 1979). In 1978, "the commission's report on ethical principles and guidelines for the protection of human subjects of research was released, and it was published in 1979 in the Federal Register" (Office of Research Integrity, 1979). "The document was then named 'the Belmont Report' at the Belmont conference center where members of the National Commission met to develop the first draft report" (Office of Research Integrity, 1979). It is also reported "that the Belmont Report is one of the leading works concerning ethics and health care research" (Office of Research Integrity, 1979). Again, "the report allows for the protection of participants in clinical trials and research studies, and explains the unifying ethical principles that form the basis for the National Commission's topic-specific reports and the regulations that incorporate its recommendations" (Office of Research Integrity, 1979).

The Report explains the three fundamental ethical principles for using any human subjects for research as follows (Office of Research Integrity, 1979):

1. Respect for persons: Protecting the autonomy of all people and treating them with courtesy and respect and allowing for informed consent. Researchers must be truthful and conduct no deception;
2. Beneficence: The philosophy of 'do no harm' while maximising benefits for the research project and minimising risks to the research subjects; and
3. Justice: Ensuring reasonable, non-exploitative and well-considered procedures are administered fairly - the fair distribution of costs and benefits to potential research participants - and equally.

Additionally, "the principles remain the basis for the United States Department of Health and Human Services (HHS) human subject protection regulations" (Office of Research Integrity, 1979). Even today, "the Belmont Report continues as an essential reference for institutional review boards (IRBs) that review HHS-conducted or -supported human subjects research proposals involving human subjects, in order to ensure that the research meets the ethical foundations of the regulations" (Office of Research Integrity, 1979). Further, application of these principles to conducting research requires careful consideration of: i) informed consent, ii) risks benefit assessment, and iii) selection of subjects of research. Sims (2010, pp. 173-174) explains seven aspects that nurses, as primary caregivers for individuals participating in a study, must carry out to ensure that the rights of the participant are met:

1. Ensure the study is approved by an IRB.
2. Get informed consent from the patient.
3. Ensure that the patient understands the full extent of the experiment, and if not, will contact the study coordinator.
4. Ensure the patient wasn't coerced into doing the experiment by means of threatening or bullying.
5. Be careful of other effects of the clinical trial that were not mentioned, and report this to the proper study coordinator.
6. Support the privacy of the patient's identity, their motivation to join or refuse the experiment.
7. Ensure that all patients at least get the minimal care needed for their condition.

In addition, researchers should share the findings of their procedures regardless of the results being 'good' or 'bad'. Also, in the case someone who does not want to participate in the research but would still like treatment, they cannot be turned away and must be treated with the same standard care (Office of Research Integrity, 1979).

The Nazi researchers and concentration camp prisoners provide a good example of injustice. The principle of justice requires that the benefits and burdens of research should be justly distributed. The selection of research participants needs to be constantly monitored to determine whether some pools of participants are being systematically accessed simply because they are easily available or vulnerable or easy to manipulate, rather than chosen for reasons directly related to the research problem being studied.

Literature reveals that "as recently as 1950, the United State federal government had a relatively minor role in regulating research conduct" (Amdur & Bankert, 2011, p. 9). In that era, there were no federal regulations that required institutional review board (IRB) approval to carry out research with humans. What ethics policies and procedures had been established were not uniformly applied or accepted (Amdur & Bankert, 2011). These authors go on to say that "today the situation is very different" (Amdur & Bankert, 2011, p. 9). The US federal government now regulates all aspects of the research process through specific agency regulations (Amdur & Bankert, 2011). The policy and procedures in the federal regulations apply to both biomedical and social science research and define the modern IRB system for monitoring research conduct (Amdur & Bankert, 2011). These authors examine the question of how ethical oversight of research went from so little to so much regulation in a relatively short time (Amdur & Bankert, 2011). The answer to this question is to be found within the history of modern institutional research ethics boards (IRBs) or research ethics committee (REC)

system. This “is a fascinating story that involves the national media, community activism, high powered science, and big-government politics” (Amdur & Bankert, 2011, p. 9).

2.2.3.8 The modern REC system

According to Amdur and Bankert (2011), the modern REC system was established by the United States National Research Act (NRA) of 1974, to regulate research involving human subjects. Amdur and Bankert (2011) explain that the Act passed federal regulations that required REC approval to conduct most kinds of research involving human subjects. The policies and procedures that a REC must follow when reviewing research are also provided in the Act. The NRA defines the criteria that an REC must use to approve research (Amdur & Bankert, 2011).

Having provided a broad view about the history of international research ethics and how it originated, it will be appropriate to also look at how research ethics has evolved in Africa. The following section covers the history of research ethics review in Africa and its necessity.

2.3 Health research ethics review in Africa

This section provides an overview of research ethics review in some selected African countries including South Africa, Malawi, Zimbabwe, Tanzania, Nigeria, and Ghana. The reason for selecting these countries was due to accessibility of information at the time of writing the research protocol. First, literature reveals that “the past few decades have witnessed significant growth in health research in Africa, in response to the serious health challenges of the continent, of which developed countries funded a significant proportion” (Ndebele, Mwaluko, Kruger, Oukem-Boyer & Zimba, 2014, p. 3). According to Ndebele and colleagues, “the increase in the volume of research in Africa has not necessarily been accompanied by improvements in health research oversight systems, including ethical review committees, leaving the continent vulnerable to potential exploitative research funded by resource-rich countries” (Ndebele et al., 2014, p. 3). As a result, several concerns have been raised, firstly, that “researchers from developed countries may conduct research in Africa that cannot easily be done in their own countries due to a robust research regulatory framework there, which is often not found in most African countries” (Ndebele et al., 2014, p. 3). Furthermore, “the abuses of human research participants in the western world have played a significant role in shaping present-day research protection norms, standards and requirements.” (Ndebele et al., 2014, p. 3). Another concern arose from “the unethical experiments that were conducted by Nazi scientists during the Second World War led to the formulation of the Nuremberg Code of research ethics in 1946, which has, since then, influenced the international research ethics environment in several ways” (Ndebele et al., 2014, p. 3). These “trials led to the promulgation of the Declaration of Helsinki by the World Medical

Association in 1964." (Ndebele et al., 2014, p. 3) as well as the "development of the International Ethics Guidelines for Biomedical Research Involving Human Subjects (CIOMS Guidelines) of 1982" (Ndebele et al., 2014, p. 3). In addition, "the UN Human Rights Charter, the Declaration of Helsinki, and the CIOMS guidelines, due to their international scope, have all significantly influenced the African research ethics landscape" (Ndebele et al., 2014, p. 3).

2.3.1 Research ethics in South Africa

Moodley and Myer (2007) maintain that, "the system of ethical review in Africa dates back to 1966 when the first Research Ethics Committee (REC) was established in South Africa at the University of the Witwatersrand". They explain that most major tertiary institutions have developed research ethics committees. In 2007, there were approximately 34 local RECs in South Africa, "two of which are part of private and non-academic institutions" (Moodley & Myer, 2007). Further, following this, "in 2002 the Office for Human Research Protections (OHRP) visited South Africa and granted Federal Wide Assurances (FWAs) to eight RECs in the country" (Moodley & Myer, 2007). Also, "the FWAs were part of the OHRP's Quality Assurance process whereby written policies and procedures were compared to practice" (Moodley & Myer, 2007). In addition, "this is a voluntary process and that the FWA is an endorsement of an institution's commitment to quality assurance" (Moodley & Myer, 2007).

More recently, the National Health Act has made provision for the establishment of a National Health Research Ethics Council (NHREC) in South Africa in order:

> To set guidelines for the functioning of local RECs, to register and audit local RECs, to set norms and standards for research, to adjudicate complaints about the functioning of RECs and to institute disciplinary action against those who violate norms or guidelines for research in terms of the Act. (Moodley & Myer, 2007)

Thereafter, in 2000, the South African Good Clinical Practices (GCP) was published by the Department of Health (DoH). The GCP guideline "specifies composition of RECs in terms of race, gender and occupational identity" (Moodley & Myer, 2007).

2.3.2 Research ethics in Zimbabwe

Literature reports that the research ethics arm of the Medical Research Council of Zimbabwe (MRCZ) is the National Ethics Committee (NEC), and that the NEC was established in 1974 in terms of the Research Act of 1959, and Government Notice Number 225 of 1974, to provide health researchers and institutions with guidelines for the conduct of research with human participants, independent ethical advice on research conducted by those researchers or research within those institution (Medical Research Council of Zimbabwe (MRCZ), 2004). It is said that the Government of Zimbabwe, through the Ministry of Health and Child Welfare, supports activities of the MRCZ

Members who include scientists, medical experts, lawyer, ethicists, and religious community representatives. In addition, "it is independent in its reflection, advice, and decision" (MRCZ, 2004, p. 2). Again, the operations of the MRCZ are funded through an annual grant from the Ministry of Health and Child Welfare, and individual donations (MRCZ, 2004).

2.3.3 Research ethics in Malawi

According to Mfutso-Bengo and colleagues, bioethics in Malawi is historically closely linked with the University of Malawi, College of Medicine, where bioethics started in this country (Mfutso-Bengo, Manda-Taylor, Jumbe, Kazanga & Masiye, 2014). It is said that, "today, the University of Malawi, College of Medicine, is one of the very few medical colleges in Africa that considers the subject of bioethics and research ethics as necessary and indispensable" (Mfutso-Bengo et al., 2014, pp. 1271-1272). For example, "it is one of the few medical schools in Africa that introduced a compulsory biomedical ethics curriculum, which covers all five years of medical training" (Mfutso-Bengo et al., 2014, p. 1272). In addition, an important role-player is the Centre for Bioethics in Eastern and Southern Africa (CEBESA) which leads all the initiatives in the areas of bioethics and research ethics at the College (Mfutso-Bengo et al., 2014). CEBESA was established in 2001, and falls under the Department of Community Health at the College of Medicine. Mfutso-Bengo et al. (2014, p. 1272) note that CEBESA "is committed to helping healthcare professionals, researchers, students, and policy-makers in addressing ethical issues in Malawi"

Some of the main concerns of the Centre are "the ethical practices of medicine and ethical conduct of biomedical research in Malawi"; the Centre also "seeks to interact with various institutions, projects, researchers, and communities on such issues through various means" (Mfutso-Bengo et al., 2014, p. 1272). The Centre also supplies training on research ethics, and good clinical trial practices to research ethics committee members and researchers (Mfutso-Bengo et al., 2014). Additionally, "stakeholders including government, health practitioners, research ethics committees, hospitals, members of the public and others receive advice on issues related to bioethics, research ethics, and good clinical practice" (Mfutso-Bengo et al., 2014, p. 1272).

Further, a Medical Rights Watch initiative has been established by CEBESA with the aim of taking bioethics to the grassroots, thereby making people aware of their rights and responsibilities (Mfutso-Bengo et al., 2014). The organisation's aim is to draw the attention of all key health decision makers on basic ethical values at all levels, with the aim of changing the health system into a vibrant and effective organisation that applies the principles of justice, beneficence and autonomy when dealing with human subjects. This is being done "through making basic ethics knowledge available to all these decision makers, and also giving them guidance on how to resolve ethical dilemmas" (Mfutso-

Bengo et al., 2014, p. 1272). The reason for all these measures is to protect the rights and responsibilities of patients, research participants, and health practitioners in Malawi (Mfutso-Bengo et al., 2014).

2.3.4 Health research ethics in Tanzania

Literature reveals that, the national research ethics committee in Tanzania which was constituted and functions according to the guidelines of the Office of Human Research Protections, was established in 2002 (Ikingura, Kruger, & Zeleke, 2007. These authors report that "the committee operates under the auspices of the Medical Research Coordinating Committee (MRCC) established in early 1980s" and that this is the overall coordination body for health research in Tanzania (Ikingura et al., 2007, p. 154). Further, the MRCC "has formed the National Health Research Ethics Review Committee (NHRERC), with the mandate to oversee ethical review and approval of health research to be conducted in the country" (Ikingura et al., 2007, p. 155). According to Ikingura and colleagues, the NHRERC is hosted and operates under the National Institute for Medical Research (NIMR). However, in recent years, "NIMR Centres have formed local RECs, which issue institutional ethical approvals, and forward research proposals, with recommendations to the national REC, for further review of ethical issues" (Ikingura et al., 2007, p. 155). Further, deliberate efforts have been made to empower local RECs in the country to review research so as to reduce the workload of the NHRERC (Ikingura et al., 2007).

2.3.5 Biomedical research regulation in Kenya

Wekesa (2015, p. S25) reports that the "regulation of biomedical research in Kenya has been uncoordinated for many years" He explains that "the Ministries in charge of Wildlife of Science/ Technology, and that in charge of Health were involved" and that "several institutions had their own clearing houses that worked independently" (Wekesa, 2015, p. S25). It is reported that "for a very long time, attempts to standardise ethical review procedures and guidelines in Kenya were unsuccessful" (Wekesa, 2015, p. S27). As a result, this situation was exploited by scientists, especially foreign ones, to carry out experiments which did not meet the international ethical standards and which they could obviously not carry out in their own countries. In addition, biological materials and specimens were exported without controls (Wekesa, 2015).

