

Ethical Issues Raised by a Malawian Research Ethics Committee

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

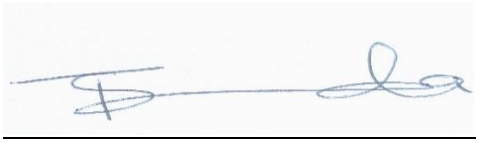
July 2018

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Dedication

The thesis is dedicated to my family: Sungani, my husband, for moral support and taking care of my two sons Kwezekani Paul and Akuzike Josh, to whom I am also indebted for their love and inspiration.

Acknowledgements

My thesis would not have been possible without the divine help from God Almighty. I am very thankful. Secondly, I am grateful for the intellectual support from Professor Douglas Wassenaar, my academic supervisor, my thesis supervisor and also the Principal Investigator of the South African Research Ethics Training Initiative (SARETI). Research reported in this publication was supported by the Fogarty International Center and NIAID of the US National Institutes of Health under Award Number 3R25 TW001599-16. The content is solely the responsibility of the author and does not necessarily represent the official views of the National Institutes of Health.

The advice and support of Dr Yohannie Mlombe and Professor Joseph Mfutso-Bengo who made it possible for the Research Ethics Committee to release minutes of protocol review meetings for academic analysis. This was a landmark of good research governance and public accountability.

Finally, I thank the 2015 SARETI scholars for all the support and the relevant Research Ethics Committee for accepting my proposal to review their minutes. It was not easy to allow critical academic review of their confidential documents.

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ABSTRACT

In 2004 Emanuel and colleagues analysed most major existing ethics codes and produced a framework of eight principles and benchmarks to guide Research Ethics Committees (RECs) during review of research proposals. Although the framework was intended for use in all settings, it is not known whether the ethical issues raised by a Malawian REC are compatible with the framework. This study sought to identify the main ethical issues raised during review of research proposals submitted to a Malawian REC and assess their comparability with the Emanuel *et al.* (2004) principles and benchmarks.

Protocol review minutes of 2013 and 2014 meetings were analysed. The minutes contained the concerns that applicants received. Only minutes of newly submitted applications were included in the study. We excluded expedited and continuing reviews, annual reports, protocol resubmissions and reports.

During the study period there were 139 protocols for initial submission. In total, the REC raised 1274 concerns. Of these, 88.8% were accommodated or coded using the eight principles of the Emanuel et *al.* Framework (2004) as follows; scientific validity (38.3%), informed consent (22.1%), independent review (9.3%), collaborative partnership (4.7%), respect for recruited participants (3.8%), social value (3.7%), favourable risk benefit ratio (3.5%) and fair selection of study population (2.9%). Other non-ethical or administrative concerns frequently raised were language errors (9.7%) and inappropriate referencing and plagiarism (2%).

Most ethical concerns raised by the Malawian REC were compatible with the Emanuel et al. framework (2004). Scientific design and inappropriate research methods are major concerns raised during protocol review implying that the REC is protecting human subjects from participating in studies that require strengthening of their scientific merit.

Keywords: Malawi, research ethics committee, REC, Emanuel et al. framework, queries,

List of abbreviations

BREC	-	Biomedical Research Ethics Committee
CIOMS	-	Council for International Organizations of Medical Sciences
COMREC	-	College of Medicine Research Ethics Committee
CI	-	Conflict of Interest
IRB	-	Institutional Review Board
ICH-GCP	-	International Conference on Harmonisation Good Clinical Practices
MSocSc	-	Master of Social Science
NHSRC	-	National Health Sciences Research Committee
NCRSH	-	National Committee on Research in the Social Sciences and Humanities
REC	-	Research Ethics Committee
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 Introduction and background

This chapter will briefly introduce the research and its background. Research that involves human participants is crucial in order to generate knowledge that is beneficial to individuals and society as a whole. The overarching question is: How can we uphold the rights and dignity of human subjects within the demands of scientific enterprise (Emanuel, Crouch, Arras, Moreno, & Grady, 2008).

Numerous international guidelines for ethical conduct of research emerged after the revelations of brutal medical experiments in the past, and became a blueprint for research guidelines in various jurisdictions. Among these international guidelines, one of the fundamental recommendations is to conduct independent review of research protocols (CIOMs, 2016; OHRP, 2009; World Medical Association (WMA), 2000). Independent committees in the United States are known as institutional review boards (IRBs), elsewhere they are called research ethics committees (RECs) (Kass, Hyder, Ajuwon, … & Tindana, 2007). They have a duty to provide oversight of health research as well as provide a public forum for the accountability of researchers (Ashcroft & Pfeffer, 2001). When the REC is reviewing a research protocol, it can typically come to the decision that a given project: (1) is acceptable as presented, (2) needs to be modified before it can be accepted, (3) requires more information to make a decision, or (4) is unacceptable in its current form.

Typically, RECs rely on international and national guidelines to review research protocols. However, several sets of international guidelines exist and there are concerns about how to interpret and harmonise some clauses within these guidelines. In an effort to help RECs in their work, Emanuel and colleagues (2004, 2008) analysed existing ethical codes and produced a framework of eight principles as benchmarks to guide the review of research proposals in developing countries. Although the Emanuel, Wendler and Grady (2008) framework was intended for use in low and middle-income countries, it is unknown whether the ethical issues arising from REC review in these settings are compatible with the framework (Tsoka-Gwegweni & Wassenaar, 2014).

Given the cultural, political, and educational background, as well as disease burden and socio-economic situations that usually influence health research in Africa, there is a need to assess the applicability of this framework to different settings. For instance, Malawi is a low-income sub-Saharan Africa country with a gross national product (GDP) of US$ 360 billion. It is 118,480 km² in size with a population of 16.36 million (IMF, 2014). The country has a very high disease burden that has put pressure on health care management. Almost 10.6% of the population in Malawi is HIV infected (*Malawi Demographic and Health Survey*, 2012). Due to the high disease burden, the country has become a popular destination for international collaborative

research. Understanding the compatibility of the Emanuel et al. framework (2004, 2008) to the Malawian setting is necessary.

Ethics review of protocols started in 1988 in Malawi. Currently, the RECs mandated to review research proposals are the National Health Science Research Committee (NHSRC), the College of Medicine Research Ethics Committee (COMREC) (Mfutso-Bengo, Manda-Taylor, Jumbe, Kazanga & Masiye, 2014) and the National Committee on Research in the Social Sciences and Humanities (NCRSH) (M. Kachedwa, personal communication, April 7, 2017). Since the establishment of these RECs there has been no study to evaluate their operations. The report by the office of the Inspector General of the United States Government cautioned that REC processes must be monitored and evaluated because they play a vital role in research enterprise. The report stated that evaluations can allow easy identification of areas that require improvement to ensure that the REC is protecting human subjects effectively, is operating efficiently, and that it has adequate authority (*Protecting Human Research Subjects Status Recommendation*, 2000). In this case, the Emanuel et al. (2008) framework was used to evaluate the concerns of one Malawian REC. This is the first empirical study reporting on the ethical concerns raised by a Malawian REC. The study used a qualitative approach to analyse minutes of protocol review meetings. The main study aims were to identify ethical issues frequently raised during review of research proposals and then assess their relative weight using Emanuel et al.'s (2008) framework. This is a replication of a South African study done by Tsoka-Gwegweni and Wassenaar (2014).

CHAPTER 2: LITERATURE REVIEW

2.1 Towards regulatory practices for research involving human participants

Several scandals and tragedies in past medical experiments stimulated the need to regulate research activities. This has also led to research ethics as a discipline which aims at protecting the rights and welfare of those volunteering to participate in research. Of course, presently research ethics is extending into areas such as scientific misconduct and plagiarism (Wassenaar, 2006). When revelations of brutal medical experiments were made, numerous guidelines for ethical conduct of research were developed. For instance the Nazi war crime ruling lead to the Nuremberg code and the Tuskegee syphilis study facilitated the creation of the US Common Rule and the Belmont Report. Most of these guidelines have recommended the independent review of research protocols (WMA, 2000; CIOMS, 2016). Additionally, many individual countries have also developed legislation that regulates research involving humans (Mokgatla, IJsselmuiden, Wassenaar et al., 2017).

In Malawi (Mfutso-Bengo, 2015) ethics review of research started in 1988 but the strengthening of the Malawian ethics review system came after there were changes in United States (US) research policy on research funding for overseas studies in 2001. There was a requirement that any US government-funded research involving human research volunteers had to follow the prescribed US regulations (Mfutso-Bengo, 2015). This US research ethics requirement was a blessing in disguise to improve the operations of Malawian RECs. Later, in 2005, a document was developed known as the *National Policy Measures and Requirements for the Improvement of Health Research Co-ordination in Malawi* (*National Commission for Science and Technology*, 2012). The *policy* document was revised in 2012 and it provides guidance to research institutions, researchers and RECs on how they ought to operate in the country.

Below, selected scandals and guidelines are reviewed, especially those that have informed global research ethics guidelines and practices.

2.2 Scandals and tragedies in medical experiments

There are many scandals and tragedies that have occurred in medical research including in Malawi. Some of the notable ones are discussed below.

2.2.1 Nuremburg trials of Nazi war crimes

After World War II, the Allies brought charges at Nuremburg against twenty-three Nazi doctors and bureaucrats for using thousands of concentration camp prisoners in experiments that challenged the legitimacy of human experimentation. As described by Faden, Lederer and Moreno (1996), some of the experiments done were as follows: putting the prisoners into low-pressure tanks to see how long they could survive; prisoners were infected with malaria and then given anti-malaria drugs; prisoners were given poison

in their food - most of them died immediately and those who did not die were killed for the purposes of autopsy; prisoners were burned with phosphorus material from bombs so that doctors could examine the wounds. In the court judgment, ten conditions were laid down that must be fulfilled in future health research involving human volunteers, generally referred as the Nuremberg Code (Amdur, 2011 p. 8). The guidelines in the code emphasise the importance of voluntariness and informed consent (Amdur, 2011, p. 8).

2.2.2 Brooklyn Jewish Chronic Disease Hospital study (1963)

Two physicians from Brooklyn Jewish Chronic Disease Hospital in the United States of America (USA) performed this cancer research in 1963 (Emanuel et al., 2003). As described by the authors (Emanuel et al., 2003) the aim was to determine the rate of rejection of human cancer cells injected into patients. The study procedures involved injecting living cancer cells into elderly patients without their full informed consent. The study results provided important evidence in terms of cancer treatment. The findings showed cancer cells would cause an immune reaction that would lead to expulsion from the body. A New York court brought charges against the two physicians. It was argued that although non-disclosure in the physician-patient relationship can be justified, non-disclosure in a researcher-participant relationship is unacceptable. A lesson learned from this incident is that a physician-researcher might have conflicting loyalties that are of ethical importance (Emanuel et al., 2003).