Wekesa (2015) reports that Kenya now has the Science, Technology and Innovation Act, 2013, which came into force in 2014. Additionally, three institutions were established by the Act. These institutions are: i) the National Commission for Science, Technology and Innovation; ii) the Innovation Board; and iii) the Research Fund Board (Wekesa, 2015). The functions of the National Commission for Science, Technology and Innovation functions as enumerated include:

> Accreditation of research institutions and approval of all scientific research in Kenya; coordination, monitoring, and evaluation of activities relating to scientific research, and development of technology; development as well as the enforcement of codes, guidelines, and regulations; and undertaking regular inspections, monitoring, and evaluation of research institutions (Wekesa, 2015, pp. S27-S28).

According to these regulations, research projects involving human subjects must be licensed before the research is started (Wekesa, 2015).

Further, accreditation of research institutions is provided for under section 17 of the Act (Wekesa, 2015). Accordingly, all institutions that intend to undertake biomedical research must be accredited by the commission. According to the Act, such institutes must form an Institutional Review Committee (IRC) in line with standard operating procedures established by the commission. "It is the duty of such an institutional Review Committee to approve protocols on behalf of the commission, to monitor adherence of researchers to their protocols, and to submit an annual report of its activities to the commission" (Wekesa, 2015, p. S28).

2.3.6 Research ethics in Nigeria

Literature explains that the first attempts to set up a national ethics regulatory infrastructure in Nigeria took place in 1980; however, "this effort faltered largely because of lack of sustained interest and funding" (Adebamowo, Mafe, Yakubu, Adekeye, & Jifa, 2008, p. 16). Adebamawo et al. (2008, p. 16) note:

> Subsequent attempts were also unsuccessful because the decades of 1980s and 1990s were marked by military misrule and socio-economic dislocation. The advent of civilian democracy in Nigeria in 1999 coincided with a period of increased international attention to the problems of unethical health research that occurred, particularly in developing countries.

Again, Adebamowo and colleagues explain that "by 2004, several Nigerians had graduated from the older US National Institute of Health/Fogarty International Centre (NIH/FIC)-funded international research ethics training programmes, in the United States, Canada, and South Africa" (Adebamowo et al., 2008, p. 16). Thereafter, institutions which did not have ethics committees were pressured to make sure that they set up their own ethics review committees (Adebamowo et al., 2008). Further, the existing ethics committees were strengthened and provided with local bioethics training.

Adebamowo and colleagues explain that momentum was gathered "such that during a 2006 presidential retreat on the health of Nigerians, the fact that Nigeria needed an ethics regulatory infrastructure for health research to meet its United Nations Millennium Development Goals targets was strongly highlighted" (Adebamowo et al., 2008, p. 17). As a follow up on this, the National Health Research Ethics Committee in Nigeria was reconstituted and strengthened by the Federal

Government in Nigeria. It was also backed with legislation in order to set some objectives for implementation (Adebamowo et al., 2008).

Further, to fulfil the objectives, the Federal Ministry of Health in Nigeria, together with the West African Bioethics Training Programme (WAB), which is a United States NIH/FIC-funded programme, which is also located in Nigeria, signed a Technical Cooperation Agreement located in Nigeria to provide biomedical and bioethics training for researchers in Nigeria and West Africa (Adebamowo et al., 2008). With the bioethics training programme in place, national codes for health research ethics, standard operating procedures for ethics committees, as well as other related documents were developed to strengthen health research ethics in Nigeria (Adebamowo et al., 2008).

A draft copy of the national code and the standard operating procedures which were developed by the committee were then submitted to NHREC in 2006, and they were adopted after amendments. Thereafter, the draft code was "published on the NHREC website and disseminated within and outside the country for consultation and comments by the research community and stakeholders" (Adebamowo et al., 2008, p. 17). Later, the comments, suggestions, and corrections, received were incorporated as one full document by the NHREC (Adebamowo et al., 2008). It was then submitted to the government for adoption as the first domestic legal regulation establishing ethical review of research in Nigeria (Adebamowo et al., 2008). It is said that "the code has now been released for implementation by Nigeria HRECs and biomedical researchers" (Adebamowo et al., 2008, p. 17). The code outlines "the norms and standards that must be applied for the ethical review of research in Nigeria" (Adebamowo et al., 2008, p. 17).

2.3.7 Health research ethics review in Ghana

In Ghana, where the present study was carried out, the only institution that has the parliamentary backing to review scientific and health research is the Centre for Scientific and Industrial Research (CSIR) but it was only in 2011 that an IRB was officially inaugurated to review protocols for research within the CSIR facilities and Ghana as a whole. The establishment of institutional Research Ethics Committees RECs is very recent. Up until the year 2000, there were no such committees or boards in Ghana. Following collaboration between the National Institutes of Health (NIH) (US) with two pioneer RECs, namely Noguchi Memorial Institute for Medical Research REC (NMIMR) and the Navrongo Health Research Centre (NHRC), the REC finally came into existence.

As part of the requirement for the release of funds, the two institutions (NMIMR) and (NHRC) were to establish their institutional RECs/IRBs to have oversight of research to be carried out in Ghana,

especially in their facilities and their environs. Since then, there has been an upsurge in the formation of such boards and RECs because of increasing human participant research conducted in Ghana. It is worth mentioning that before the establishment of RECs, there was no system in place to review research protocols, so approvals of research with humans were given by the heads of institutions where research was conducted.

There are 15 institutional RECs established by individual institutions in Ghana as at the time that this study was conducted. As described above, the first REC was formed in 2000 by the Noguchi Memorial Institution of Medical Research (NMIMR) of the University of Ghana to review protocols for research to be conducted in its institution. Eight were established between 2001 and 2010, whilst the most recent, the Korle-Bu Teaching Hospital Institutional Review Board was formed in 2015. The functions of these institutional RECs/IRBs are to review and approve protocols proposed studies to be conducted in their various institutional facilities before initiation of such studies.

Currently, Ghana does not have a National Health Research Ethics Committee (NHREC), nor are there any national ethics guidelines to monitor the conduct of the research activities in the county. Yet, each of these institutional IRBs and RECs has its own Standard Operating Procedures that guide the conduct of their activities as prescribed by the institution that established them. The RECs/IRBs are also mindful of existing research ethics guidance on how RECs should operate and conduct their activities to ensure maximum compliance with international guidelines and principles. These include the Nuremberg code, CIOMS guidelines, the Belmont Report, WHO guidelines (2000, 2001), and the Declaration of Helsinki.

These institutional RECs are required to review and approve research protocols prior to study initiation. Yet, it is not known what these institutional RECs' concerns are when they review research protocols, and whether their review processes conform to the Emanuel et al. (2004; 2008) framework. Research reveals that "RECs are designed to provide third party review thereby minimising conflict of interest, protect the welfare of research participants through attention to risk, benefits, and informed consent, and avoid exploitation of vulnerable individuals and populations" (Kass et al., 2007, p. 1). Also, "the process of ethics review helps to distinguish unethical research from research conducted to the benefit of society at large" (Emanuel et al., 2004; 2008).

It is said that "several authors have also reported difficulties that research participants have in understanding key clinical trial concepts" (Ndebele, Wassenaar, Masiye & Munalula-Nkandu, 2014, p. 2). Thus, in clinical trials, it is always difficult to explain the terms: randomisation, double-blinding, and placebo (which are usually used for studies) to participants involved in the study, owing

to the nature of the terms and where they originated. Also, “disadvantaged populations, comprising the majority of research participants in developing countries, lack familiarity with scientific language (Featherston & Donovan, 1998; Kerr et al., 2004; Mandava, Pace, Campbell, Emanuel & Grady, 2012; Pace et al., 2005; Pucci et al., 1999; Stead et al., 2005; Yuval et al., 2000)” (Ndebele, Wassenaar, Masiye et al., 2014, p. 2). This is ethically problematic, “particularly if participants do not understand the implications of research participation and these three trial concepts for themselves and their health (Dunn, Palmer & Keehan, 2006), suggesting that there may be problems in the way study information is received and understood during the informed consent process” (Ndebele, Wassenaar, Masiye et al., 2014, p. 2). Ndebele and colleagues (2014) report that an informed and understood decision is likely to reduce the possibility of regret after joining a study.

2.4 Challenges that research ethics committees face in Africa

A report from a study by Milford and colleagues mentions that “research in developing countries is often financed by well-resourced, developed countries and conducted in vulnerable host communities with diverse cultural backgrounds” (Milford, Wassenaar & Slack, 2006, p. 1). Again, it is reported that multinational research is often undertaken according to the regulatory frameworks of the wealthier sponsor countries. However, this “may be inappropriate to host country conditions and raise ethical concerns about potential exploitation of host communities and participants, insensitivity to community ethos, the scope of sponsor-investigator obligations, and the appropriate communication of research results to participants” (Milford et al., 2006, p. 1).

According to Nyika and colleagues, “international collaborative research usually involves funding from developed countries and shipment of samples to high-tech laboratories in developed countries” (Nyika, Kilama,,Tangwa et al., 2009, p. 150). This often occurs because the “collaborating institutions in developing countries generally have inadequate expertise and technology to perform some of the more complicated research procedures” (Nyika, Kilama, Tangwa et al., 2009, p. 150). For example, “some scientists are now working in the controversial field of genetic engineering of human beings”. (Nyika, Kilama, Tangwa et al., 2009, p. 150)**.** African RECs are faced with challenges of reviewing more and more protocols than before, and that some of these studies are increasingly complex. For example, the studies are more complex due to various factors, including technological developments, the emergence of new diseases, and the shift from local research projects to international collaborative projects; these often “involve participants and collaborating research drawn from different countries with diverse cultural and socio-economic backgrounds” (Nyika, Kilama, Tangwa et al., 2009, p. 150). Research reveals that the high disease burden of Africa, the emergence of new diseases and efforts to

address the 10/90 gap have led to an unprecedented increase in health research activities in Africa (Nyika, Kilama, Tangwa et al., 2009).

It is said that "in the wake of such an increase in health research on mostly poverty-stricken and poorly educated populations, given Africa's weak civic protection systems, it is imperative that attention be paid to the ethical review capacity of African health institutions" (Nyika, Kilama, Chilengi et al., 2009, p. 189). Therefore, the "review of research protocols before implementation is now regarded as one of the cornerstones of ethical research involving human participants, and some countries have made it a legal requirement" (Nyika, Kilama, Chilengi et al., 2009, p. 189). Similarly, most international and national guidelines require that ethical approval must be obtained before the commencement of research involving humans (Nyika, Kilama, Chilengi et al., 2009). Therefore, in developing countries, the primary purpose of reviewing research protocols is to make sure that internationally acceptable scientific and ethical standards are met in the conduct of the research (Nyika, Kilama, Chilengi et al., 2009.

As argued previously, "it would be unethical for poorly designed research involving human beings to be approved, since data generated from such research would not contribute to the improvement of disease prevention or management" (Nyika, Kilama, Chilengi et al., 2009, p. 189). Additionally, the issue of community engagement has recently been recognised as an important activity that could help establish a friendly relationship between researchers and the research participants' communities (Nyika , Kilama, Chilengi et al., 2009). Researchers are therefore encouraged to have respect for communities which are seen as major stakeholders in the research. Further, it is essential that "ethical review committees (ERCs) that review the protocols are adequately knowledgeable about all these requirements" (Nyika, Kilama, Chilengi et al., 2009, p. 189).

Lidz and colleagues report that RECs in developing countries play a pivotal role in protecting human research participants involved in international collaborative studies conducted in their respective countries. However, despite the importance of these RECs, relatively very little is known about what the main concerns of members of the Committees/Boards are, when they review study protocols (Lidz et al., 2012). Currently, there is no existing data or research that has examined exactly what RECs/IRBs in developing countries' ethical concerns are when they review research protocols. According to Lidz and colleagues, "in the 1970s, Gray and Cooke examined the performance of a single IRB by reviewing its meeting minutes" (Lidz et al., 2012, p. 970). It is also reported that "more recently, there have been several ethnographic descriptions of one or two REC/IRB panels. One of the most important questions that remains unanswered is the degree to which IRB deliberations address the primary elements of human subjects protection regulations" (Lidz et al., 2012, p. 970).

Additionally, Milford and colleagues report that developing countries frequently cite the lack of capacity of research ethics committees to review research protocols" (Milford et al., 2006). It is said that "RECs, which are required to interpret international ethics guidelines in specific socio-economic and cultural conditions, often operate in complex environments characterised by power inequalities among government, funders, researchers, and/or communities" (Milford et al., 2006, p. 1). In addition, ethical review can be influenced by factors such as interests of government and other institutions, money, prestige, customs, or ignorance which can compromise the independence of RECs, especially where it is difficult to challenge authority and debate complex issues (Milford et al., 2006). It is also said "that developing country RECs may lack transparency, and conflicts of interest may be present (Milford et al., 2006, p. 1).