2.2.3 Willowbrook study (1955-1971)

This study sought to find methods for preventing hepatitis that was endemic at a state facility in New York. Emanuel et al. (2003) narrate that the researchers used disabled children and adolescents in the trial. The study procedures involved deliberately exposing them to hepatitis. The researchers hypothesised that by exposing incoming (new) patients to the hepatitis virus and then injecting them with protective antibodies, they would have slim chances of developing symptoms associated with more serious cases of hepatitis and would ultimately become immune to the virus. However, the conditions under which participants were recruited were coercive. The health facility was full but the researcher mailed parents of children who were on the waiting list that their children could be admitted into the institution only if they accepted a placement in the research ward from where they could be transferred into the facility. Study findings showed that, from the time this research was initiated, the rates of hepatitis declined. The researchers were also criticised for using intellectually handicapped children (Emanuel et al., 2003).

2.2.4 Tuskegee syphilis study (1932-1972)

Only a year after the Willowbrook scandal, more revelations on human rights violations were brought to the public about the Tuskegee syphilis study (Reverby, 2000). As narrated by Amdur (2003), there was a need to describe disease progression of syphilis. Therefore, researchers proposed a case-control study involving 300 cases and 200 controls to examine effects of syphilis. In 1932 the researchers received sponsorship from the US Public Health Service to conduct this trial. There is no record to show if informed consent was obtained.

In 1950, participants were not informed nor given treatment when penicillin, an effective new treatment became available. It was thought the treatment would undermine the scientific purpose of the study. Many participants died of advanced sequelae of untreated syphilis. After public exposure, the study was stopped in 1972 and the US government apologised to study participants and their families and this led to the development of the National Research Act in 1974 (Amdur, 2011 p. 15).

2.2.5 Guatemalan Study

As narrated by Reverby (2012), there was a motivation to learn about the effectiveness of penicillin, as such the US National Institutes of Health sponsored a study which was conducted in Guatemala from 1946 to 1948. The purpose of this study primarily was to see if penicillin, as a newly available drug, could serve not just as a cure for early syphilis, but also as a prophylaxis for several STDs (Reverby, 2012). The study population included 1,500 Guatemalan orphans, soldiers, mental health patients, prisoners and sex workers. Confirmed records indicate that participants did not give their consent. The study procedures involved deliberately infecting participants with syphilis and gonorrhoea or the participants were coaxed to have sex with commercial sex workers who had a syphilis infection. If a participant failed to present symptoms of the infections, some had bacteria rubbed into scrapes on their penises, faces and arms (Reverby, 2012). Besides the unacceptable research standards in the trial, records show that academic institutions and government agencies in the US were aware of the study but their priority was to learn the study outcomes. While making investigations about a physician named John C. Cutler who was a researcher in the syphilis study in Tuskegee in the 1950s, Reverby discovered reports about this Guatemalan study which the public was not aware of (Reverby, 2012). Later, Reverby published her discoveries. A commission of the US government was instituted to find out the details of the Guatemalan study. The report prompted President Obama to apologize to the Guatemalan government and people for the U.S. sponsored trial that undermined participants' rights and welfare in pursuit for knowledge.

2.2.6 Malawi research scandal at St. Luke's Hospital: The cancer clinical trial

Despite the establishment of Malawian RECs, the country's research oversight system had a rude awakening in 2008 when news emerged of study results from a cancer drug trial that was never approved by any Malawian REC. The researcher was a medical technician from St Luke's Hospital in Zomba. Mkoka (2008) narrates that in 2006, he applied for ethics review of his research protocol at a Malawian REC. The REC raised a concern that the applicant was not sufficiently qualified to conduct the trial so he should involve an oncologist. The applicant failed to address the concern and he resubmitted the same protocol to another Malawian REC that did not approve the trial. The applicant was not satisfied with the responses from the REC, so he submitted the research protocol to a department that oversees HIV implementation in the country under the Ministry of Health (MoH). He didn't receive feedback from Ministry of Health (Mkoka, 2008). Regardless of the lack of ethics clearance from any Malawian REC, the researcher reportedly began recruiting study participants. The trial sought to assess the safety and efficacy of a new treatment combination for

cancer patients. Twenty participants were recruited. The study population included very sick patients who had tumours and were in the final stages of HIV/AIDS according to World Health Organisation (WHO) staging (*World Health Organisation, 2003*). There were two study arms, whereby ten participants were randomised to each arm. Overall, there were six deaths from one study arm. Preliminary findings were released in 2008. The hospital administration was surprised by the study findings and inquired if there was any ethics clearance. The National REC was notified and members of this REC visited the research site to investigate, but they failed to verify whether informed consent was obtained and did not find patient files. However, the researcher confirmed that he conducted the trial. According to Malawi pharmacy guidelines, only oncologists are allowed to prescribe the cancer drugs used in this trial (Pharmacy Medicine and Poisons Board Act, 1988). Zomba court brought charges against the researcher. The case was contested in court. Eventually the accused was acquitted (Mkoka, 2008). Later, an appeal was submitted by the Pharmacy and Poisons Board but the accused was no longer living in Malawi and could not be traced.

This section has attempted to provide examples of the history of research abuses that led to the development of research ethics guidelines that are outlined in the following section.

2.3 Introduction of guidelines and ethical codes for researchers

Most guidelines and ethical codes for research were developed to respond to a tragedy or scandal that occurred (Emanuel et al., 2003). Several guidelines have been published since World War II, all aiming to codify the rules that should govern the conduct of research. The sections below present selected important guidelines.

2.3.1 The Nuremberg Code

The presiding judge of the Nuremberg trial presented ten conditions that must be fulfilled in research, including the provision that voluntary informed consent is absolutely essential (Amdur, 2011). Despite many researchers agreeing to the principles in his ruling, some researchers later complained that it was too restrictive in terms of persons who could not provide consent to research; for example, it meant that studies involving children could not be conducted (Emanuel et al., 2003). Further, there was a concern that the Nuremberg code which was developed at the end of the Nazi doctors' trial in 1947 had some clauses that were very hard to understand. For instance, human experiments *"should not be random and unnecessary in nature"* (*Nuremberg Code*, Guideline no.2) yet there are some important medical breakthroughs such as anaesthesia, X-rays, and penicillin that were a result of random experimentation (Emanuel et al., 2003). Doctors thought the code was inadequate.

2.3.2 Declaration of Helsinki

The World Medical Association (WMA), a medical practitioners' grouping, developed guidelines which received widespread approval in the United States. The guidelines stated that physicians are required to

obtain consent from patient-subjects unless it was not 'consistent with patient psychology,' and there was an allowance for surrogate consent if approved by a REC. Emphasis was made that clinical research involving human volunteers cannot be conducted in the absence of the person's free consent after being fully informed. Here it was also stated that all biomedical research studies involving humans must be reviewed by an independent REC. The declaration was received as a more practical guide to the conduct of ethical research than the Nuremberg code since it offered rules that are closely related to clinical settings rather than the idealised language of the Nuremberg Code (Emanuel et al., 2003). The WMA general assembly adopted the guideline in 1964 in Helsinki, but the most recent amendment occurred in 2013 (WMA, 2013).

2.3.3 The Belmont Report

Reflecting on past injustices, some investigators felt the rules and instructions that were already in place did not offer adequate safeguards to address exploitation and abuse of humans in research (Emanuel et al., 2003). The rules were not fit to address complex situations case by case (Emanuel et al., 2003). Therefore, there was a need to develop principles relevant to research involving humans (Emanuel et al., 2003). The principles provided an ethical framework that would guide the resolution of ethical dilemmas arising from research. In 1979 a special committee was established and it eventually developed a report known as the *Belmon*t *Report; Ethical Principles and Guidelines for the Protection of Human Subjects of Research, Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research.* In the report they came up with three main principles: respect for persons, beneficence, and justice (Belmont Report, 1979). Firstly, the principle of respect for persons implies that a human being is an autonomous agent and those with diminished autonomy must be protected. Secondly, the principle of beneficence entails the need to confer benefit and protect humans from harm and making efforts to secure the well-being of humans, while the third principle of justice addressed fairness in the distribution of the benefits and burdens of research (*B*elmont Report, 1979).

2.3.4 The Common Rule: Title 45, Code of Federal Regulations 46

The Office of Human Research Protections (OHRP) in the US is mandated to guide researchers and IRBs/RECs to ensure the rights, welfare and wellbeing of participants in US federally funded research are protected. The OHRP enforces Federal Policy according to 45 CFR 46 and subpart A is referred as the *Common Rule*. The *Common Rule* was originally promulgated in 1991 but keeps being revised to enable it to meet challenges of the rapidly changing landscape of research. The issues addressed are mainly institutional assurance, IRB review and Informed consent. Institutions conducting research involving human volunteers are obliged to comply with the Common Rule. The rule is clear that research protocols must be reviewed and approved by an independent IRB before commencement of the study and it also guides the operations of an IRB. Additionally, this rule has detailed guidance on issues to do with obtaining informed consent. Cleaton-Jones and Wassenaar, (2010) have compared the Common Rule and South African national guidance and laws. It showed that South African guidance is more stringent than the then extant US Common Rule.

2.3.5 Council for International Organisations of Medical Sciences (CIOMS)

The Council for International Organisations of Medical Sciences (CIOMS) is an international non-governmental organisation based in Geneva. The organisation was formed in 1949 and is a partnership between the World Health Organisation (WHO) and the United Nations Educational, Scientific and Cultural Organisation (UNESCO). CIOMS is involved in many ways of supporting improved ethical standards and review processes for research. The aim is to provide guidance on health related research in three areas: Bioethics, pharmacovigilance and product development. A revision of CIOMS ethics guidelines for health related involving humans was published in 2016 (CIOMS, 2016).

2.3.6 The International Council for Harmonisation-Guideline for Good Clinical Practice ICH-GCP Guideline)

The increase in international guidelines resulted in varying requirements that researchers and sponsors had to fulfil (ICH-GCP Guidelines, 1996). There was also an increase in international multi-centre clinical drug trials. In this case the need to harmonise regulatory requirements for the development of pharmaceutical products emerged (ICH-GCP, 1996). Thus in 1996 the United States, the European Union and Japan initiated the process of harmonising their drug trial guidelines leading to Good clinical practice (GCP) (ICH-GCP, 1996). An effort was made to avoid duplication of studies by making data generated from trials in one country acceptable in other countries. The approach aimed to accelerate drug development process.

RECs use these international guidance to ensure ethical implementation of research. Malawi has also benefited from these international standards.

2.4. Research Ethics Review in African Settings

The international guidance documents described above have significantly influenced African research ethics standards (Kass et al., 2007). Some African RECs are using the US IRB system as an exemplar in their operations while others are in accordance with the World Health Organisation (WHO) guidelines (Ndebele et al., 2014). It is widely recognised that low income settings pose unique ethical challenges in research involving human participation. These international guidelines nevertheless support the review of protocols in low income settings.

Despite agreement on the principles of research ethics, there are variations in their application (Emanuel et al., 2008). Hyder et al. (2004) compared ethics reviews between a sponsor REC and a host REC, and found significant differences. According to these authors (Hyder et al., 2004), the sponsor RECs frequently raised issues regarding gate keepers permission, informed consent and selection of control arm, while the host RECs frequently raised issues relating to cultural appropriateness of the study followed by the relevance of research to the host country, the informed consent and availability of intervention (if successful). Similarly, two case studies by Mfutso-Bengo and Taylor (2002) and Love and Fost (2003) also reported differences

between host and sponsoring country RECs. Although there are differences, Mzayek and Resnik (2010) cautioned that it could be because the members of RECs hosting the research are strongly influenced by their own culture and sometimes coupled with the lack of training in ethical principles of biomedical research, unknowingly they may inject their own values into study protocol and procedures, eventually engaging in a kind of ethical relativism where local norms take precedence over universal ethical principles. However, Mzayek and Resnik (2010) also point out that members should not subscribe entirely to western ethical norms because they may end up approving a study that is legally valid, but ethically inappropriate.