Considering the numerous issues raised by the different studies mentioned above, it has become very difficult to know exactly what RECs in developing countries are concerned with when they review international collaborative research protocols.

A study by Silaigwana and Wassenaar reported that "the growth in volume and complexity of biomedical research involving human participants underscores the need to enhance ethics oversight and review capacity of RECs in Africa and other developing countries to maximise protection of human participants" (Silaigwana & Wassenaar, 2014, p. 170). These authors also reflected on the concerns expressed by various ethics experts and scholars about the growth of biomedical research activities. They note that this growth "has not been complemented by a corresponding research ethics capacity enhancement in developing countries" (Silaigwana & Wassenaar, 2014, p. 170). In addition, "studies evaluating RECs in Africa are scarce, although such information is important for guiding ethical review capacity-enhancement programs in this setting" (Silaigwana & Wassenaar, 2014, p. 170).

On the other hand, a paper published by Ndebele and colleagues reports that there has been a substantial increase in investment in research ethics capacity development globally (Ndebele, Wassenaar, Benatar et al., 2014). These researchers "collected data from grants awards' documents and annual reports supplemented with questionnaires completed by the training programme directors" (Ndebele, Wassenaar, Benatar et al., 2014, p. 24). These programmes "provided long-term training in research ethics to 275 African professionals, strengthened research ethics committees in 19 countries in Sub-Saharan Africa, and created research ethics curricula at many institutions and bioethics centres within Africa" (Ndebele, Wassenaar, Benatar et al., 2014, p. 24). Ndebele and colleagues reported that when these trainees returned to their home countries, they were able to lead new national systems and

policies on research ethics, as well as establish improved methods of monitoring compliance with research ethics guidelines (Ndebele, Wassenaar, Benatar et al., 2014). In response to the challenges that arose, the training programs adapted in various ways. These challenges included trainees' varied "background knowledge in ethics, duration of time available for training, spoken and written English language skills, administrative obstacles, and the need to sustain post-training research ethics activities" (Ndebele, Wassenaar, Benatar et al., 2014, pp. 24-25). That notwithstanding, it is still not known whether these supports have really made any positive impact on RECs' functioning in terms of reviewing research protocols, nor what their concerns are.

According to White (1999, p. 87), the "increase in the scope of international collaborative medical research involving human subjects is raising the problem of whether and how to maintain international ethical standards when research is conducted in countries with very different social and ethical values". White, (1999) explains that existing international ethical guidelines for research are said to reflect Western concepts of human rights, focusing on the bioethical principles of respect for persons, beneficence, and justice. However, "in countries and societies where these values are understood differently or are not expressed in local cultures and institutions, it may be impossible or of no practical value to insert them into the research setting" (White, 1999, p. 87). For instance, in most Western countries (like the United States), it is essential to obtain consent from individuals who take part in research (White, 1999.

That notwithstanding, sometimes it becomes difficult to introduce this great value into societies where the decisions taken by individuals are dependent on relatives, household heads and their group leaders (White, 1999). Thus, studies conducted in societies with these kinds of cultural practices pose problems for RECs/IRBs when assessing such protocols. The question concerns the choice of ethical or legal standards according to which such protocols should be reviewed US regulations acknowledge that ethical conflicts may arise in research conducted in foreign countries, in which case foreign procedures for human participants' protection may be substituted for US requirements - but only if the substituted procedures offer protections at least equivalent to those provided by US Policies (White, 1999). However, "beyond this vague provision, the regulations offer no further comment on how to assess risks accurately in foreign countries or how to conduct REC/IRB review of cross-cultural protocols" (White, 1999, p. 87).

Further, it is explained that issues of cross-cultural research are not properly addressed by international codes which are developed based on Western ethical standards (White, 1999). Examples of such codes are the Nuremberg Code, the Declaration of Helsinki, and the guidelines developed jointly by the Council for International Organizations of Medical Sciences with the World Health

Organization (CIOMS guidelines). Each of these codes outlines the principles for the conduct of research, and requires respect for persons, beneficence, and justice (White, 1999). In terms of cross-cultural research, the CIOMS guidelines are said to be "the most comprehensive, giving significant attention to cross-cultural conflicts in research and making a number of recommendations for RECs/IRBs review" (White, 1999, p. 88). Despite the fact that these guidelines provide an initial platform to assist REC review processes, their recommendations are not specific enough to help RECs/IRBS to evaluate cross-cultural research; in addition, there is insufficient enforcement of guidelines is lacking (White, 1999).

Again, literature reports that "collaborative, multinational clinical research, especially between developed and developing countries, has been the subject of controversy" (Participants in the 2001 Conference, 2002, p. 2133). A major focus of this attention the standard of care used in randomised trials" (Participants in the 2001 Conference, 2002. However, less attention has been paid to "the claim that, in order to avoid exploitation, interventions proven safe and effective through research in developing countries should be made 'reasonably available' in those countries" (Participants in the 2001 Conference, 2002, p. 2133). This could be considered more important in terms of its impact on health. In general, the agency sponsoring the research should commit before the research starts to make reasonably available any product developed through such research to the inhabitants of the host community, or country, after the research is completed (Participants in the 2001 Conference, 2002).

Furthermore, "collaborative partnership means that researchers must engage the research population in developing, and evaluating research, and benefiting from the research" (Participants in the 2001 Conference, 2002, p. 2134). Currently, however, there is no shared, international standard of fairness; in part, this is because of conflicting conceptions of international distributive justice (Participants in the 2001 Conference, 2002). Despite the claim, very little is known whether the members of the REC are aware of this claim, and if they are, what ethical issues they raise when reviewing research protocols to ensure that concern is fulfilled so research participants and communities benefit fully from the studies in which they participate in (Participants in the 2001 Conference, 2002).

Two studies reported an increase in the workload of a South African institutional REC over the past decade (Cleaton-Jones, 2012; Cleaton-Jones & Vorster, 2008). Furthermore, Silaigwana and Wassenaar (2015) report a steady annual increase in the workload of another South African biomedical REC over the past seven years Again, "the growth in volume and complexity of international collaborative biomedical research involving human participants underscores the need to enhance ethics oversight and review capacity of RECs in Africa and other developing countries to maximise protection of human participants" (Silaigwana & Wassenaar, 2015, p. 2). It is reported that

"the growth in the volume and complexity of biomedical research has resulted in an increased workload for RECs" (Silaigwana & Wassenaar, 2015, p. 2).

2.5 Assessment of ethical issues that are raised by RECs

A study conducted by Jones and colleagues identified several issues of concern to RECs in the United States. These include study design, informed consent, unacceptable risk, and poor scientific justification (Jones, White, Pool & Dougherty, 1996). Also, informed consent seems to have been the major concern in studies conducted by Agre et al. (2003); Flory and Emanuel (2004); and Speers (2008). Further, related to informed consent were confidentiality and privacy, which were also identified by Dixon-Woods (2008) as a priority area of ethical concern to most. Levine et al. (2004) and Dixon-Woods (2008) also found that vulnerability was identified as an important issue. Vulnerability is identified by Emanuel et al. (2008) under fair participant selection (Principle 4) and emerged among the most frequent issues that received most queries from an index REC (Emanuel et al., 2008).

Bueno et al. (2009) conducted a cross-sectional study to evaluate research projects involving human beings to ascertain reasons for resubmission of research projects to the Research Ethics Committee of a University Hospital in São Paulo, Brazil. The study found that the main reasons for returning the projects to the researchers were the use of inadequate language and/or difficulty of understanding the informed consent form (32.2%), lack of information about the protocol in the informed consent form (25.8%), as well as doubts regarding methodological and statistical issues of the protocol (77.1%). Other reasons for returning the research projects involved lack of, inaccuracy on or incomplete documentation, need for clarification or approval for participation of external entities on the research, and lack of information on financial support (Bueno et al., 2009). Additionally, a study conducted by Dixon-Woods (2008) found that informed consent comprised 96% of queries in letters to applicants that were reviewed, identifying problems with language and exaggeration of study benefits. According to Tsoka-Gwegweni and Wassenaar (2014), other studies also published similar findings, but the order of priority of issues of concern was different.

Further, Angell and colleagues conducted a study to identify issues raised by research ethics committees (RECs) in letters about applications to conduct research involving children. Analysis of 80 provisional and unfavourable opinion decision letters written by RECs in response to applications to conduct research involving child participants revealed that RECs were most likely to be concerned about issues relating to consent; recruitment, care and protection of participants; and scientific design and confidentiality opinions (Angell, Biggs, Gahleitner & Dixon-Woods, 2010). The RECs involved

focused on children's status as 'vulnerable'. They sought to ensure that child participants would be protected, that appropriate written language would be used to communicate with such children and that an appropriate person would give consent for the child to participate. The implications of this are that researchers should be attentive to issues of potential vulnerability when preparing applications concerning children. REC letters may be improved by being given clear and explicit reasons for their opinions (Angell et al., 2010).

Tsoka-Gwegweni and Wassenaar (2014) reported that Cleaton-Jones and colleague conducted a study in 2010 and identified informed consent (55%) and protocol incompleteness (43%) as the most frequent issues among 203 ethics applications to the University of the Witwatersrand REC (Tsoka-Gwegweni & Wassenaar, 2014). In addition, Cleaton-Jones reported that the queries were about typing errors and incompleteness of application forms in 15% of the applications and that the latter issue was not a priority for the REC in their current study. Amdur and Bankert (2011, in Tsoka-Gwegweni & Wassenaar, 2014) also suggest that typos should not be raised in ethics review unless meaning is obscured by them.

Again, Tsoka-Gwegweni and Wassenaar (2014) explain that Abbott and Grady (2011) reported that informed consent issues were the main reason for protocol rejections in the 43 studies in their systematic review. Dixon-Woods (2008) also identified other areas of concern with regard to informed consent including patient care and protection, risks, inconveniences, and discomforts, as well as inadequate details given to participants and risk minimisation, and types and amount of incentives and reimbursements. Tsoka-Gwegweni and Wassenaar (2014) also mentioned that similar issues were identified in a study conducted by Angell and Dixon-Woods (2009), but the authors reported a much higher percentage of queries than reported by Cleaton-Jones (2010).

Further, Tsoka-Gwegweni and Wassenaar (2014) reported that in 2013, Adams and colleagues conducted a study and retrospectively analysed submissions to the Ethics Committee of the Faculty of Tropical Medicine in Thailand. Issues related to the process and outcomes of proposal review, and the main issues for which clarification/revision were requested on studies, were discussed extensively. It is said that 373 proposals were submitted; 44 studies involved minority groups with 21 extra-vulnerable minorities (Tsoka-Gwegweni & Wassenaar, 2014). In that study, the main issues needing clarification/revision differed between all studies and those involving minorities and these included participant information sheet (62.2% vs. 86.4%), informed consent/assent form (51.2% vs. 86.4%), and research methodology (80.7% vs. 84.1%), respectively (Tsoka-Gwegweni & Wassenaar, 2014). It is reported that the main ethical issues arising during the REC's meetings regarding studies involving minorities included ensuring no exploitation, coercion, or pressure on the minority to participate;

methodology not affecting their legal status; considering ethnicity and cultural structure; and providing appropriate compensation (Adams et al., 2013). Though the researches were conducted more than 15 year ago their findings are still applicable today (Tsoka-Gwegweni & Wassenaar, 2014).

Again, in the study conducted by Tsoka-Gwegweni and Wassenaar (2014), confidentiality and privacy (grouped under Principle 8 - respect for participants - of the Emanuel et al. (2008) criteria) received most queries in this category and were also related to storage and export of human tissues (Tsoka-Gwegweni & Wassenaar, 2014). The focus on export of human tissues is in line with the South African Health Act of 2003, which requires that researchers lodge an MTA with the REC and obtain an export permit from the Department of Health for export of human samples (Department of Health, 2004; Tsoka-Gwegweni & Wassenaar, 2014).

This is in contrast to Lidz et al.'s (2012) study, which found that most US IRBs neglected to comment on critical issues required by the US Common Rule, that is, risk minimisation, risk-benefit analysis, subject selection, data monitoring, privacy and confidentiality, and protection of vulnerable populations (OHRP, 2009; Tsoka-Gwegweni & Wassenaar, 2014). With the exception of data monitoring, all these other criteria emerged strongly in the studies conducted by Levine et al. (2004) and Dixon-Woods (2008), suggesting that this REC demonstrated attention to protection of research participants as required by the US Code of Federal Regulation 45 No. 46 (OHRP, 2009). The same criteria are in line with the former South African national guidelines for ethical review of research involving humans (Department of Health, 2004) and other international guides such as the Belmont Report (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1978). The index REC, though bound by structured national guidance and regulations, yielded decisions that could easily be accommodated by the Emanuel et al. (2008) framework for ethical review of biomedical research in developing countries (Tsoka-Gwegweni & Wassenaar, 2014).