Meanwhile, improving the capacity of African ethics review systems remains crucial. An early report by Nuffield Council on Bioethics raised concerns that RECs in developing countries may not adequately promote high ethical standards because they are poorly funded and lacked proper trained staff (Nuffield Council on Bioethics, 2002). Indeed, a survey by African Malaria Network Trust (AMANET) in 2007 revealed that that 8 RECs out of 27 lacked SOPs; 10 RECs out of 28 lacked training of members on joining; 15 out of 28 lacked continuing training of members (Ndebele et al., 2014). There has since been much progress. Ndebele et al. (2014) list the considerable past and ongoing training outputs in Africa over the past 15 years, including funded training by organisations committed to build African ethics review capacity such as African Malaria Network Trust (AMANET), European and Developing Countries Clinical Trials Partnership (EDCTP), Welcome Trust UK and the Fogarty International Centre.
A brief discussion of the Malawi ethics review system follows below.

2.4.1 Research oversight system in Malawi

The legislation in Malawi has a provision to avoid abuses during the conduct of research involving human beings. Section 19 subsection 5 of the Constitution of Malawi states that no person shall be subjected to medical or scientific experiment without his/her consent (*Constitution of the Republic of Malawi*, 1996). In addition, through an Act of Parliament, the National Commission for Science and Technology (NCST) was established to coordinate and promote research in Malawi and to ensure that all research involving human beings is subjected to research ethics committee review (National Policy Measures and Requirements for the Improvement of Health Research Coordination in Malawi*,* 2012). The NCST has the mandate to establish RECs. According to the 2012 National Policy Measures and Requirements for the Improvement of Health Research Coordination in Malawi, Malawi has two RECs, the NHSRC established in 1988 and COMREC, established in 1996. Furthermore, in one of the email conversation with the personnel working at the National Commission for Science and Technology, the researcher of the present study was informed that there is a third REC known as and the National Committee on Research in the Social Sciences and Humanities (NCRSH) (Kachedwa, personal communication, April 7, 2017).

Mfutso-Bengo et al. (2014) reports that documents like the Declaration of Helsinki, CIOMS, Belmont Report, Common Rule and ICH-GCP provide guidance for the operations of Malawian RECs. To help guide reviewers

of protocols, the RECs have a template which a reviewer uses, see Appendix VII. It is the duty of the REC to develop SOPs outlining how the review processes ought to be done.

Besides the aforementioned RECs, the Pharmacy Medicines and Poisons Board (PMPB) has the mandate to regulate the pharmaceutical industry in Malawi and to complement the role of RECs (Pharmacy, Medicine and Poisons Board Act, 1988). The PMPB issues product licenses for clinical trial-related products. Since 2008, soon after the St Luke cancer trial scandal, the NHSRC and PMPB have conducted joint review of vaccine and drug development clinical trials (Mkoka, 2008).

2.5 The Emanuel et al. (2008) framework

Studies have shown that different RECs reach different conclusions when reviewing the same research protocol (Hirshon, Krugman, Witting, Furuno & Limcangco, 2002; Silverman, Hull, Sugarman, 2001; Stair et al., 2001). Furthermore, researchers have complained and criticised RECs for being dysfunctional (Fost & Levine, 2007), overburdened (Burman, Reves, Cohn, & Schooley, 2001), and over-reaching (Gunsalus et al., 2006), irrational, incompetent, and inconsistent in decision-making (Edwards, Ashcroft, & Kirchin, 2004; Hannigan & Allen, 2003; Lux, Edwards, & Osborne, 2000). To help RECs, Emanuel and colleagues in 2000, 2004 and 2008 analysed key international ethics codes and produced a framework made up of eight principles and benchmarks to provide a unified and consistent ethical guideline for reviewing biomedical research. According to the ethical framework, studies should be assessed to ensure that there are collaborative partnership, social value, scientific validity, fair participant selection, and a favourable risk-benefit ratio (Emanuel et al., 2004; 2008). According to the framework, it is presumed that studies must also undergo independent ethics review, have informed consent, and be able to demonstrate ongoing respect for participants. The Emanuel et al. (2008) framework is summarised below and Table 1 shows the principles and their benchmarks.

1. Collaborative partnership requires the involvement and contributions of the host community. The partnership includes shared responsibilities as well as research benefits, and when conducting the study, the values and needs of the host community must be respected.
2. Social value is a principle that ensures that the proposed research has the potential to generate knowledge to benefit the participants, community, society, and research community or health system, without any wastage of resources.
3. Scientific validity ensures that the proposed research is using reliable and valid research designs and methods to obtain data, and is relevant to the objectives. The results from the study must be applicable to the health problem being studied. In addition, the researchers ought to be appropriately qualified.
4. Fair participant selection entails the need to appropriately choose a study population that is relevant to the research objectives.

5. A favourable risk-benefit ratio firstly ensures the identification and minimisation of all forms of potential harms to participants in terms of nature, size, and its likelihood. Secondly, the identification, quantification and maximisation of possible benefits should be considered. Thirdly, there is need to balance the potential risks and benefits among the participants and society.

6. Independent ethics review requires the REC to be independent from external influence and should be guided by law and have and follow documented standard operating procedures. The review process must be transparent to ensure justified decisions. RECs should be fair at handling multiple reviews.

7. The principle of Informed consent ensures that the research recruitment procedures and incentives involved must be appropriate to the local setting and that disclosure documents and procedures are tailored to respect the participants' local context. Informed consent requires disclosure of complete, accurate, and adequate information to participants; there is also provision for obtaining surrogate consent, if required; provision for obtaining permissions from relevant gatekeepers; and clearly informing the participants of their right to participate, refuse, or withdraw from research.

8. Ongoing respect for participants requires monitoring of the health status of participants and minimising risks and upholding confidentiality. Even when participants decide to withdraw from the study they may not be deprived of effective health care services, and the researchers must have plans for dissemination of research findings and post-research obligations.

Table 1: The eight principles and benchmarks, reproduced from Emanuel et al. (2008)

Principle	Benchmarks
Collaborative partnership	Develop partnerships with researchers, makers of health policies, and the community.
	Involve partners in sharing responsibilities for determining the importance of health problem; assessing the value of research; planning, conducting, and overseeing research; and integrating research into the health-care system.
	Respect the community's values, culture, traditions, and social practices.
	Develop the capacity for researchers, makers of health policies, and the community to become full and equal partners in the research enterprise.
	Ensure that recruited participants and communities receive benefits from the conduct and results of research.
	Share fairly in financial and other rewards of the research.
Social value	Specify the beneficiaries of the research.
	Assess the importance of the health problems being investigated and the prospective value of the research for each of the beneficiaries.
	Enhance the value of the research for each of the beneficiaries through dissemination of knowledge, product development, long-term research collaboration, and/or health system improvements.
	Prevent supplanting the extant health system infrastructure and services.
Scientific validity	Ensure that the scientific design of the research realizes social value for the primary beneficiaries of the research.
	Ensure that the scientific design realizes the scientific objectives while guaranteeing research participants the health-care interventions to which they are entitled.
	Ensure that the research study is feasible within the social, political, and cultural context or with sustainable improvements in the local health-care and physical infrastructure.
Fair selection of study population	Select the study population to ensure the scientific validity of the research.
	Select the study population to minimize the risks of the research and enhance other principles, especially collaborative partnership and social value.
	Identify and protect vulnerable populations.
Favorable risk-benefit ratio	Assess the potential risks and benefits of the research to the study population in the context of its health risks.
	Assess the risk-benefit ratio by comparing the net risks of the research project with the potential benefits derived from collaborative partnership, social value, and respect for study populations.
Independent review	Ensure public accountability through reviews mandated by laws and regulations.
	Ensure public accountability through transparency and reviews by other international and non-governmental bodies, as appropriate.
	Ensure the independence and competence of the reviews.
Informed consent	Involve the community in establishing recruitment procedures and incentives.
	Disclose information in culturally and linguistically appropriate formats.
	Implement supplementary community and familial consent procedures, where culturally appropriate.
	Obtain consent in culturally and linguistically appropriate formats.
	Ensure the freedom to refuse participation or withdraw.
Respect for recruited participants and study communities	Develop and implement procedures to protect the confidentiality of recruited and enrolled participants.
	Ensure that participants know they can withdraw without penalty.
	Provide enrolled participants with information that arises in the course of the research study.
	Monitor and develop interventions for medical conditions, including research-related injuries, for enrolled participants, at a level at least as good as existing local norms.
	Inform participants and the study community of the results of the research.

2.5.1 The relevance of the Emanuel at al. (2008) framework

Many authors have cited the Emanuel framework and it is commonly used in research ethics training. This framework is often used to review both published and proposed research (Budin-Ljosne, 2012; Fakruddin, Chowdhury, Hossain, & Mannan, 2012; Miller & Brody, 2003; Miller & Shorr, 2002; Shaw & Elger, 2013; Union Graduate College & Vilnius University, 2012; Wassenaar, 2006). It has also been adapted for use in reviewing social science research (Wassenaar & Mamotte, 2012).

In 2002 Miller and Shorr used the seven principles of an earlier (Emanuel et al., 2000) version of the Emanuel et al. (2004, 2008) framework to illuminate ethical issues posed in an industry-sponsored trial concerning an asthma drug in the USA. Following the framework's guidance, the authors managed to raise several serious ethical problems about the drug trial. Later in their article the authors called the framework a valuable tool for REC/IRB members in reviewing research protocols (Miller & Shorr 2002). Similarly, in 2012 Farkruddin and colleagues published an article highlighting the need to develop ethics guidelines for the conduct of health research in Bangladesh. They reported that most studies in Bangladesh were not being published in reputable journals because they failed to satisfy the requirement for Independent ethical review. In the article the authors managed to list principles that should be considered when developing Bangladesh guidelines for ethical review of research proposals. All principles and benchmarks proposed by Emanuel et al. (2004) were included. In 2016 Mfutso-Bengo (2016) reported a study to understand the decision-making process of Malawian women who participated in clinical trials. He found that participants were able to differentiate between clinical research and clinical care. The women reported that they chose to participate in clinical research in order to access better health care and not for generalisable knowledge. Mfutso-Bengo raised some ethical questions;

> "Is it reasonable to join research in order to get good care? What is the difference between a researcher who joins a research team for the sake of desire to publish [to advance his/her career] and the research participant who joins a study with a desire to get better medical care? Are both decisions rational?" (Mfutso-Bengo, 2016, p. 13)

However, Mfutso-Bengo (2016) argues that if a study conducted in a limited resource setting can satisfy the requirements proposed by the Emanuel et al. (2004; 2008) framework, those ethical questions automatically gets resolved. In South Africa, Tsoka-Gwegweni and Wassenaar (2014) reported concerns raised by a South African REC to determine whether their concerns could be accommodated in the proposed framework by Emanuel and colleagues (2008). The findings are reported in the following section.

2.5.2 A review of the Tsoka-Gwegweni and Wassenar (2014) study

The present study is a replication of Tsoka-Gwegweni and Wassenaar's (2014) study. Their study used the eight principles of the Emanuel et al. framework (2004) to review the minutes (2008-2012) of a South African Biomedical REC (Tsoka-Gwegweni and Wassenaar, 2014). They found that there were 1043 queries raised by the REC. Of these, 99.7% of the queries were accommodated by the Emanuel framework. The most frequent

concern was about informed consent followed by scientific validity. Informed consent queries covered the biggest percentage (27.4%) of the 1043 concerns raised; issues like appropriate disclosures, documents, and processes, the language used, research setting, and completeness of the essential information given to participants, presentation and truthfulness of information, applicability of recruitment methods and incentives to local context, site gatekeepers' permission, respect for autonomy, and context of consent process. These findings correlate with the vast literature showing how informed consent plays a dominant role in research. Since the 1940s, it has become a key principle of the Nuremberg Code and was adopted by the Declaration of Helsinki in 1946. For many years, it was marked as an obligation for a researcher to obtain informed consent; however, the focus has shifted from researchers' obligation to disclose information to a focus on the quality of participants' understanding the consent (Beauchamp & Childress, 2013).

Scientific validity ranked second (21.4%) in the Tsoka-Gwegweni and Wassenaar (2014) study. Research that is not sound scientifically is harmful and shows a lack of respect for participants because the study results cannot be trusted and because it would be wasting participants' time and other resources. This study was the first of its kind to rank the REC queries from protocol review minutes using the Emanuel et al framework (2004). The findings from the present study will also be used to compare the SA findings.

2.6 Empirical studies on Research Ethics Committee Operations

Studies on RECs are relatively rare. Evaluating RECs may be challenging, but their operations ought to be assessed (Fernandez Lynch, 2018). It is standard practice for members of the REC to conduct protocol review in closed meetings and their minutes are confidential. RECs communicate to the investigators the reasons why the REC has made a particular decision. The Declaration of Helsinki (2013) highlights the need for RECs' transparency and accountability. The REC letters are required to give justifications. A study by Clapp et al. (2017) found that a significant number of letters from UK RECs rarely cite the regulations as justification for the suggested/proposed changes to the investigators. In addition, Dixon-Woods et al. (2007; 2008) found that RECs often use 'authoritative tone' in their correspondence with investigators even on an issue where there is significant debate in the bioethics community. Gunsalus et al. (2006) reported that in the American context IRBs have been accused of 'mission creep' because they are crossing a line beyond their ethico-regulatory authority.

Regardless of the challenges identified in the above studies, Clapp et al. (2017) found that RECs raise issues of informed consent with greatest frequency, followed by study designs, even when protocols have been peer reviewed. A study by Humphreys et al. (2014) who interviewed REC members, described that members felt that participant safety and ethical factors could only be deemed appropriately addressed if the study methods were scientifically sound. Sound design was seen as necessary for approval of a research protocol. Elsewhere, queries relating to study design were common in investigator-initiated studies with non-physical procedures, while fewer queries were raised when evaluating clinical drug trial protocols (Happo, Alkoaho,

Lehto, & Karanen, 2016) suggesting that in drug trials, there is considerable investment made by drug companies to ensure positive peer review.

There is evidence of increasing efforts to improve research ethics capacity in developing countries. Ndebele et al. (2014) reports initiatives for capacity building in the past fifteen years, but the authors mentioned that the increasing amount and complexity of health research being conducted in Sub-Saharan Africa suggests the need for continued investment in research ethics capacity development. The present study follows the cited empirical studies to examine ethical issues raised by an African REC because they can also be used to inform further training of REC members and support ongoing efforts of improving ethical oversight in Malawi and possibly in Africa more generally.

CHAPTER 3: RATIONALE OF THE STUDY

3.1 Introduction

To date, there is limited empirical evidence of what ethical issues are raised by RECs in developing countries (Silaigwana & Wassenaar, 2015, 2019). Mostly, the evidence is anecdotal, and sometimes develops from the practical difficulties that investigators experienced while seeking ethics clearance (Dixon-Woods, Angell, Ashcroft, & Bryman, 2007). Empirical evidence is important to inform policies and guidance documents. To the best of our knowledge, there has not been an empirical study to identify ethical issues commonly raised by Malawian RECs. This study sought to fill the gap.

Given the poverty, limited health care services, illiteracy, cultural and linguistic differences, and limited understanding of the nature of scientific research, the weight given to particular ethical principles during review of health research by RECs may differ. A recent paper (Tsoka-Gwegweni & Wassenaar, 2014) presents findings for a South African REC but there are no other data with which to compare such findings. A closer and systematic examination of the ethical issues raised by a Malawian REC may shed more light on this question, comparatively. It will also consider the applicability of the Emanuel et al. (2004) framework to an African context because this study forms part of a broader multi-national study taking place in Ghana, South Africa, Cameroon, Nigeria, and Zimbabwe.

3.2 Aims of the study

The study aimed firstly to identify the main ethical issues raised during ethics review of research proposals submitted to a Malawian REC and secondly to assess their relative weight using Emanuel et al.'s (2004, 2008) principles and benchmarks of ethical review of clinical research.

The overarching questions are as follows;

1) What ethical concerns does a REC in Malawi raise when reviewing protocols?
2) Is there a systematic prioritisation of some ethical issues over others?
3) Is there an observable pattern to the ethical concerns raised by committee members? If so, what is the pattern?
4) Are the concerns raised consistent with the framework developed by Emanuel et al. (2004, 2008)?
5) Does any feature of the Emanuel et al. (2004, 2008) framework dominate the concerns? If so, which one?
6) Are there other concerns raised by the REC which are not consistent with the framework discussed by Emanuel et al. (2004, 2008)?

3.3 Specific objectives

The specific objectives of this study were:

1. to identify and describe the pattern of ethical concerns and issues raised in reviews of research proposals.
2. to analyse and rank the ethical issues and concerns raised by the REC using Emanuel et al.'s (2004, 2008) framework and to determine whether they do or do not fit the framework.

The methodology used is presented in the next section.

CHAPTER 4: RESEARCH METHODOLOGY

4.1 Research design

This research consisted of a case study based on content analysis of archived written documents, which were the minutes of protocol review meetings of a Malawian REC. As described by Yin (2013), a case study is an empirical approach that is used mostly by a researcher whose goal is to answer 'how' or 'why' questions about an existing issue (the case). The case study design was suitable to identify ethical issues raised by a REC and understand how they relate to the principles and benchmarks of the Emanuel et al. framework (2004, 2008). Here, the plan was to test whether the concerns raised by one Malawian REC during protocol review do or do not fit this framework. This study does not attempt to answer the 'why' question, however. Additionally, qualitative research methods were employed by conducting a content analysis. As described by Hsieh and Shannon (2005), content analysis starts with theory and findings from prior studies which then guide the initial codes. Therefore, the codes for the present research were derived from Emanuel et al. (2004, 2008) framework. This research is part of an international collaboration involving the 2013 and 2015 South African Research Ethics Initiative (SARETI) Master's degree students from the University of KwaZulu-Natal (UKZN), South Africa. In Malawi two RECs are under study while other countries include Ghana, Nigeria, Zimbabwe, Uganda, and South Africa. This report covers the findings from one Malawian REC. Partners will research and present findings from individual RECs, this research will eventually be compiled into an international group report.

4.2 Sampling method

For this study to be able to contribute to the international group project, a standard methodology and analytic framework had to be adopted across all countries. As such, minutes from all participating countries should ideally have covered the same period. The minutes for a period of two years (2012-2013) were selected. However, the 2012 minutes for the REC were missing; thus the protocol was formally amended to include the 2013-2014 minutes of the REC under study.

The sample size was not pre-specified because it depended on the workload of the REC within the specified study period. These minutes provided the ethics feedback that applicants received. Considering that the REC under study had 11 scheduled meetings per year, 22 sets of minutes for this period of review were expected. Only recorded minutes of all newly submitted full review protocols were included in this study, without any consideration of the type of study (clinical trial, social research, biomedical, or behavioural study). The sample excluded expedited and continuing reviews, annual reports, undergraduate studies, and study final reports.

4.3 Study setting

The membership of the REC under study has representation from other Malawian RECs and a lay member representing the community. The REC is composed of members from various disciplines but major categories are biomedical sciences, research methods (epidemiology and biostatistics), behavioural sciences, and bioethics. The composition also considers gender equity and the maximum number of members is fifteen. Duration of member appointment is three years but this is managed in a way to promote institutional memory and good succession. The REC guidelines also state that members can only serve two consecutive terms.

The REC has a secretariat. There is a requirement that new members undergo research ethics training which covers the following: Functions and operations of a REC; research guidelines; how to conduct scientific and ethical review of protocols; and good research practice. According to the REC's standard operating procedures (SOPs), all members are required to declare potential conflicts of interest, if relevant, and must recuse themselves from deliberating and decision-making for that protocol.

The REC has a list of external experts who can be engaged to act as independent reviewers in a specific area e.g., specific diseases or study methodologies, particular community, patients, and special interest groups which are not represented among the REC membership but are applicable to a submitted research protocol. Whenever there is a need to engage an external expert to support the review process, the names of experts can only come from a standard list. This list is developed by the REC from the beginning of its term. The external expert is then informed and asked to submit a curriculum vitae. According to the SOP, external experts do not vote.

The REC has a subcommittee on participant safety that reviews adverse events and provides recommendations to the REC. The REC has a system that helps to monitor approved research. In cases of misconduct a report is generated which is reviewed by the REC and an appropriate decision is made. If there is a need for termination of a clinical trial, the investigator is informed and the REC submits a notification to the Malawi Pharmacy and Poisons Board, the National Commission for Science and Technology and the trial sponsors.

According to the REC SOPs, protocol submissions are received by the secretariat where administrative work including registration of applicants is done. All applicants are required to pay a standard fee for review and once the protocol is approved, the applicant pays 10% of the study budget. The secretariat verifies completeness of the application; if the application is incomplete, the applicants are informed within two working days. Principal investigators submit a full protocol plus a completed ethics application form for all new applications. Following this, the REC administrator assesses the risk level and decides which protocols can go for expedited review and which need full committee review. The chairperson and administrator then

assign primary and secondary reviewers based on expertise in the subject area of study. Secretariat personnel submit a package to reviewers by the tenth of every month.

According to the review process SOP, reviewers must use a standard protocol assessment form to ensure a structured process. Reviewers must submit the completed protocol assessment forms (see appendix VII) to the secretariat seven days before the full REC meeting. The issues raised by these reviewers are then compiled on a standard form and distributed during the full REC review meeting. During REC meetings, the primary reviewer presents the protocol and members discuss issues arising. If all members agree, the protocol is approved by consensus and, if there is any disagreement, the chairperson calls for a vote and a decision is made based on a simple majority vote. According to their SOP, deliberation on one protocol may not exceed thirty minutes. The secretariat documents the proceedings and retains custody of correspondence with applicants. REC meetings are conducted on pre-announced dates, set at the beginning of each year. Finally, the outcomes of the reviews are communicated to applicants within seven days of the meeting date, in writing by letter. These letters are extracted from the relevant minutes.