2.6 Description of Tsoka-Gwegweni and Wassenaar (2014)

In 2014, Tsoka-Gwegweni and Wassenaar conducted a study using the Emanuel et al. framework to assess, code, and rank the most frequent ethical issues considered by a biomedical REC during review of research protocols for the years 2008 to 2012 in South Africa. A total of 98 protocols were selected through systematic random sampling from the years 2008 to 2012 for assessment. Thirty-five of the protocols were selected from submissions to the biomedical REC in 2009, 20 in 2008, 15 each in 2010 and 2011, and 13 in 2012 (Tsoka-Gwegweni & Wassenaar, 2014). The average number of protocols considered at each meeting was 6.5, ranging from one to 13. Out of the 98 protocols assessed, 47 proposed research on adult participants, 16 on children only, 18 on both adult and child participants,

nine had unknown participants as these were not recorded in the minutes, and the remaining protocols were listed as not applicable because they used records or stored biological samples as the source of data. The majority of the selected protocols used mainly clinical trial (31) or cross-sectional research (30), followed by cohort and quasi-experimental (or laboratory) study designs (Tsoka-Gwegweni & Wassenaar, 2014). A small number of the protocols planned to use descriptive (including qualitative research) and case-control study designs. There were 88 protocols that sought to collect primary data and ten to use secondary sources of data. The majority of the protocols intended to study HIV, tuberculosis (TB), or both (Tsoka-Gwegweni & Wassenaar, 2014)

At the end of data collection, the queries of the reviewers were coded and counted in the minutes of all 98 protocols; it was found that 99.7% of the total 1,043 queries raised could be accommodated or coded by using the eight Emanuel et al. (2008) principles (Tsoka-Gwegweni & Wassenaar, 2014). The most frequent issues that emerged from the study were informed consent or Principle 7 (appropriate disclosure documents and processes, and presentation and accuracy of information), scientific validity or Principle 3 (study design feasibility and appropriate design and methods), followed by fair participants selection or Principle 4 (suitable study population), and ongoing respect for participants or Principle 8 (Tsoka-Gwegweni & Wassenaar, 2014). The study represents the first known attempt to analyse REC responses/minutes using the Emanuel et al. framework, and it suggests that the framework may be useful in describing and categorising the core activities of an REC (Tsoka-Gwegweni & Wassenaar, 2014, p.3).

2.7 Problem statement

Research reveals that over the last 60 years, there has been a great deal of guidance on the ethical conduct of research with humans (Emanuel, Wendler & Grady, 2000). Given this multiplicity of reference frameworks, little data exists on the issues that RECs raise and query when they review health research protocols. This study attempted this exercise on a Ghanaian REC to supplement the data from a study on one South African REC reported by Tsoka-Gwegweni and Wassenaar (2014) and currently being replicated as a group project in several African countries.

2.8 The Emanuel et al. (2004) framework

Like Tsoka-Gwegweni and Wassenaar (2014), the researcher used the Emanuel framework as a theoretical and conceptual framework to code the minutes of the REC in question. As mentioned above, due to the confusing multiplicity of international ethical codes, Emanuel et al., (2004; 2008) analysed major international guidance documents and developed a synthesised framework consisting of eight principles and benchmarks to guide ethics review of biomedical research to assist research

ethics committees (RECs) and researchers with the review process (Emanuel et al., 2000; 2004; 2008). An earlier version of the framework (Emanuel et al., 2000) had seven principles and did not include the new first principle of collaborative partnership (Emanuel et al., 2000). According to the framework, RECs are required to assess each research protocol ensuring that the proposed research has: (i) collaborative partnership, (ii) social value, (iii) scientific validity, (iv) fair participation selection, (v) favourable risk benefit ratio, (vi) undergoes independent ethics review, (vii) informed consent, and (viii) will demonstrate ongoing respect for participants (Emanuel et al., 2008; Tsoka-Gwegweni & Wassenaar, 2014). Each of these is summarised in Table 1 below.

2.8.1 Description of framework

Table 1: Description of Emanuel et al. (2004) framework

Item	Principle	Benchmarks
1.	*Collaborative partnership*	Requires that relevant community representatives in the research setting form part of the research in all stages of the research to share responsibility, benefits, and ensure that local context is respected (Emanuel et al., 2004; Tsoka-Gwegweni & Wassenaar, 2014).
2.	*Social value*	Requires that the research is beneficial to the participants, community, society, and research community or health system without any wastage of resources (Emanuel et al., 2004; Tsoka-Gwegweni & Wassenaar, 2014).
3.	*Scientific validity*	Requires that the proposed research uses reliable and valid research designs and methods of obtaining data, and is relevant to the objectives; the findings obtained must be relevant to the health problems being studied; and study design should not affect provision of health care services and should be feasible within the local context of the research setting (Emanuel et al., 2004; Tsoka-Gwegweni & Wassenaar, 2014).
4.	*Fair participant selection*	Requires that the selection of the study population is relevant to the research objectives; risk minimisation and maximising participant benefits and protection of vulnerable groups (Emanuel et al., 2004; Tsoka-Gwegweni & Wassenaar, 2014).
5.	*A favourable risk-benefit ratio*	Requires identification and minimisation of all forms of potential risks to participants in terms of type, magnitude, and probability; identification, and quantification of all types of possible benefits; and balancing the potential risks and benefits to the participants (Emanuel et al., 2004; Tsoka-Gwegweni & Wassenaar, 2014).
6.	*Independent ethics review*	This applies to the REC and requires that its standard operating procedures ensure its independence from external interference, and are guided by law and documented ethics guidance; REC members must be appropriately qualified and declare conflict of interest; have a transparent review process with justified decisions; and ensure a fair handling of decisions from multiple reviews (Emanuel et al., 2004; Tsoka-Gwegweni & Wassenaar, 2014).

7.	*Informed consent*	Requires that recruitment procedures and incentives are appropriate to the local context; disclosure documents and procedures are tailored to respect participants' local context. Informed consent also requires disclosure of complete, accurate, and adequate information to participants. Provision for obtaining consent from legally authorised representatives if required; provision for obtaining permissions from relevant gatekeepers; consent within the local context and clearly indicating participants' right to participate, refuse, or withdraw From research (Emanuel et al., 2004; Tsoka-Gwegweni & Wassenaar, 2014).
8.	*Ongoing respect for participants*	This can be achieved by monitoring the health status of participants and minimising risks, maintaining confidentiality, allowing participants to withdraw without loss of access to their entitled health care services, having plans for dissemination of research findings and post-research obligations (Emanuel et al., 2004; Tsoka-Gwegweni & Wassenaar, 2014).

The framework provides a comprehensive and systematic way of guiding the ethical conduct of clinical research and thereby minimising the possibility of exploitation. Again, the principles are general and identify considerations necessary to justify research as ethical. They are conceptually included in most of the previously mentioned guidance, although existing guidelines do not necessarily include all of them. In addition, they are presented sequentially, going from the development of research proposal to the conduct of research to monitoring during research (Emanuel et al., 2011).

According to Tsoka-Gwegweni & Wassenaar, the Emanuel et al. framework was also designed as a universal tool for use in many settings including developing countries. However, it is not known whether the work of African health research ethics committees (RECs) is compatible with this framework (Tsoka-Gwegweni & Wassenaar, 2014). In addition, the absence of any normative or empirical weighting of the Emanuel et al. (2008) principles suggests that different RECs may raise some ethical issues more frequently than others when reviewing protocols. It is also not immediately clear whether the frequency of issues raised corresponds with the importance attached to ethical issues (Tsoka-Gwegweni & Wassenaar, 2014).

Each principle in the Emanuel et al. framework is specified by benchmarks that offer a specific elaboration and understanding of each principle. The benchmarks are practical interpretations of what is required to fulfil each principle (Tsoka-Gwegweni & Wassenaar, 2014). They thus provide "a set of measures that can serve as a reminder and common reference for all those planning, conducting, and

evaluating research" (Emanuel et al., 2004, p. 936). Emanuel et al. (2004, p. 936) explain that "agreement on the benchmarks would mean that consensus on the broad principles could be extended to ever more specific and more substantive aspects of the ethical framework such that it narrows the disagreement that Macklin justifiably laments". However, it is worth noting that some degree of disagreement is inevitable in that multiple ethical principles and benchmarks must be considered simultaneously (Emanuel et al., 2004). That notwithstanding, application of the basic principles and benchmarks can help reduce any potential disagreements that may seem ethically worrisome. But then again, overlooking application of the basic principles or rejecting the benchmarks during design of a research protocol and conduct a research study could raise ethical concerns. (Emanuel et al., 2004).

As suggested above, researchers and RECs may accept the principles and benchmarks, but disagree on how to balance them in a particular case. This epitomises how challenging and complex it is to make ethical judgements when there are multiple considerations (Emanuel et al., 2004). Hitherto, what researchers should note is that "disagreement on balancing of the various benchmarks does not necessarily make one assessment ethical and the other unethical; rather it promotes diversity of opinions which are legitimate ways of resolving conflicting ethical issues" (Emanuel et al., 2004, p. 396). On the whole, it is intended that the framework can help reduce disagreements and explain the different opinions as they emerge. What is important is that research must be ethically conducted and that researchers and RECS must consider carefully the ethical aspects of any case (Emanuel et al., 2004).

Finally, the framework and the benchmarks might help RECs in developing countries live up to their primary responsibility, and also assist them in assessing ethical issues in a research protocol, to ensure that research participants and communities get the full benefit of international collaborative studies conducted on the African continent, irrespective of who is conducting the study or who the sponsors of the studies are. There is no existing data to show exactly what the ethical concerns of the RECs under study are during review process.

2.8.2 How the framework has been applied in this study

The researcher used the framework to code the minutes of the index REC following the work done by Tsoka-Gwegweni and Wassenaar (2014). In this study, 153 protocols were assessed from recorded minutes of an institutional index REC in Ghana. The data obtained was captured using Microsoft Excel and analysed. The counts of issues per proposal were considered as scores and conventionally analysed. All identifiers linking the index REC and its gatekeeper to the study were removed during data processing and analysis. The analysed data from the minutes was coded, and a frequency graph was produced to show patterns of concerns that the index REC raised when they reviewed the

protocols. The coding was done according to the variables of the Emanuel et al. framework (principles and benchmarks).

CHAPTER 3: METHODOLOGY

This chapter provides an overview of the nature of the research, the research design, procedures, data processing, management and analysis for the conduct of the study.

3.1 Study aims

The purpose of the study was to consider the functioning of the index REC by identifying the ethical issues that were frequently raised during protocol review, and to assess their relative weight using Emanuel et al.'s (2004; 2008) recommended principles, and examine whether the principles of the Emanuel framework were applied by the index REC in the context of Africa during protocol review. Thus, the aim of this research was to study and describe the ethical concerns of the index REC using Emanuel et al.'s (2004; 2008) eight principles and benchmarks for ethical research. These principles are (i) collaborative partnership, (ii) social value; (iii) fair selection of study population; (iv) scientific validity; (v) independent review; (vi) favourable risk benefit ratio; (vii) informed consent; and (viii) on going respect for study participant and study committee. The research aimed to reveal ethical concerns raised by the index REC during protocol review and to provide insight about the applicability of the framework (principles and benchmarks) to an African REC, as the framework claims to.

3.2 Main objectives

The main objectives of the study were to:

- Study and code review meeting minutes for 2011-2013 of the index institutional REC in Ghana to identify and describe the pattern of ethical concerns and issues raised by members of the REC in their review of research protocols.

  Analyse the ethical issues and concerns raised by the index REC during protocol review (2012 -2013), ranking them and identifying whether they do or do not fit into the framework.
- Compare the results from the present study with those of Tsoka-Gwegweni and Wassenaar (2014).

3.3 The research questions

The study answered the following questions:

- What concerns does the index REC raise when reviewing protocols?

- Is there a systematic prioritisation of some ethical issues over others?
- Is there any observable pattern to the ethical concerns raised by the committee? If so, what is the pattern?
- Does any feature of the framework dominate the concerns? If so, which one?
- Are there other concerns raised by the REC which are not consistent with the framework discussed by Emanuel et al. (2004)?

3.4 Background to the research

This research was part of an international collaboration involving the 2013-2015 Masters students of the South African Research Ethics Training Initiative (SARETI) at the University of KwaZulu-Natal. These countries with partners include Ghana, Nigeria, Malawi, and Zimbabwe. This thesis covers the findings on one institutional REC in Ghana. The aim of the study was to analyse the minutes of the REC to determine the distribution of ethical issues that the Committee raised, with application of Emanuel framework, and also compare results with those of Tsoka-Gwegweni and Wassenaar (2014). This study was based on content analysis of archived written documents – the minutes for a period of two years (2012-2013) of the index REC's meetings. For this study to be able to contribute to the international group project, a standard methodology and analytic framework were adopted across all the countries, and thus minutes from all four countries covered roughly the same time period.

3.5 Research design

This was a qualitative study in which content analysis of existing data (REC's review meeting minutes) was conducted to ascertain the concerns raised by the index REC.