4.4 Data collection

Data was collected in March 2017. Firstly, a staff member from the REC secretariat sent the minutes through email to a colleague who also has access to REC minutes. The colleague went through all the minutes received and removed identifiers such as names before sending them to the researcher. Once the minutes were made available to the researcher, they were reviewed to check if there were any missing sets or missing pages. Of the expected 22 sets of minutes, three sets were missing i.e., only 19 complete sets were received. The REC secretariat confirmed that three sets of minutes were missing.

Each set of minutes contained a list of applications received and these were categorised as: new application, resubmission, student proposals, progress reports, and serious adverse events (SAEs). The study sample included new applications only.

4.5 Data analysis

Deductive content analysis (Babbie, 1998) was used to evaluate the recorded concerns. With this approach, the contents of the queries raised were analysed according to predesignated domains as per the principles and benchmarks of the Emanuel et al. (2008) framework. There was also a provision for an 'other' category to cater for issues that were not covered by the framework. Firstly, we assigned numbers to the principles and benchmarks (e.g. collaborative partnership was number 1 and the four benchmarks within this principle were 1a, 1b, 1c, and 1d, see Appendix VI). For each proposal, the concerns in the minutes were coded and the occurrence of the principles and benchmarks were recorded. Thus, the concerns from the minutes were converted to numbers assigned to a particular principle. Then the data were double entered into Microsoft

Excel (Redmond, Washington, USA).The Excel spreadsheets were convenient and provided tools for checking outliers using the filter command. Using simple descriptive univariate analysis, frequencies were generated and presented in table and graph format. This approach provided insight into how often the principles were raised.

Independently, two people reviewed each set of the minutes. The researcher (myself) and a colleague who did the coding are both SARETI scholars (2015 and 2016 intake). Throughout the SARETI course work, the coders were trained to use the Emanuel framework (2004, 2008), so it provided the coders the necessary skill for coding the data.

In the analysis, a particular concern occasionally required the use of more than one principle. In such cases we double-coded. In cases of disagreements on the application of certain principles, we were able to resolve this by reaching a consensus in our weekly meetings.

4.6 Ethical considerations

In this section, the Emanuel et al. framework (2008) is used to evaluate the present study. Firstly, this study has demonstrated collaborative partnership. This study was conceptualised by a professor of research ethics at the University of KwaZulu-Natal (UKZN) in South Africa, and the one implementing the study is his student from Malawi. Malawi's only professor of Bioethics supported the study, (see Appendix II). At the end of the research process, it will be the duty of the student researcher to share the study findings with the Malawian REC.

Secondly, this study has social value. It will generate evidence on the ethical issues commonly raised during REC review meetings, being the first such study to evaluate such issues in Malawi. Findings may be helpful to inform growing efforts to understand health research governance in the country.

Thirdly, scientific validity has hopefully been addressed. There was a need for an in-depth investigation to test how the framework is applicable to a Malawian setting. The case study design was suited to understand the 'how' question (Yin, 2013). Additionally, the use of content analysis for archived documents was the only practical approach to obtaining reliable data for this type of study. The study protocol was developed and followed without any deviation. Experienced researchers, trained in good clinical practice (GCP) and SARETI scholars did the data abstraction and coding. The design is a replication of a study by Tsoka-Gwegweni and Wassenaar, (2014).

The fourth principle in the framework is fair selection of the study population. In this study, we used minutes of meetings. Since this is a group project involving the 2013 and 2015 SARETI students, for our study to contribute to the project, we aimed at adopting a standard methodology and analytic framework including

studying minutes for a period of two years (2012-2013). However, because the Malawian REC secretariat was missing the 2012 minutes, therefore the 2013-2014 minutes were used. No human participants were involved.

After appraising the risks and the benefits of the study, we acknowledged that REC minutes are confidential and that accessing and analysing them could appear as policing the work of the REC. Similarly, a breach of confidentiality is a major risk. Considering that Malawi has two RECs that review clinical research, even if we made an agreement stating that the name of the REC would not be printed in any publication of results, it would be difficult to prevent deductive identification. Nevertheless, the study was deemed beneficial; therefore, efforts to minimise unnecessary risk were employed by removing identifiers before the minutes were made available to the researcher. The name of the REC under study will not be mentioned in any publication. Thus, we were able to attain a favourable risk-benefit ratio.

The sixth principle in the framework is the independent review of the research protocol. We can confirm that this research has received ethics approval from two independent RECs that have federal-wide assurance (FWA) numbers. One is COMREC (Appendix III and IV) from Malawi, whose FWA number is 00011868, while the other is the UKZN Biomedical Research Ethics Committee (BREC) from South Africa (Appendix V), FWA number 678. Firstly, the protocol was submitted to the UKZN BREC and provisional approval was granted on September 16, 2016. It stated that full approval would be issued only after obtaining Malawian ethics approval. The Malawian REC approved the study on December 1, 2016, and an amended approval was issued February 1, 2017. This amendment was done to change the study duration of minutes from 2012-2013 to 2013-2014. The researcher then submitted the COMREC approvals to UKZN BREC and full approval was obtained on March 17, 2017 (BCA 342/16).

The seventh principle to consider is informed consent. The nature of the study did not require individual informed consent. It just required the gatekeeper's approval and this approval was obtained when the REC accepted the proposal to have the minutes studied by the researcher and ethics approval was issued.

The eighth principle is respect for recruited participants and study communities. In this study, the REC chairperson will read the draft report to ensure that he accepts findings before wider dissemination of the results. The results will be shared with the REC in question.

4.7 Validity, reliability, generalisability and reflexivity

When evaluating the internal validity of a study, the key consideration is whether the conclusions from the findings follow from the data and the procedures used in this research. The researcher started by developing a study protocol which was approved by two RECs and then the researcher followed the research protocol without deviations. Two researchers independently coded the data throughout the analysis. The engagement

of a second coder was aimed at comparing and discussing the principles used, in an effort to reduce bias (Baxter & Jack, 2008).

Reliability is generally understood to concern the replicability of research findings and whether or not they would be the same if another study using the same or similar methods was undertaken. In addition, Richie and Lewis (2003) report that there are some schools of thought which believe that qualitative research is dynamic and should only be conducted effectively in a responsive manner; however, they urge that such studies can never be, nor should be, repeated. Despite this reported line of thinking, this study sought to find ways of increasing reliability. In our case, confirmability and 'trustworthiness' will be considered (Richie & Lewis, 2003). Confirmability in the study was achieved by asking the chairperson of the REC being studied to review the final report before dissemination of the results (Baxter & Jack, 2008). Additionally, well-known Malawian REC members were consulted periodically throughout the research process. This consultation process hopefully makes the findings of this study trustworthy.

Generalisability refers to the extent to which findings from a study apply to a wider population or to different contexts. As described by Green and Thorogood (2007), in a sample survey, random sampling is likely to be statistically representative of the larger population of interest, so findings can be extrapolated to that population. However, in our case, no random sampling was involved but purposive sampling was used to study the 2013 and 2014 minutes. Of the 22 meetings held, 19 sets of minutes were studied. In addition, generalisability from this type of sampling arises from conceptual transferability of the concepts generated rather than statistical representativeness of the sample (Green & Thorogood, 2007). The hope is that the findings from this study are helpful to the health research ethics community in Malawi. Considering that this is a relatively under-researched topic, generalisability may be less salient than that of 'sensitising' the research community (Green & Thorogood, 2007). Researchers may be sensitised to research ethics data relevant to the Malawian context. The present study is a replication of an existing design by Tsoka-Gwegweni and Wassenaar, (2014) which should enhance reliability and validity.

Reflexivity is a process whereby the researcher considers how her own values, life experiences and assumptions have influenced the research (Pitard, 2017). In the present study the investigator is a Malawian who has worked as an IRB officer for three years at a biomedical research institution in the country. As an IRB officer, her role was to guide principal investigators on regulatory and ethical issues and respond to concerns raised by the Malawian RECs. Therefore the researcher was keen to learn the decision-making outcomes of the Malawian REC under study so as to identify training areas in her institution and also to find areas in which the REC can improved. Furthermore, Pitard (2017) states that the researcher also ought to consider the trustworthiness and rigour of research design and methodology. The investigator interacted with members of the REC secretariat and it was easy to consult occasionally in order to understand the contents of the minutes. These consultations were made to enhance trustworthiness of the study findings.

Overall, all the study procedures were followed without deviation to enable the researcher to move from research questions to its answers (Yin, 2013). The next chapter details the results of the study.

CHAPTER 5: RESULTS

5.1 Introduction

This chapter presents findings of the content analysis study that was done on the 2013 and 2014 minutes of REC protocol review meetings. The analysis excluded expedited and continuing reviews, resubmissions, protocol amendments, annual reports, study final reports, and any other reports. The findings are from the recorded minutes of newly submitted protocols during the study period.

The results describes the ethical issues raised during review of proposals and the ranking of ethical issues and concerns raised using Emanuel et al.'s (2004, 2008) framework to understand whether they do or do not fit the framework. However, the first section outlines a summary of the research protocols that were reviewed and received queries.

5.2 Data summary

A total of 139 protocols was submitted for ethics review. Of these, 3(2.1%) protocols received full approval on initial submission and 136 (97.8%) received various comments. Of the 136 protocols that attracted comments, 52 were reviewed in 2013 and 84 were reviewed in 2014. Figures 1, 2 and 3 presents summaries of the study designs of the 136 protocols while Table 2 presents their areas of study. Fig 4 presents outcomes of the review meetings.

Fig 1: Summary of protocols reviewed in 2013 and 2014

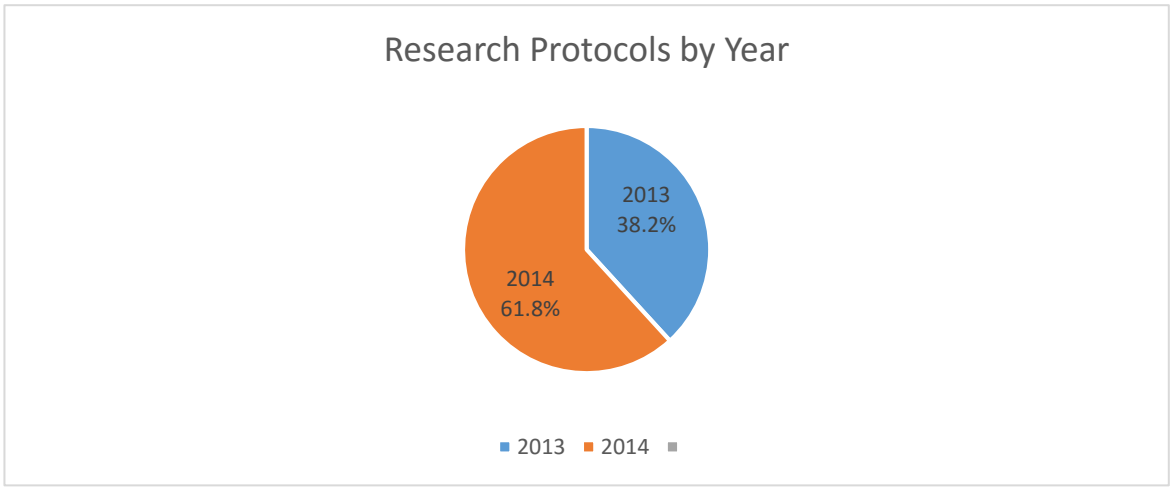


Fig 2: Study designs proposed in the reviewed research protocols

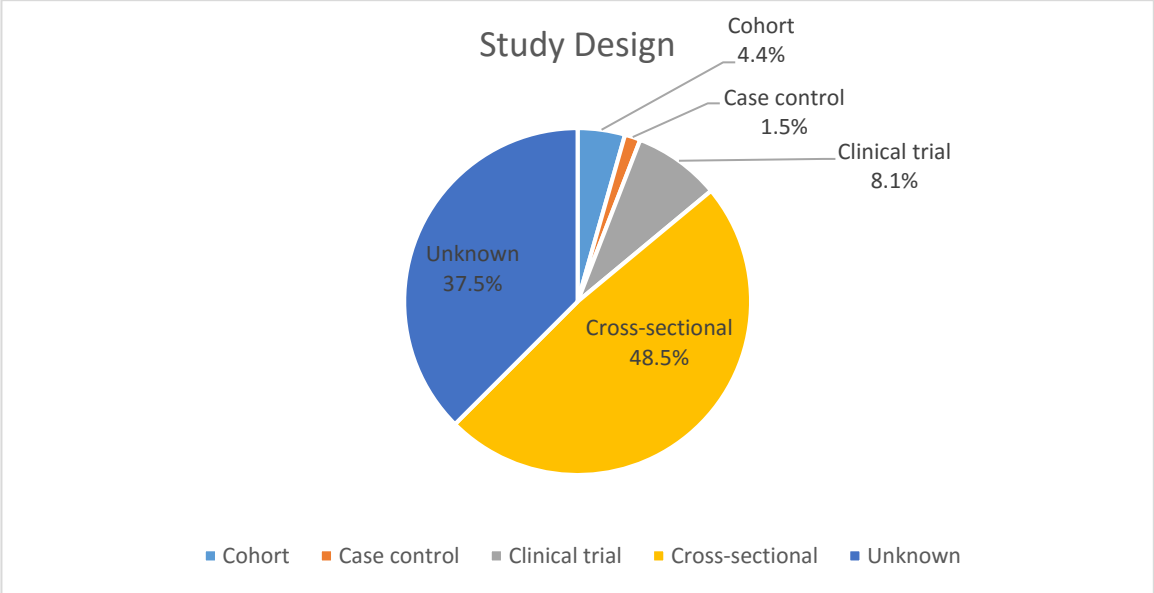


Fig 3: Proposed research participants in the reviewed protocols

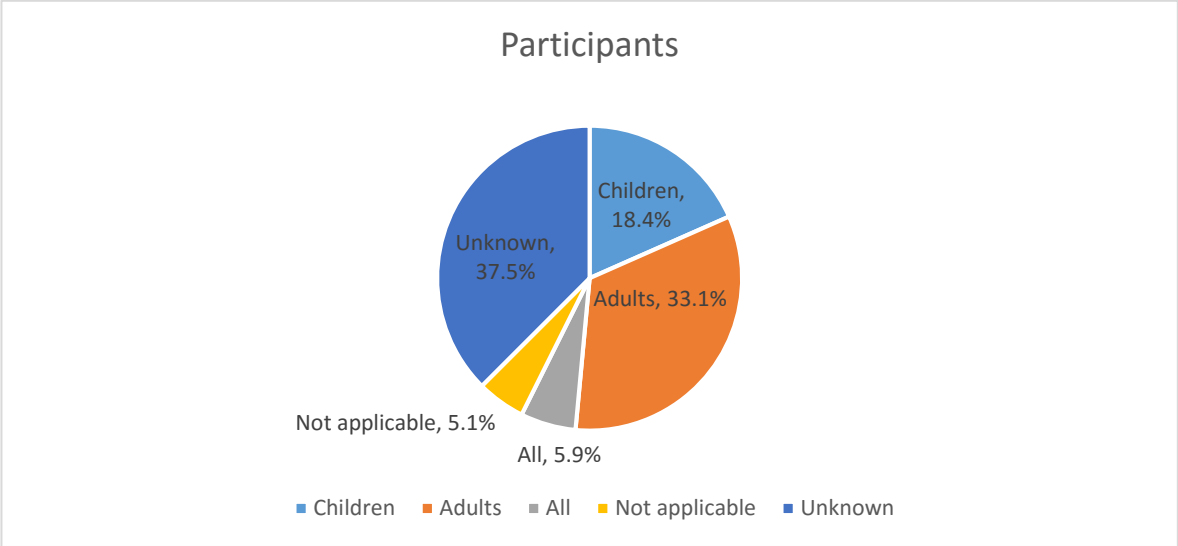


Fig. 3 shows that, of the 136 protocols, 33.1% proposed research on adults, 18.4% on children only, 5.5% on both adults and children, and 37.5% had unknown participant demographics because these were not recorded in the minutes. Furthermore, 5.1% of protocols were listed as 'not applicable' because they used records or laboratory stored samples as their data source. Fig. 2 shows that among the reviewed protocols, 48.5% proposed a cross-sectional study design, while 37.5% were listed as unknown design because these were not recorded in the minutes. There were also 8.1% clinical trials, 4.4% cohort studies, and 1.5% case control studies.

Table 2: Summary of Proposed Study Area (*N*=136)

Study Focus	Number	Percentage
Malaria	18	13.2%
HIV	16	11.8%
Reproductive health	12	8.8%
Health system strengthening	10	7.4%
Maternal and child health	7	5.1%
Nutrition	6	4.4%
TB	5	3.7%
Cancer	4	2.9%
Unknown	4	2.9%
Diabetes	3	2.2%
Disability	3	2.2%
Eye	3	2.2%
Haematology	3	2.2%
HIV & Cancer	3	2.2%
Nursing education	3	2.2%
Pneumonia	3	2.2%
Ear and hearing care	2	1.5%
Epidemiology of diseases	2	1.5%
Influenza	2	1.5%
Rotavirus	2	1.5%
Trauma	2	1.5%
Amblyopia	1	0.7%
Antibiotic use	1	0.7%
Autism & Malaria	1	0.7%
Bronchoscopy	1	0.7%
Burns	1	0.7%
Heart	1	0.7%
Diarrhoea	1	0.7%
Ethics	1	0.7%
Family medicine	1	0.7%
Family planning	1	0.7%
HIV & Cardio-respiratory Disorders	1	0.7%
HIV & Diabetes	1	0.7%
HIV & Diabetes & Hypertension	1	0.7%
Hygiene	1	0.7%
Hypertensive Retinopathy	1	0.7%
Kidney injury	1	0.7%
Malaria & HIV	1	0.7%
Medicine education	1	0.7%
Health	1	0.7%
Pharmacy education	1	0.7%
Radio programme evaluation	1	0.7%
Respiratory infection	1	0.7%
Schistosomiasis	1	0.7%

Table 2 presents the area of study and it shows largest proportion of the proposals intended to study malaria (13.2%), then HIV (11.8%), and reproductive health (8.8%).

Fig 4: Outcomes of protocol review (*N*=136)

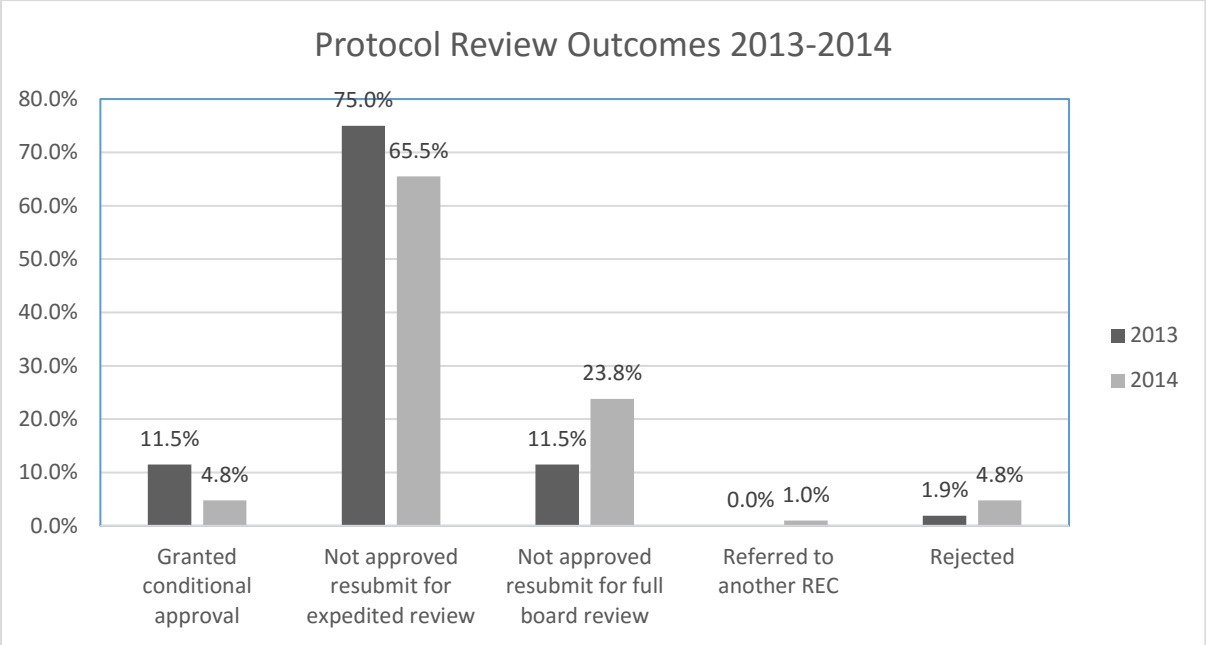
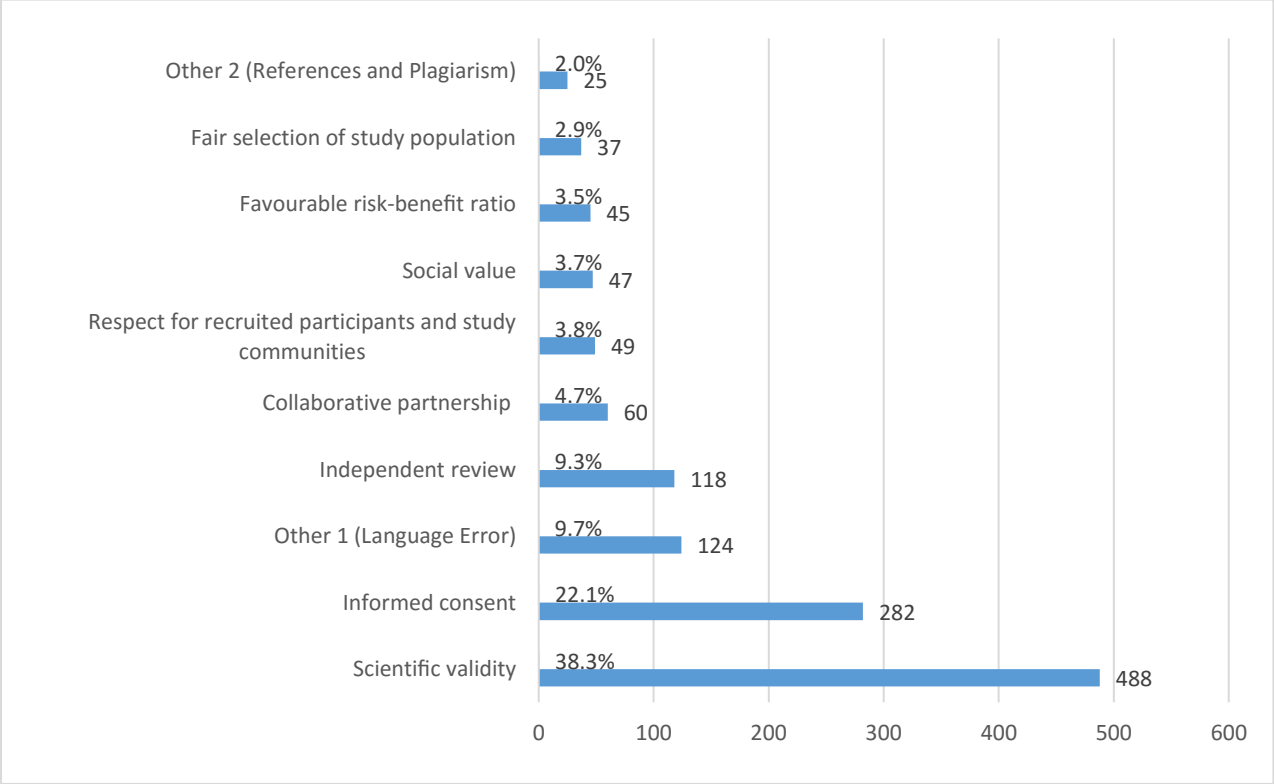