3.6 Selection of the study site/study sample

There are fourteen (14) institutional RECs in Ghana, but since in a research study one cannot use the entire population, a proportion from the population was selected for this research. Terre Blanche et al. (2006) indicate that sample is influenced by the unit of analysis. The unit of analysis in this research was the protocol review process within the health sector of Ghana. The sample in this case was one particular institutional REC in Ghana. The research used purposive sampling because it made the data representative of the area under study. In addition, the institution that established that particular REC is the largest health service provider in Ghana, and the majority of research activities conducted in Ghana are usually carried out in the index REC's institutional facilities or engage the services of health sector workers for research activities. This particular index REC was established with the mandate to review and approve protocols of all research undertaken within the facilities of its mother institution or in collaboration with the mother institution. Although the index REC was established to

review and approve proposed studies that are conducted within its affiliated institutional facilities, it also reviews studies outside the REC's institutional jurisdiction.

A brief note on the institutional REC whose meeting minutes were used for this study would be helpful here. The REC's mother institutional policy requires all national and international prospective researchers who want to use its facilities and staff for research activities to submit their proposed research protocols to the REC, to register and to seek ethics approval prior to the initiation of their research. The index REC was selected based on the easy availability of the minutes and the volume of their work output. Again, the REC's institutional affiliation is the only organisation that has parliamentary backing to provide accessible health care for the people of Ghana; hence the majority of the health-related research activities are carried out within its jurisdiction and this has increased the REC's volume of work.

This study was conducted in Ghana in an institution where I work as the administrator for the index REC whose minutes were used for the study. The data was purposively collected from this particular institutional REC's. I want to emphasise that although I was and I am still the administrator for the index REC, this did not influence the data collection in any way. Because of a potential conflict of interest (COI), the investigator hired and trained research assistants to collect the needed information from the minutes and to code the data as well.

The inclusion criteria specified only minutes recorded on all newly submitted (without any consideration of the type of study) clinical trials, biomedical studies, epidemiological studies, social science research, behavioural research, implementation research, operational research or studies. Only recorded minutes for the years under review (2012 and 2013) were assessed. The REC meets six times in a year, thus 12 sets of recorded minutes were considered and assessed. The REC reviewed one hundred and fifty-three (153) protocols during the period under review. In accordance with procedures described by Tsoka-Gwegweni and Wassenaar (2014), this study included only new protocols considered for full review meetings, and excluded expedited (minimal risk) protocols that were reviewed by the entire committee members.

Again, all expedited reviews, continuing reviews, amendments, annual reports, and final study reports were not considered for this research. The researcher's index REC is located within the country where this research was conducted. The researcher sought permission from the gatekeepers of the institution that manages the index REC before gaining access to the REC's minutes.

Ethical approval was also obtained from the UKZN Social Sciences and Humanities REC, approval number BCA342/16(HSS/1450/014CA). Ghanaian ethics approvals and gatekeeper permission were also applied for and received before UKZN granted final ethics approval. Also, ethics approval was

obtained from the local ethics committee. These permissions are on record and are not included in the appendices to retain confidentiality of the REC in question.

3.7 Research procedure

In this present research the information required was collected in two stages. First, after receiving the necessary clearances and permissions, the researcher trained research assistants to access the two-year (2012-2013) meeting minutes of the index REC in question on her behalf, due to conflict of interest. Second, the research assistants coded the minutes using the variables in the framework of Emanuel et al. as a tool to ascertain information on what the index REC flagged when they reviewed the research protocols. Thus, the primary *a priori* codes were the principles in the Emanuel et al. framework namely: (i) 'community participation/engagement'; (ii) 'social value'; (iii) 'scientific validity'; (iv) 'fair selection of study participants'; (v) 'favourable risk-benefit ratio'; (vi) 'independent ethics review'; (vii) 'adequate informed consent'; and (viii) 'on-going respect for recruited participants and study communities' (Emanuel et al., 2004; 2008) used in the research conducted by Tsoka-Gwegweni and Wassenaar (2014).

Data was collected through the review of meetings minutes for a period of two years (2012 & 2013) of the index REC. A standard data capture sheet (Appendix 1) was developed on which simple frequency counts for each type of ethical issues raised were coded. This was designed in accordance with the principles of the framework to categorise the needed information required from REC's meeting minutes (Emanuel et al., 2004; 2008).

The minutes were coded according to the eight principles and benchmarks (framework) to record the observable patterns in ethical concerns raised during the REC's review of the research protocols. 'Other' categories of review comment in relation to the research protocols considered by the REC during the year under review, but not covered in the principles of the Emanuel et al. framework, were also captured. Again, comments raised per each minute were recorded. The frequencies of occurrence per category or principle per minutes were recorded. A count of issues raised in relation to each protocol mentioned in the REC minutes was also recorded.

3.8 Data processing and analysis

The data obtained was captured using Microsoft Excel and analysed. The counts of issues per proposal were considered as scores and conventionally analysed. All identifiers linking the index REC and its gatekeeper were removed during data processing and analysis. The analysed data from the minutes was coded, and a frequency graph was produced to show patterns of issues of concern that

the index REC based on variables outlined in the Emanuel et al. framework (principles and benchmarks).

3.9 Other ethical issues that could not be accommodated by the framework

The study also identified other issues that were not accommodated by the Emanuel et al. (2004) framework and codes were developed for these.

3.10 Validity, reliability, and rigour

According to Hammersley (1990, p. 57), "validity in research is defined as truth; interpreted as the extent to which an account accurately represents the social phenomena to which it refers". Furthermore, Cook and Campbell (1979) developed a taxonomy of threats to research validity, namely: statistical conclusion validity, construct validity; external validity; and internal validity. Internal validity refers to whether the inferences made from the collected data are accurate (i.e. valid) and external validity to the ability to generalise from the results of the study to other environments and populations. For both practical and logistical reasons, it was possible for the researcher to incorporate all of the above strategies into this study; however, the strategies of peer review of methods (with fellow researchers doing the same topic), as well as clarifying researcher bias were considered in the design of this study and throughout its conduct. Furthermore, the researcher identified the specific problem of 'anecdotalism' – the inclination of some researchers to convince both themselves and their readers that the findings of their study are genuine results, based on a critical unbiased analysis of the data collected and not based on a few 'well-chosen examples' – as a potential threat to the overall validity of the study.

Again, other threats to both the internal and external validity of the present study were identified by the researcher during the design process. The researcher acknowledges Cook and Campbell's (1979) taxonomy of threats to validity and recognises that: a) because the research is a desk review, carried out on specific documents kept for specific purposes with a specific group of people working in a specific environments, it is possible that the study will not return results that are high in external validity (i.e., that it is not possible to generalise the results to other populations and/or to other environments) and b) that because the sample population was primarily selected using purposive methods, the element of randomness is not present in the selection process. This may, therefore, impact upon the internal validity of the study's results (Cook & Campbell, 1979). At the same time, the sample represents the workload of the index REC for the two-year period (2012 & 2013) respectively.

3.11 Criteria for classifying the dominant ethical issue

The counts of issues per proposal were considered as scores and conventionally analysed. The researcher was mindful that all eight items of the Emanuel et al. framework are weighted as equally important. That notwithstanding, ONE issue in each protocol was flagged as the most important issue based on the observable pattern with reference to the description of the Emanuel et al. framework (principles and benchmarks).

3.12 Ethical issues related to this research

All identifiers linking the index REC and its gatekeeper were removed during data analyses.

3.12.1 Consent and confidentiality

Individual consent was not applicable to this research because the research was done using secondary (existing) data. However, permission was obtained from the head (the gatekeeper) of the mother institution of the index REC, whose meeting minutes were used for the research**.** (Letters are available on request – withheld from this thesis for confidentiality reasons). Again**,** full ethics clearance was obtained from a Ghanaian REC and the UKZN HSSREC for the conduct of the study (see Appendices).

To ensure confidentiality of the minutes, the research was done at the index REC's mother institution and in a private workspace. Further, an agreement was signed between the student researcher and her supervisor, and the REC's gatekeeper to ensure confidentiality of the data. All identifiers linking to the REC's name, the names of REC members, and the REC's mother institution, as well as the study title were anonymised during data collection and data analysis. Data collected has been kept under lock and key and only the student researcher has access to the information thereof. Data from this research will be kept under lock and key for five years after which it shall be destroyed by the researcher.

3.13 Usage of data and conflict of interest

A potential conflict of interest lies in the fact that the investigator was the administrator of the index REC during the period of the minutes review. To avoid this conflict, an agreement was signed between the student research and her supervisor, and between the student researcher and the gatekeeper of the REC's mother institution, ensuring that information gathered from the minutes was used solely for my academic work. A copy of the signed agreement is attached to this report as Appendix 3. As the REC's administrator, the researcher was not a reviewer for the REC and had no role in conducting the reviews which formed the raw data of the present study.

3.14 Problems encountered

The only major problem encountered was the initial reluctance of the REC's gatekeeper to allow the use of their meeting minutes since these are considered confidential and private, and the fear that the REC's reputation could have been tarnished through publication of the results. This was resolved after discussion and a confidentiality agreement was signed between the researcher and her academic supervisor, and the REC's gatekeeper, ensuring that all identifiers linking the REC to the study would be anonymised.

Another problem was potentially incomplete or inaccurate minutes; for example, some of the issues identified, debated and/or resolved might not have been fully reflected in the minutes. According to Atkinson and Coffey (2004, in Bryman, 2008, p. 561), documents such as minutes may "have a distinctive ontological status, in that they form a separate reality which they refer to as 'documentary reality' and should not be taken to be 'transparent representations' of an underlying organisational or social reality". Thus, Atkinson and Coffey (2004) argued even 'official' records may not be firm evidence of what is contained in them. In addition, according to Bryman (2008), well-known people may "have one eye firmly fixed on the degree to which they really reveal themselves in their writings, or alternatively ensure that they convey a 'front' that they want to project" (Bryman, 2008, p. 548).

Thirdly, there was possible conflict of interest due to the fact that the investigator served as administrator of the index REC during the period under review. It is possible that the researcher might have wanted to present the REC in a favourable light, but, as has been mentioned, no norms exist indicating the benchmarks of optimal ethics review. Lastly, the study collected large volumes of data which necessitated recruitment of research assistants for data collection. In addition, it became necessary to engage second and third coders, in order to verify the coding. All disagreements in coding were resolved through discussion.

CHAPTER 4: RESULTS

This chapter describes the findings of the research, the type of protocols reviewed, the number and percentage of ethics queries raised by the index REC, and findings on the ability of the Emanuel framework to contain the issues raised. These data are presented in tables and graphs below.

4.1 Description of the data

A total of 153 protocols were considered in this study (see Table 2). All newly submitted protocols that underwent full committee review in 2012 and 2013 were purposively included. In 2012, 79 protocols were reviewed, while 74 were reviewed in 2013. Two data collectors were trained on the benchmarks proposed by Emanuel et al. (2004; 2008). They read and categorised the queries of reviewers according to the framework. Disagreements (11.2% of cases) were reconciled by discussion and reference to the Emanuel et al. benchmarks, and data finalised.

The protocols considered in the minutes reflected various research designs. A small majority (52.9%) of the protocols employed cross-sectional study design, 14.4% were clinical trials, 9.8% were biomedical/epidemiological, and fewer than 8% involved cohort studies. Explanatory studies, case studies, quasi-experimental studies, observational studies, situational analysis and case-control studies recorded between 1% and 4%. A single ethnographic study was reviewed (see Table 2).

Nearly two-thirds (64.7%) of the protocols involved adults as study participants, 18.3% covered children, while 17.0% covered all or mixed age categories. Most protocols (92.2%) sought to collect primary data, 4.6% sought to analyse secondary data and 3.3% involved both data sources (see Table 2). The protocols and their associated health issues appear to reflect many of the primary health concerns of Ghana’s epidemiology.

Table 2: Summary of protocols reviewed 2012-2013

Year under review	**Number of protocols reviewed (*N*-153)**	**Percentage**
2012	79	51.6
2013	74	48.4
Study design		
Cross-sectional	81	52.9
Clinical trial	25	14.4
Biomedical/epidemiological	15	9.8
Cohort	11	7.2
Exploratory	6	3.9
Case study	4	2.6
Quasi-experimental	3	2.0
Observational	3	2.0
Situational analysis	2	1.3
Case control	2	1.3
Ethnography	1	0.7
Study participants		
Adults	99	64.7
Children	28	18.3
All	26	17.0
Data source		
Primary	141	92.2
Secondary	7	4.6
Both	5	3.3
Research areas		
Maternal/child health	33	21.6
Health policy/primary health care issues	20	13.1
Malaria	18	11.8
Sexual and reproductive health	18	11.8
STDs	15	9.8
Communicable diseases	13	8.5
Environmental sanitation/human waste management	6	3.9
Lymphatic Filariasis	4	2.6
Mental health	4	2.6
Eye care	3	2.1
Mobile technology	2	1.3
Blood donation/lancet procedures/intravenous injections and infusions	2	1.3
Substance/prescription drug abuse	2	1.3
Clinical research with vulnerable groups	1	0.7
Depression	1	0.7
Tobacco control	1	0.7
Supply chain management	1	0.7

4.2 Ethical issues of concern that were raised by the index REC

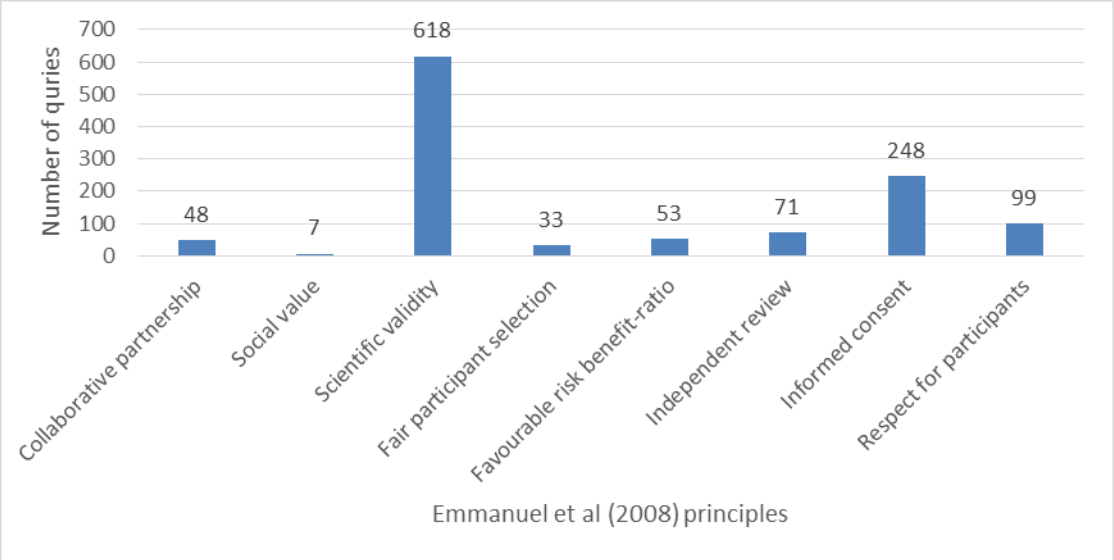
Compatibility of comments by the REC with the Emanuel et al. framework was computed to be 97.7%; thus 2.3% of the comments or queries could not be placed under any of the Emanuel et al. (2004; 2008) principles and benchmarks. Full details are presented in Table 3 below. Note that the main analysis in the present study is based on the shaded rows of Table 3.

Table 3: Ethics queries raised by the Index REC (2012-2013)

Emanuel et al. (2008) principles and benchmarks	**Number of queries (*N*=1,205)**	**Percentage (%) of queries**
Principle 1: Collaborative partnership	**48 queries**	**4.0**
Community representatives	12	25.0
Responsible sharing	36	75.0
Principle 2: Social value	**7 queries**	**0.6**
Research beneficiaries	3	42.9
Impact on health systems	4	57.1
Principle 3: Scientific validity	**618 queries**	**51.3**
Appropriate design and methods	571	92.4
Applicability of results	2	0.3
Impact on provision of health care services	2	0.3
Study design feasibility	43	7.0
Principle 4: Fair selection	**33 queries**	**2.7**
Suitable study population	28	84.8
Risk minimisation	1	3.0
Benefits to participants	1	3.0
Vulnerability	3	9.1
Principle 5: Favourable risk-benefit ratio	**53 queries**	**4.4**
Risk identification and minimisation	53	100.0
Principle 6: Independent review	**71 queries**	**5.9**
Regulatory compliance	41	57.7
Minimisation and reconciliation of multiple reviews	30	42.3
Principle 7: Informed consent	**248 queries**	**20.6**
Recruitment and incentives applicability to local context	18	7.3
Appropriate disclosure documents and processes	133	53.6
Presentation and accuracy of information	64	25.8
Legally authorised representatives	1	0.4
Gatekeeper's permission	21	8.5
Context of consent process	11	4.4
Principle 8: Respect for participants	**99 queries**	**8.2**
Monitoring health and well-being	3	3.0
Confidentiality and privacy	54	54.5
Voluntariness	42	42.0
Other ethical issues not accommodated by the framework	**28 queries**	**2.3**

The distribution of ethical issues (as percentages) from Table 3 is depicted in Figure 1 below. This is followed by a description of the results according to each principle.

Figure 1: Ethical queries raised by a Ghanaian REC 2012-2013 (*N* =1,205)



4.2.1 Principle 1: Collaborative partnership

Out of a total of 153 protocols sampled and a total of 1,205 queries raised, 48 (4%) queries concerning issues of collaborative partnership were raised. Of these, 75% (36/48) of queries related to responsible sharing, and 25% (12/48) concerned community representations. Respect for local context, fair research benefits, and sharing research products had no queries raised.

4.2.2 Principle 2: Social value

Of the 153 protocols, just 7 (0.6%) queries were raised regarding social value, representing the lowest number in all the categories. Under this principle, impact on health systems registered 57.1% (4/7) of the queries while research beneficiaries concerned 42.9% (3/7) of the concerns. Research benefits and enhancing research benefits recorded no concerns.

4.2.3 Principle 3: Scientific validity

Queries of scientific validity were raised in 135 of 153 protocols, representing the highest number of queries raised, with a total of 618 of the 1,205 (51.3%) queries in this category. Under this principle, 92.4% (571/618) of queries were raised under appropriate design and methods, while 7.0% (43/618) came up under study design feasibility. Under applicability of results and impact on provision, the REC raised 0.32% (2/618) of queries on each.

4.2.4 Principle 4: Fair participant selection

A total of 23 protocols out of the 153 sampled had issues of fair participant selection. In all, 33 queries (2.7%) were raised relating to fair participant selection. Of these 33 queries, 84.8% (28/33) were categorised under suitable study population and 9.1% (3/33) were observed under participant vulnerability. Risk minimisation and benefits to participants attracted 3.0% (1/33) of the queries under this principle.

4.2.5 Principle 5: Favourable risk-benefit ratio

Fifty-three (53) of the 153 protocols sampled had queries (4.4%) raised in them relating to the principle of favourable risk-benefit ratio and each protocol had one query each on the principle under consideration. As such, all queries (100%; 53/53) under this principle were coded under risk identification and minimisation. The sub-classifications of type, probability and magnitude of benefits, and comparison of risks and benefits under the principle of favourable risk-benefit ratio attracted no queries.

4.2.6 Principle 6: Independent ethics review

Out of the 153 protocols sampled, 48 raised questions about independent ethics review in accordance with the principles of the Emanuel et al. framework. Of the 71 queries (5.9%) that were raised by the REC, regulatory compliance attracted the most comments within this category at 57.7% (41/71), while minimisation and reconciliation of multiple reviews attracted 42.3% of the queries (30/71). Conflict of interest (regarding REC members) and transparent reviews received no comments under this principle.

4.2.7 Principle 7: Informed consent

A total of 121 of the 153 protocols concerned issues of informed consent. This constituted 20.6% (248/1205) of the total number of queries. Under this principle, issues of appropriate disclosure attracted the most queries at 53.6% (133/248). Issues in relation to presentation and accuracy of information attracted a significant number of queries at 25.8% (64/248). This was followed by issues concerning gatekeepers' permission at 8.5% (21/248), recruitment and incentives at 7.3% (18/248) and context of consent process at 4.4% (11/248). Matters regarding legally authorised representatives received less than 0.5% of queries and issues regarding respect for autonomy attracted no queries.

4.2.8 Principle 8: Respect for participants

Fifty-five protocols attracted 8.2% (99/1205) of queries in relation to respect for participants. Under this principle, 54.5% (54/99) of queries were raised in relation to matters of confidentiality and privacy while 42.4% (42/99) of queries concerned voluntariness. Issues regarding monitoring health

and well-being of participants attracted 3.0% (3/99) of the queries under this principle of the Emanuel et al. framework.

Figure 2: Ethical queries raised by a Ghanaian REC 2012-2013 (*N* =1,205) (percentages)

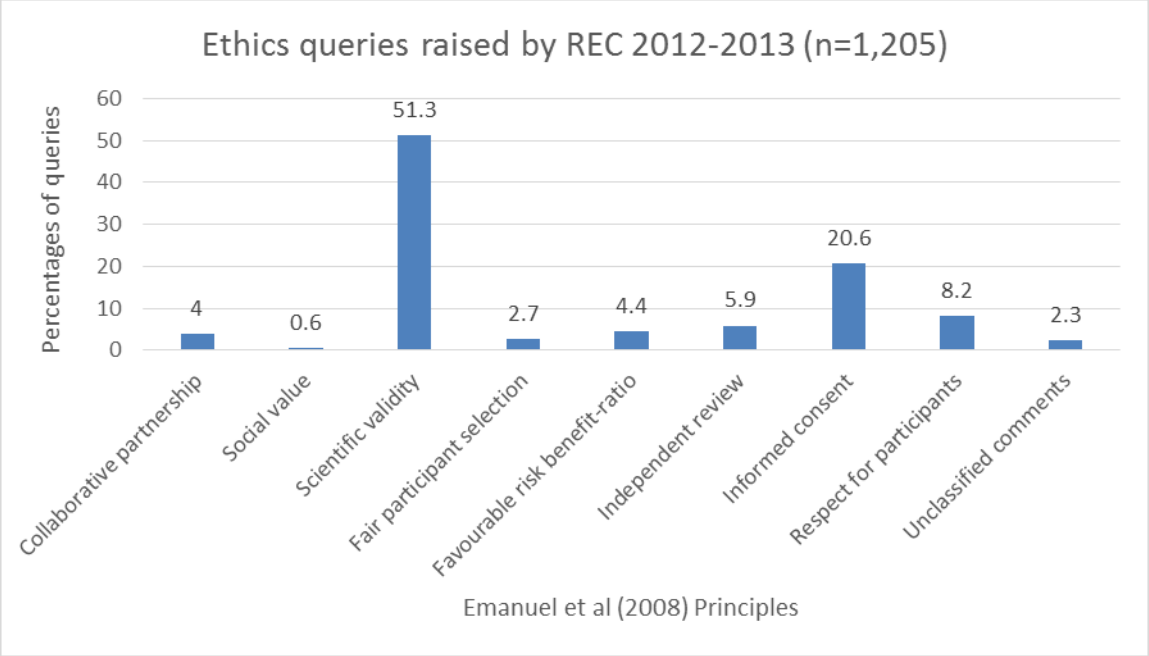


Figure 2 above shows that scientific validity constituted the highest percentage of queries (51.3%), while informed consent followed with 20.6%. Respect for participants, independent review and favourable risk-benefit ratio and made up 8.2%, 5.9% and 4.4% respectively. Collaborative partnership and fair participant selection made up 4% and 2.7% respectively while social value occurred least frequently at 0.6%.

Figure 3: Percentage of ethical queries raised - South African REC 2008-2012 (Tsoka-Gwegweni & Wassenaar, 2014)