Figure 4 shows the final decision of the review process. There were very few protocols that the Malawian REC approved on initial submission. Likewise, there were very few protocols were rejected outright, although there was an increase of such rejections in 2014.

5.3 Issues and Patterns of ethical concerns raised by a Malawian REC

A total of 1,274 concerns were raised. Figure 1 shows the distribution of concerns using the Emanuel et al framework (2004, 2008) and other concerns that did not fit in the framework. The highest proportion of the concerns raised were issues concerning scientific validity (487; 38.2%), followed by informed consent (282; 22.1%), and independent review (118; 9.3%). Then, issues concerning collaborative partnership (60; 4.7%), respect for participants (49; 3.8%), social value (47; 3.7%), favourable risk-benefit ratio (45; 3.5%), fair selection of participants (37; 2.9%) were also raised. Furthermore there were other concerns such as language errors (124; 9.7%) and inappropriate references/plagiarism (25; 2%) which are not part of the Emanuel et al framework (2004, 2008).

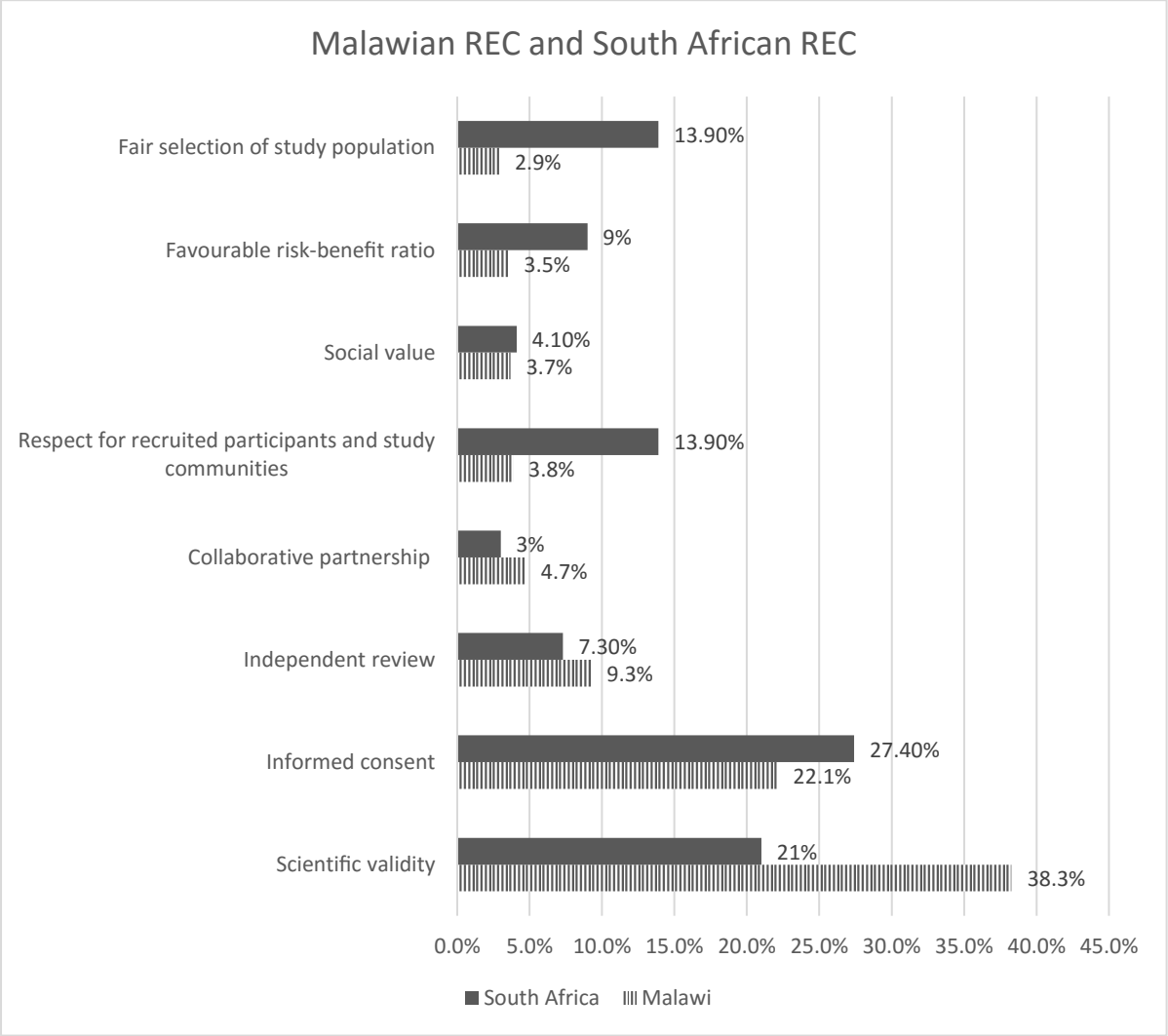
Figure 5: Pattern of queries raised by a Malawian REC in 2013 and 2014 (*N*=1,274)



5.3.1 Comparison of patterns of ethical issues raised by a Malawian REC (*N*=1,274) and South African RECs (*N*=1,043)

Although not a stated goal of this study, it was decided to compare the Malawian data with some South African findings that used the same methodology. Figure 5 shows findings from the present study and findings from the study by Tsoka-Gwegweni and Wassenaar (2014) in South Africa. The South African REC had informed consent (24.7%) and scientific validity (21%) covering the highest proportion of the concerns raised during review of research protocols; these are the same top two concerns from the Malawian REC but the ranking is different.

Figure 6: Graph comparing ethical concerns from a Malawi REC and South African RECs



5.4 How well the ethical issues fit the Emanuel et al. (2004, 2008) framework

When all the queries of the reviewers were coded and counted in the minutes of the 136 protocols, it was found that 88.8% of 1,274 queries raised could be accommodated or coded by using the eight Emanuel et al. (2008) principles. Queries that could not fit in the framework were coded as language errors (10%) and inappropriate referencing and plagiarism (2%) (see Table 3 below). In Table 3, details of the queries have been disaggregated by principles and benchmarks.

In terms of ranking the issues by principle, scientific validity was the most frequent principle. This covered issues dealing with appropriate study design and methods, with issues raised mostly because of unsound statistical methods (64.3%), feasibility of study design (25.2%), and applicability of study findings (9.8%).

Informed consent was ranked as the second most frequently raised concern. Major issues emerging were dealing with inadequate information: presentation of accurate information (41%), recruitment and incentives not applicable to local context (27%), gatekeeper permission missing (21%), and inadequate disclosure in the study documents and processes (21%).

The third most frequent queries were issues concerning language errors (10%). These are incomplete sentences, grammar, and typographic errors. The Emanuel et al. (2004, 2008) framework does not have a principle relating to language issues as these are administrative rather than ethical concerns.

Principle of independent review ranked fourth in the present study. There were concerns regarding lack of compliance with REC regulations; 93% issues dealing with regulations of the REC and efforts to minimize multiple review (7%).

Collaborative partnerships ranked fifth in the study findings; the concerns were about the sharing of responsibilities among research partners and ensuring fair research benefits the host community. The principle of collaborative partnership were about sharing of responsibilities (66.1%), respect for local context (13.6%), fair research benefits for communities (10.2%), and community representation (10.2%).

Of the total queries (*N* =1,274), 4% were about the principle of respect for participants, 4% were on social value of the study, 4% were about favourable risk-benefit ratio, 3% were on fair selection of participants, and 2% were issues to do with inappropriate references and plagiarism.

Table 3: Using the Emanuel et al. (2008) framework to rank queries raised (Ranked descending)

Principle and benchmarks			No. of queries	Percent
Scientific validity			**488**	**38%**
	3a	Appropriate design and methods	314	64.3%
	3d	Study design feasibility	123	25.2%
	3b	Applicability of results	48	9.8%
	3c	Impact on provision of health care	3	0.6%
Informed consent			**282**	**22%**
	7c	Presentation and accuracy of information	117	41%
	7a	Recruitment and incentive applicability to local context	77	27%
	7e	Gatekeeper permission	58	21%
	7b	Appropriate disclosure documents and processes	22	8%
	7f	Context of consent process	5	2%
	7g	Respect for autonomy	2	1%
	7d	Legally authorized representative	1	0%
Other 1 (Language errors)			**124**	**10%**
	9a	Language errors (grammar, typing errors, incompleteness)	124	100%
Independent review			**118**	**9%**
	6a	Regulatory compliance	110	93%
	6b	Minimization and reconciliation of multiple reviews	8	7%
Collaborative partnership			**59**	**5%**
	1b	Sharing responsibilities	39	66.1%
	1c	Respect for local context	8	13.6%
	1d	Fair research benefits for community	6	10.2%
	1a	Community representatives	6	10.2%
Respect for recruited participants and study communities			**49**	**4%**
	8b	Confidentiality and privacy	26	53%
	8c	Voluntariness	12	24%
	8d	Research results dissemination	9	18%
	8a	Monitoring health and well-being	2	4%
Social value			**47**	**4%**
	2c	Enhancing research benefits	24	51.1%
	2d	Impact on health system	10	21.3%
	2b	Research benefits	9	19.1%
	2a	Research beneficiaries	4	8.5%
Favourable risk-benefit ratio			**45**	**4%**
	5a	Risk identification and minimization	42	93.3%
	5b	Type, probability, and magnitude of benefits	3	6.7%
Fair selection of study population			**37**	**3%**
	4a	Suitable study population	18	48.6%
	4b	Risk minimization	12	32.4%
	4c	Benefits to participants	4	10.8%
	4d	Vulnerability	3	8.1%
Other 2 (References and plagiarism)			**25**	**2%**
	10a	Inappropriate referencing and plagiarism	25	100%

In summary, the findings can be described as follows; 139 protocols were reviewed as initial submissions, out of which 3 protocols (2.2%) were approved, 5 protocols (3.7%) were rejected and 131 protocols (94.2%) required modification and resubmission for either expedited review or further full REC review. The REC raised 1274 concerns, and among these 88.8% were accommodated or coded using the eight principles of the Emanuel et *al.* Framework (2008) as follows; scientific validity (38.3%), informed consent (22.1%), independent review (9.3%), collaborative partnership (4.7%), respect for recruited participants (3.8%), Social value (3.7%) ,favourable risk benefit ratio (3.5%) and fair selection of study population (2.9%). Other queries frequently raised were 9.7% language errors and 2.2% inappropriate referencing and plagiarism. These results will be discussed in the next chapter.