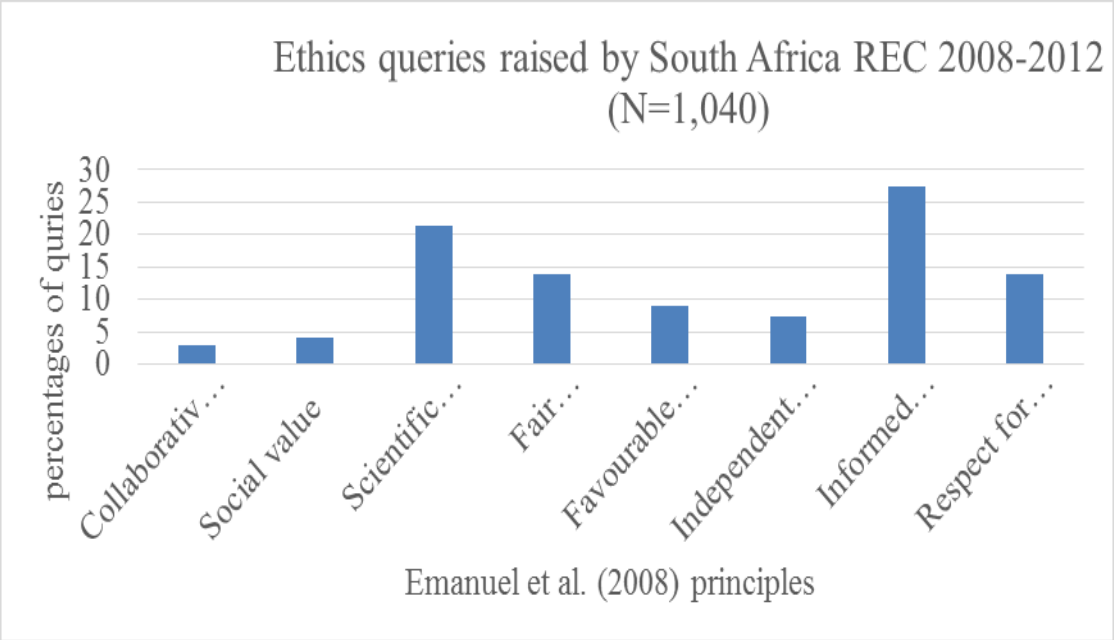


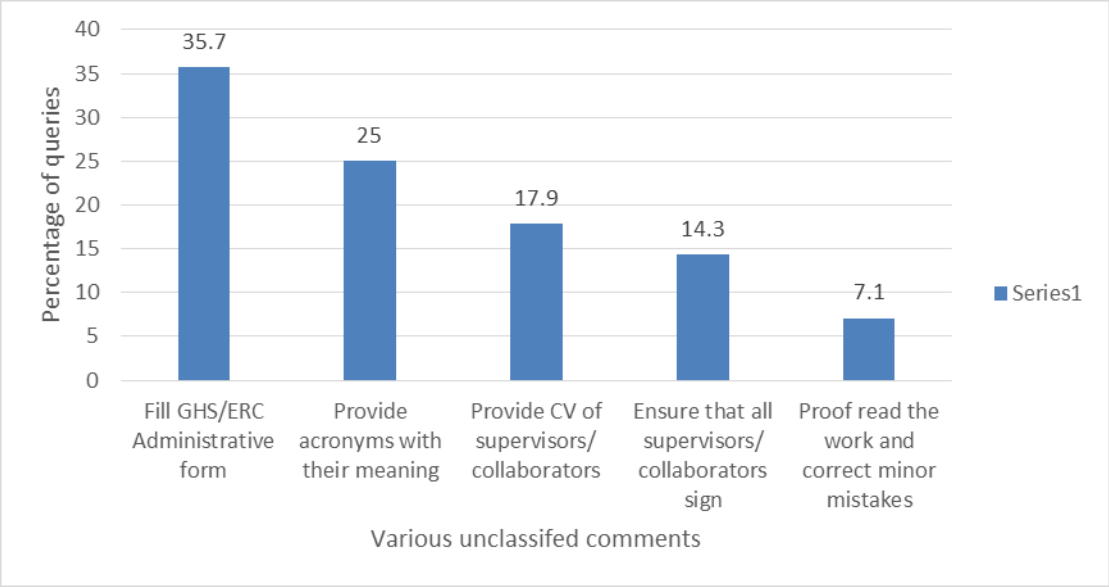
Table 4: Comparing Tsoka-Gwegweni and Wassenaar (2014) paper with the results from this research

	Ghana		South Africa	
The Emanuel et al. (2004) principles and benchmarks	**Number of queries**	**Percentage of queries**	**Number of queries**	**Percentage of queries**
Principle 1: Collaborative partnership	48 queries	4	31 queries	3.0
Principle 2: Social value	7 queries	0.6	43 queries	4.1
Principle 3: Scientific validity	618 queries	51.3	222 queries	21.4
Principle 4: Fair selection	33 queries	2.7	145 queries	13.9
Principle 5: Favourable risk-benefit ratio	53 queries	4.4	94 queries	9.0
Principle 6: Independent review	71 queries	5.9	76 queries	7.3
Principle 7: Informed consent	248 queries	20.6	285 queries	27.4
Principle 8: Respect for participants	99 queries	8.2	144 queries	13.9

4.3 Other ethical issues not accommodated by the Emanuel et al. framework

There were 28 queries (28/1205 = 2.32%) that are not accommodated in the framework of the Emanuel et al. (2004; 2008). The most frequent of these concerned completion of the REC's administrative checklist (35.7%), which is one of the major requirements of protocol submission to the REC. The checklist helps the reviewers to know at a glance what the investigators have captured in the protocol. It also helps the investigators to identify issues that need to be captured in their protocols and address them appropriately before submission. This was followed by requests for explanation of acronyms in the protocols (25%). Provision of CVs of supervisors and for collaborators to make sure that they sign their portion of the protocol made up 17.9% and 14. 3% respectively, while ensuring that PIs proof read their work to correct all mistakes made up 7.1% of the unclassified queries. These are captured in Figure 2 below.

Figure 4: Percentage of queries (*n*=28) not accommodated by Emanuel et al.'s framework



4.4 Summary of main findings

Scientific validity constituted the highest percentage of queries (51.3%), while informed consent followed with 20.6%. Respect for participants, independent review and favourable risk-benefit ratio and made up 8.2%, 5.9% and 4.4% respectively. Collaborative partnership and fair participant selection made up 4% and 2.7% respectively while social value occurred least at 0.6%.

CHAPTER 5: DISCUSSION

This chapter discusses the results, including the application of the framework by the index REC studied and how the principles and benchmarks were rated during data analysis.

5.1 Discussion of results

As discussed earlier, RECs have as their core mandate to provide third party review, minimize conflict of interest, and protect the welfare of research participants through attention to risks, benefit and informed consent and prevent the exploitation of the vulnerable (Kass et al., 2007). This present study hopefully provides useful new information about the review activities of an African REC in terms of whether or not it made decisions in accordance with the Emanuel et al. framework in evaluating research protocols/proposals before it. This may give critical insight the trends of review queries in Africa.

Data from 153 proposals reviewed by a REC in Ghana reveals that 97.7% of the concerns raised by the index REC could be in accordance of the Emanuel framework. It is evident that the REC in Ghana, with or without express reference to the Emanuel et al. (2004; 2008) principles and benchmarks, to a large extent reviews protocols in a way that is compatible with the framework. This in turn suggests the applicability of the framework by the index REC in evaluating investigational protocols.

Studies which examined critical and prominent ethical concerns raised by other RECs tended to highlight informed consent as the most recurrent issue. Angell, Bryman, Ashcroft, and Dixon-Woods (2008), in reviewing RECs' letters to applicants, pointed out that more than 75% of ethical concerns related to informed consent; Lidz et al. (2012) identified similar trends.

The only study to date applying the Emanuel framework, namely Tsoka-Gwegweni and Wassenaar (2014), examined minutes of a biomedical REC's meeting minutes in South Africa. The study revealed that out of 1,040 queries raised in 98 protocols, 27.4% related to informed consent, which was the most frequently occurring of the principles. Tsoka-Gwegweni and Wassenaar (2014) contend that most studies conducted on RECs, including those by Agre et al. (2003), Dixon-Woods (2008), Flory and Emanuel (2004), Marrero-Álvarez et al. (2013), Tamariz, Palacio, Robert, and Marcus (2013), Speers (2008), Taylor and Bramley (2012), and Weil et al. (2010), revealed that informed consent appeared to be the most common concern raised in evaluating research protocols (Tsoka-Gwegweni & Wassenaar, 2014).

In contrast to the above findings, informed consent ranked as the second most frequently raised query in the present study, while scientific validity emerged as the issue that reviewers queried most frequently. This issue ranked second in the Tsoka-Gwegweni and Wassenaar (2014) study at 21.3% of their queries. This finding is nonetheless consistent with Tsoka-Gwegweni and Wassenaar (2014), who found that almost half of all queries raised by the REC that they studied related to scientific validity and informed consent (Tsoka-Gwegweni & Wassenaar, 2014).

It is worth noting that more than 92% of the queries raised under scientific validity had to do with the appropriateness of research designs and methods. Just 7% related to the feasibility of the study designs. Again, figures in the South African REC study show that study design and methods, and study feasibility together recorded more than 77% of the queries under scientific validity (Tsoka-Gwegweni & Wassenaar, 2014). According to Freeman (1987, cited in Tsoka-Gwegweni & Wassenaar, 2014), research involving human beings must be scientifically sound because if a study is scientifically invalid, all other ethical considerations become irrelevant. It is thus justifiable that the REC under study pays particular attention to issues of scientific validity.

As it has been observed, informed consent (Principle 7) is of paramount importance to RECs globally. Perhaps it attracts particular attention given the fact that informed consent could be taken as a given when dealing health care issues (Hall, Prochazka & Fink, 2012). Hall et al. (2012) observed that it is common that some patients prefer information that focuses on realistic expectations for cure ('therapeutic misconception') rather than information that seeks decision-making (Tsoka-Gwegweni & Wassenaar, 2014). Though in this study, informed consent (Principle 7) did not attract the highest number of queries in the protocols, it did register a significant number. Like Tsoka-Gwegweni and Wassenaar (2014), Dixon-Woods (2008) in their study of REC letters revealed that the "ethical issue most frequently raised by RECs (96% of letters) was informed consent" (Dixon-Woods, 2008, pp. 14 -15).

In this study, it was noticed that more than half of the comments on informed consent had to do with appropriate disclosure of documents and processes. Interestingly, a study conducted by Dixon-Woods (2008) reported that "letters issued by RECs, advised applicants to ensure that participants in trials get access to written materials to be used in the study, in a language that they can understand and is devoid of technical terms which what this current study also observed" (Dixon-Woods, 2008, pp. 14 - 15). A quarter of the comments sought revision for presentation and accuracy of information in informed consent documents. Additionally, in this study, it was important to the REC that protocols

showed evidence of permissions from site gatekeepers and 8.5% of consent-related queries referred to the matter.

Respect for participants (Principle 8) also registered notable figures (8.2%), but ranked lower than in the REC studied by Tsoka-Gwegweni and Wassenaar (2014). It was of concern to the REC that protocols demonstrate that research participants' privacy would be respected and protected. Dixon-Woods (2008) considered issues of confidentiality and privacy to be of considerable importance in ethical reviews. Data in this study suggest that reviewers were concerned about issues of respect for research participants 8.2% of the time. Of these, privacy and confidentiality were queried 54.5% of the time and voluntariness had 42% of the queries. Importantly, reviewers deemed it critical that participants should exercise free will, without coercive undertones, in deciding their participation or otherwise in a study. Tsoka-Gwegweni and Wassenaar (2014) found that most queries on this principle in their sample related to storage and export of human tissue.

It is considered an important ethical issue that research practice considers "generating social value locally through the generation of knowledge that can lead to generalised health improvements" (Emanuel et al., 2004, in Larumbi et al., 2008, p. 735). Lairumbi and colleagues maintain that it will be of great interest when studies carried out in a developing country are sponsored by external partners (Lairumbi et al., 2008). This study suggests that reviewers paid some attention to gaps in collaborative partnerships between researchers and sponsors, *vis-à-vis* policy makers, local communities and giving information on research findings to participants of research, and stakeholders for implementation. The index REC that was studied by Tsoka-Gwegweni and Wassenaar (2014) raised 4.0% and 0.6% of the queries under 'collaborative partnership' and 'social value' respectively. These queries sought to address any critical imbalances that may exist between researchers and local collaborators in view of sharing and transferring knowledge. It is not clear whether this should be a more prominent issue – perhaps the issue was well addressed in the protocols, or the reviewers did not look for it. The issues of social value and collaborative partnership were ranked seventh and eighth respectively (4.1% and 3.0%) by Tsoka-Gwegweni and Wassenaar (2014).

Again, Lairumbi and colleagues report that a qualitative study in Kenya revealed that "dissemination of research findings within the two tracers was mainly targeted at policy-makers, with an almost total disregard of other relevant stakeholders who may have been necessary for supporting policy formulation and implementation" (Lairumbi et al., 2008, p. 745). However, "at the same time, policy-makers did not consider disseminating evidence supporting a policy change to implementers and the communities at the grassroots level" (Lairumbi et al., 2008, pp. 745-746). These gaps have the potential to limit the possible social value of research, as well as the generation of knowledge that can

result in generalised health improvements, as well as funding for research (Lairumbi et al., 2008). It was evident in this study that RECs paid some attention to these issues and made sure that research protocols addressed them.

According to Tsoka-Gwegweni and Wassenaar (2014), it is important to encourage researchers to minimise risk in any research involving human participants, since it is a central concern which operates like a filter through which protocols must pass. RECs or IRBs should require researchers to design their research in such a way that it will reduce any potential risks that have the tendency of causing harm to prospective research participants, therefore ensuring their safety. They explain that moreover, in 2001, the death of a healthy research subject that occurred in a study aimed at understanding the pathophysiologic characteristics of asthma, brought attention to the risks of research with healthy volunteers, and that it is imperative to ensure adequate protection for research subjects (Tsoka-Gwegweni & Wassenaar, 2014).

Consistent with Principle 5, risk-benefit ratio, firstly, Miller and Brody (2003) observed that RECs must ensure that risks to the research participant or society must be minimised and benefits maximised. If not, there is the tendency that prospective participants will be exploited when they take part in unethical and unscientific research. It is therefore imperative that researchers ensure that some greater scientific value is achieved if a research study poses burdens, inconvenience, discomfort, and risks of serious harm to prospective participants. In addition, the risk-benefit ratio (Principle 5) is closely linked to the principle of fair selection, Principle 4, since inherent in a comparative assessment of risks and benefits lies the requirement for fair selection (Emanuel et al., 2004; 2008). It is thus not insignificant that the REC under study identified issues under risk-benefit ratio and fair selection as only 4.4% and 2.7% at that time, respectively.

It is observed that although the index REC was not expressly instructed to use (as far as can be determined) the Emanuel et al. (2004; 2008) framework, yet it made decisions that could mostly (97.7%) easily be accommodated by the framework for review of international collaborative research in developing countries.

5.2 Strengths and weaknesses of the Emanuel et al. framework

It would be out of place if the strengths of the framework are not mentioned here. First, the originators of the framework are commended for having provided such thoughtful, empirically derived principles and benchmarks that have been arranged in an order that follows procedures of implementing an

investigational project (Emanuel et al., 2008). In addition, the principles and benchmarks described in the framework provide guidance for reviewing protocols (Tsoka-Gwegweni & Wassenaar, 2014). Further, the framework has been described as a universal tool, comprehensive, and applicable to all research settings and contexts (Tsoka-Gwegweni & Wassenaar, 2014). The framework is also seen as a valuable tool for improving the quality of research protocols because of its structural nature (Tsoka-Gwegweni & Wassenaar, 2014). According to Tsoka-Gwegweni and Wassenaar (2014), "the framework is said to be helpful for review of both ethical and scientific values of a study.

According to Tsoka-Gwegweni and Wassenaar (2014), one of the weaknesses associated with the Emanuel et al. (2008) framework is the lack of a normative weighting of the principles. For example, Emanuel et al. (2008) recognised that, depending on the type of research, conflict could arise between the principles. For instance, there is the possibility that, in an attempt to minimise risks, certain research populations may be excluded from participation in a study. As mentioned by Tsoka-Gwegweni and Wassenaar (2014), this study also found that the Ghanaian REC raised some (2.3 %) issues that could not be coded under the Emanuel et al. framework. These included inadequate completion of the administrative checklist, need for explanation of abbreviations and acronyms, CVs of supervisors, provision for collaborator signatures, and proper proof-reading of proposals.

Additionally, it is a requirement of the index REC that researchers provide information on adequate funding or resources for funding to assure the feasibility of conducting a research study to a successful completion, and avoid abandoning the research half way as a result of not having adequate funding. However, there is an aspect of funding that is not captured under the Emanuel et al. framework. The researcher noticed that during review of protocols, the index REC raised concerns about storage of human biological tissues, and requested Material Transfer Agreements for transporting such biological material from Ghana to elsewhere for analyses. But hitherto, this was not mentioned in the Emanuel et al. (2004; 2008) framework. Tsoka-Gwegweni and Wassenaar (2014, p. 7) report that "Medecins Sans Frontières has amended its ERB framework, which was initially based on the Emanuel et al. (2000) framework, to include other issues such as: MTA, GCP training certificate, data ownership (who owns multinational research data), etc., not captured in the Emanuel framework".

Review of the researcher's index REC's meeting minutes revealed that, in their research protocols, researchers are required to declare all stakeholders involved in their research and to show the responsibilities, roles, and commitments of each part. But Tsoka-Gwegweni and Wassenaar (2014) report that under the Emanuel et al. framework, only REC members are required to declare conflicts of interest in the review process. They also maintain that perhaps, one question that remains unknown

is how the distribution of issues raised in the study (in Figures 1 and 2), can be compared with that of another REC in the same country with a comparable case load and nature, over a similar time period (Tsoka-Gwegweni & Wassenaar, 2014). A similar study has been undertaken by another student researcher in Ghana using the same methodology (Selormey in progress). Further, another question to be asked is whether the distribution shown in Figure 1 is ideal, desirable, or flawed? Henceforth, the answer to this question will depend on results from several studies conducted in Ghanaian RECs and African RECs at large, yet to be compared and discussed.

5.3 Limitations of the study

Beyond description, the researcher could not really provide further interpretations to the data because, apart from some studies in progress or in press, this research work has not previously been carried out in Ghana and therefore there was no existing Ghanaian data with which to compare the present data. This research work was done on the assumption that the minutes were the true reflection of the REC meetings. Some issues might not have been included in the minutes or communicated to investigators. It may be worth emphasising that the limitations of this study are not different from the limitations identified in similar study conducted by Tsoka-Gwegweni and Wassenaar (2014) using the Emanuel et al. (2004; 2008) framework, because the same methodology was used. Only newly submitted protocols, reviewed at full REC meetings, were coded and assessed, as is also mentioned by Tsoka-Gwegweni and Wassenaar (2014). Also, protocols with minimal risks that were not reviewed at full review meeting by the REC members were not considered as part of this study.

Other limitations of the study have to do with the number of times issues of concern were raised by the index REC and the level of importance attached to them by the REC members. This is so because there is the tendency that some trivial issues were raised frequently whereas weighty issues might have been raised infrequently. There is thus a need for more similar studies to compare coding of concerns raised by RECs during protocol review. In addition, some issues raised by RECs occur under more than one principle of the Emanuel framework. These same concerns were mentioned in the study conducted by Tsoka-Gwegweni and Wassenaar (2014) and they need to be addressed in future similar studies. Again, although some of the index REC members have undergone training in international guidelines and regulations on ethics review system, there is a need for more country-specific guidance. It is important that such limitations are considered, and rolled out for further studies to be conducted on what RECs minutes capture, especially RECs in Ghana.

It is also imperative to mention that focusing on a study involving only the index REC, whose mother institution has more than one institutional review system, makes it difficult to generalise the outcome

of this research to the concerns of other IRBs of the same institution, because there is no existing data on what these IRBs look for during protocol review. Nevertheless, it is hoped that the results of this study provide, along with the Tsoka-Gwegweni and Wassenaar (2014), as well as results from Selormey's study (in progress), some exemplar findings for further investigations on other RECs, with the goal of assessing and comparing the actual concerns bothering RECs during the protocol review process. A final limitation of this study relates to the comparison with the work of Tsoka-Gwegweni and Wassenaar (2014), which is the fact that the comparison does not control for the types of study reviewed by each REC, which could influence the type and number of issues raised by research ethics committees.

5.4 Conclusion and recommendations

This study constituted one of two attempts to analyse the review meeting minutes of two selected index RECs in Ghana, applying the Emanuel et al. framework and employing the same methodology.

5.4.1 Categories of findings in descending order

The results of this study (Table 2) suggest, first, that scientific validity emerged as the most frequent issue of concern raised by the index REC and it constituted the highest percentage of queries (51.3%). Second, informed consent followed with 20.6%. Third, respect for participants, favourable risk-benefit ratio and independent review made up 8.2%, 4.4%, and 5.9% respectively. Fourth, collaborative partnership and fair participant selection made up 4% and 2.7% respectively, while social value was the least frequent issue at 0.6%. In all, 2.3% of the comments could not be classified in the framework.

5.4.2 Outcome of the research

The outcomes of this research suggest that the Emanuel et al. framework can accommodate the typical questions and issues of concerns raised by a REC during protocol review. It also gives a mechanism for consideration to conduct further comparative analyses of what RECs' concerns are during the review process in Ghana and elsewhere. The researcher thus recommends such studies involving other RECs to be carried out using the same methodology. Further, there is a need to supplement the Emanuel et al. (2004, 2008) framework to accommodate the few minor issues raised that could not be captured under any of the principles of the framework.

RECs should also consider designing and using a comprehensive application form that covers the Emanuel et al. (2004, 2008) categories, possibly generating fewer queries from the REC. Such forms are currently in use at the UKZN BREC and the SA HSRC REC (Wassenaar, personal

communication). According to Lidz and colleagues, “one of the most important questions that remain unanswered is the degree to which RECs’ deliberations and comments address the primary elements of human subject protection regulations” (Lidz et al., 2012, p. 970). There is a need to use the Emanuel et al. framework to conduct several comparative studies of REC reviews in order to generate a better understanding of what RECs are worried about, and what influences their decisions when protocols are reviewed. Additionally, it is important that RECs in Africa, especially those which are not familiar with the Emanuel et al. framework, be taught the principles and benchmarks so they can apply them in the conduct of their ethics review processes and activities.

5.5 Significance of the study

This study has hopefully shown what a particular Ghanaian REC focuses on in its review work, and has compared this data with data from one similar African study. Furthermore, it has hopefully shown that the work of this REC can be largely accommodated by the Emanuel et al. framework. Although the benchmarks seemed to be adhered to by the index REC, the findings have also brought to light some minor but possibly important issues of concern raised by the index REC that could not be accommodated by the framework. The researcher recommends that a more comprehensive framework be developed to incorporate this limitation to maximise the protection of prospective research participants and communities involved in research studies, especially in developing countries.

5.6 Best practices

The investigator strongly recommends that more Ghanaian RECs allow themselves to participate in research on their results and practices. Currently in Ghana there are no existing or published data showing exactly what the RECs’ concerns are during protocol review. Although Ghanaian RECs claim to follow international ethics guidance and also have their own standard operating procedures to guide their activities, no data is available about what their main concerns are when reviewing research protocols. It is hoped that eventually the results and recommendations from this data, when published, together with other similar studies, will help to develop and refine a more comprehensive framework which takes into consideration other issues that could not fit into the Emanuel et al. (2004; 2008) framework. This will assist and strengthen institutional RECs in Ghana, and for that matter RECs in Africa, to enable them to perform their mandated roles well so as to ensure maximum protection for prospective research participants and their respective communities.

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APPENDICES

APPENDIX 1:

Data collection tool: Criteria for Identifying Particular Ethical Issues Raised by the REC

Criteria for classifying dominant ethical issue (principle): Study Tool

1. Collaborative partnership requires:

- Community representatives
- Responsible sharing (collaboration)
- Respect for local context (environment)
- Fair research benefits for community
- Sharing research products

2. Social value requires:

- Research beneficiaries
- Research benefits
- Enhancing research benefits
- Impact on health systems

3. Scientific validity requires:

- Appropriate design and methods
- Applicability of results
- Impact on provision of health care services
- Study design feasibility

4. Fair participant selection requires:

- Suitable study population
- Risk minimization
- Benefits to participants
- Vulnerability

5. Favourable risk-benefit ratio requires:

- Risks identification and minimisation
- Type, probability and magnitude of benefits
- Comparison of risks and benefits

6. Independent review includes:

- Regulatory compliance
- REC members conflict of interest
- Transparent review
- Minimisation and reconciliation of multiple reviews

7. Informed consent includes

- Recruitment & incentives application to local context
- Appropriate disclosure documents and processes
- Presentation and accuracy of information
- Legally authorised representatives
- Gatekeepers permission
- Context of consent process
- Respect for autonomy

8. Respect for participants includes:

- Monitoring health and well-being
- Confidentiality and privacy
- Voluntariness
- Research results dissemination
- Post-research obligations

Other ethical issues such as the following that could not be accommodated by the Emanuel framework will also be rated during the minutes review:

- Data/Material transfer agreement (MTA)
- Good Clinical Practices (GCP certificates)
- Data safety monitoring board and charter of work
- Insurance cover for research participants
- Investigational brochure
- Scientific Technical committee (STC) review approval
- Communication strategy Responsible conduct of research
- Gatekeeper/site manager permission
- Regulatory approvals pending
- Administrative issues (signatures of sponsor and key research team)

Inclusion and Exclusion Criteria:

Only records of minutes for new applications that were reviewed by the full committee during its meetings for the two years 2012 and 2013 will be included. All expedited reviews would be excluded as these were not considered by the full committee.

APPENDIX 2: Approval from UKZN - Biomedical ethics approval

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

21 June 2016

Mr Hannah Frimpong (Ghana) student no: 213569689
c/o Prof D Wassenaar (PI of Study)
Discipline of Psychology
School of Applied Human Sciences
wassenaar@ukzn.ac.za

CLASS APPROVAL

Protocol: Ethical issues raised by African Research Ethics Committees.
Degree: Non-degree
***BREC reference* number:** BCA342/16 *(HSS/1450/014CA)*

The Biomedical Research Ethics Committee has considered and noted your application dated 31 May 2016.

The conditions have been met and the study is given **full ethics approval with effect from the date of the original full approval by UKZN HSSREC** *(HSS/1450/014CA)*.

This approval is valid for one year from **21 June 2016.** To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2015), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be **RATIFIED** by a full Committee at its meeting taking place on **12 July 2016.**

We wish you well with this study. We would appreciate receiving copies of all publications arising out of this study.

Yours sincerely

Professor J Tsoka-Gwegweni
Chair: Biomedical Research Ethics Committee

cc: postgraduate officer: khanyilet@ukzn.ac.za

APPENDIX 3: Local Ethics Review Committee Approval Letter

This information has been withheld due to confidentiality. Available upon Request

APPENDIX 4: Confidentiality Agreement between Supervisor and Student Researcher.

This information has been withheld due to confidentiality. Available upon request

APPENDIX 5: Researcher request letter to Gatekeeper to use Index REC's Meeting Minutes

This information has been withheld due to confidentiality. Available upon request

APPENDIX 6: Permission Letter Gatekeeper of Index REC Meeting Minutes

This information has been withheld due to confidentiality. Available upon request.