CHAPTER 6: DISCUSSION

6.1 Identifying and ranking ethical concerns raised during research protocol review meeting

In the present study, most of the REC's concerns could be coded using the principles and benchmarks of the Emanuel et al. (2004, 2008) framework. In terms of using the eight principles and benchmarks, Emanuel and colleagues (2004, 2008) cautioned that differences in health, economic, social, and cultural aspects of a research setting will affect its application. It is therefore expected that priorities or weights given to particular principles in the ethical framework may differ across research settings. However, this differences does not mean that the principles and benchmarks are relativistic; rather, it means that the adaptation and balancing of universal principles are relative to risk, resources, social practices, and similar circumstances (Emanuel et al., 2004).

The Malawian REC most frequently raised issues about the scientific validity of a research project. Scientific merit was important to this REC in this setting. These findings contradict some reports that RECs do not pay sufficient attention to scientific rigor (Altman, 1994). If study design is unscientific, it affects interpretation and the research participants are exposed to unnecessary risk. Freedman (1987) highlighted that a study cannot become ethical by trading some deficiency in scientific worth, even if the researchers can develop good consent procedures. Valid design is a non-negotiable requirement. Humphreys et al. (2014) interviewed REC members who described that participant safety and ethics factors could only be deemed appropriately addressed if the study methods are scientifically sound. They agreed that sound design was necessary for approval of a research protocol. In another study by Silaigwana (2017; Silaigwana & Wassenaar, 2019), it was reported that some members of a REC (22.25%) felt that it was not their duty to raise queries related to scientific validity. Nonetheless, scientific validity is an international ethical principle (Emanuel et al., 2004, 2008) and can best be described by quoting Rutstein (1969).

> "It may be accepted as a maxim that a poorly or improperly designed study involving human subjects - one that could not possibly yield scientific facts (that is, reproducible observations) relevant to the question under study - is by definition unethical. Moreover, when a study is in itself scientifically invalid, all other ethical considerations become irrelevant. There is no point in obtaining 'informed consent' to perform a useless study. A worthless study cannot possibly benefit anyone, least of all the experimental subject himself. Any risk to the patient, however small, cannot be justified. In essence, the scientific validity of a study on human beings is in itself an ethical principle." (Rutstein, 1969, p. 524),

As mentioned in an earlier section, scientific validity is duly included as an ethical principle in the framework by Emanuel et al. (2004, 2008). The current findings suggest that this Malawian REC saw scientific validity as an integral element of ethics review and sought to protect participants from invalid and scientifically flawed study designs. Furthermore, the findings show that a significant number of studies reviewed did not fulfil

standard requirements for valid research, suggesting the need to strengthen scientific peer review before REC submission.

During the study period, most of the reviewed proposals were not sponsored studies or drug trials. Ordinarily sponsors play a major role to ensure high quality studies are implemented. A recent study by Happo, Halkocho, Lehto and Keranen (2016) found that most concerns relating to study methods arose from non-industry sponsored clinical trial. These were research protocols that did not involve physical procedures. CIOMS (2016) states that research conducted in low- and middle-income countries must be submitted to and approved by RECs in both sponsor and host countries. The lack of sponsorship may have adversely influenced the scientific quality of studies submitted to the Malawian REC. Likewise, more than half of studies which were reviewed during the study period were cross-sectional studies. Researchers may have had limited resources to hire experts to assist with designing their studies. Partnership or collaboration to improve scientific research design may be required and encouraged among Malawian researchers.

As indicated earlier the present study is a replication of a study by Tsoka-Gwegweni and Wassenaar, (2014). Present findings show that the issues frequently raised are similar, although the order of priority is different. In Malawi, Informed consent was the second most frequently raised concern while in South Africa this was the most frequently raised issue. Another study done on RECs elsewhere found that informed consent was the most queried issue (Dixon-Woods, 2008). In addition Lidz et al. (2012) also reported that 98% of the reviews in their study raised questions about informed consent. The Malawian REC was concerned about inaccurate information given to the participants, incentives that were not applicable to local context, and lack of gatekeepers' permission and requests for waiver of consent. The REC was assessing the information in the consent forms considering the literacy levels of most study participants. There is a general presumption that informed consent must be obtained in research involving humans unless a waiver of consent is approved by the REC. The quality of information given to the research participant is crucial. Authors like Beauchamp and Childress (2013) have explained that for many years obtaining consent was marked as a primary obligation for researchers, but in recent years, the focus has shifted from the researchers' obligations and now it is about disclosing information appropriate to the quality of the subjects' understanding and ability to consent, thus suggesting that quality of informed consent is key. These findings suggest that applicants need to apply this shifting dynamic and invest more effort into the development of necessary approaches to ensure research participants are receiving accurate and easy-to-understand information in order to facilitate valid informed consent. There were cases in which researchers were seeking a waiver of consent. The waiver of consent policy in Malawi is very strict but the REC can explore conditions which may allow the consent form to be waivered or altered.

In Malawi, informed consent is a legislative requirement enshrined in section 19.5 of the Constitution of Malawi which states: “No person shall be subjected to medical or scientific experiment without his or her consent” (Constitution of the Republic of Malawi, 1996). Ordinarily, Malawian RECs do not allow a waiver of consent for studies involving identifiable research participants.

Most of the issues raised within the third-ranked principle of independent review were related to compliance with REC regulations such as payment of review fees and not including the ten percent research budget. Most often, applicants were requesting a waiver despite their eligibility to pay the required fees. It must be noted that an ideal REC must be well-financed and, considering the Malawian setting, the most practical way to finance the REC is through collecting such revenue. However, it is also a burden on researchers who are not sponsored. The regulations may also influence some researchers who are sponsored to submit false budgets for review. In addition, there were issues dealing with improper documentation of material transfer agreements. Malawian RECs do not approve sample collection and storage for unspecified study, hence material agreement forms were receiving much scrutiny. In some cases, investigators were requested to provide REC approval if the researcher stated there was more than one REC reviewing the protocol.

In the present study, almost five percent of all queries focused on the fourth-ranked principle of collaborative partnership. In the South African study (Tsoka-Gwegweni & Wassenaar, 2014), it was only three percent of queries. A majority of the concerns focused on asking for collaborating investigators to clearly document their roles in the protocol and the need to consider or respect cultural values in the selected study area. These results suggest that the REC is working to ensure fairness in the distribution of burden to conduct research and benefits among collaborators. Anecdotal evidence suggests that some investigators are included in the protocol for the sake of honour and sometimes even included during publication as gift authors. Asking the applicants to clearly indicate their roles and responsibilities may be a deliberate effort to bring about fairness among local and international investigators. Furthermore, an issue worth noting is the history of this particular principle in the Malawian setting. Initially the Emanuel et al. framework had seven principles (Emanuel et al., 2004). Later, the eighth principle of collaborative partnership was added (Emanuel et al., 2008). In his book Mfutso-Bengo (2016) reports that, in 2001, Malawi hosted a National Institutes of Health (NIH)-funded international conference, which was attended by over 200 African and international delegates to discuss emerging bioethical issues in Africa. Out of this bioethics conference, one additional concept that emerged was the concept of collaborative partnership and was added to the seven previous research ethics principles listed by Emanuel and colleagues (Emanuel et al, 2000). The present study found that queries relating to the collaborative partnership principle were considerably higher compared to South African findings. We can speculate that the 2001 conference may have had a lasting impact on Malawian RECs to put substantial value on this principle, unless the variance is due to coding differences.

The principles of respect for recruited participants, favourable risk-benefit ratio, and fair selection of study population directly relate to participants' well-being. The data from the study show there were very few clinical trials but more cross-sectional studies. Furthermore, a number of protocols had non-physical procedures hence considered lower risk studies. It is therefore not surprising that very few concerns were raised that are directly affecting a study participant's well-being compared to the SA study which had at least 31 clinical trials. In some protocols, the principle of social value was raised where it was deemed that the research activity was likely to compromise health service delivery at a health facility.

6.2 Issues commonly raised during review meeting that were not accommodated by the Emanuel et al (2008) Framework

Some other concerns frequently raised could not be accommodated in the framework such as grammar, typographic errors, inappropriate referencing, and plagiarism. These were coded as 'other' additional concerns. According to the recorded minutes, ten percent of all queries exhibited typographic errors. These are not ethical issues but were identified and considered unacceptable by the REC. We can only speculate that the applicants rush through their work in order to submit within REC deadlines and that might prevent them from having their work edited for language and grammar. Cleaton-Jones (2010) reported that 15 percent of applications to the University of Witwatersrand REC received queries related to typing errors and incomplete applications. On the other hand, Amdur and Bankert (2011) suggested that typos should not be raised in REC's review unless meaning is obscured. In most of the concerns raised in the present study, the REC was requesting the applicant to proof-read the entire protocol due to numerous typing errors that made the meaning unclear. The secretariat of the REC must ensure completeness of the submissions and should not accept incomplete applications; only completed applications should be sent for review by the committee. Considering that most Malawian REC members are academics, applicants need to put in more effort and proof-read the entire protocol before submission.

Similarly, issues of inappropriate referencing and plagiarism were raised frequently. Among the highlighted issues were cases where the applicants were informed that the references provided did not contain the concepts or the data cited in the section or paragraph. Wassenaar (2006) highlights that the original purpose of research ethics is to protect the welfare of research participants but its concerns are now extending into areas such as scientific misconduct and plagiarism. It is commendable if RECs are able to identify and raise plagiarism concerns although it is difficult to identify plagiarism manually unless technology tools such as Turnitin are in used as part of the pre-review analysis, possibly by the REC secretariat.

6.3 Limitations of this study

Despite involving two trained coders for the content analysis, it is possible that some concerns raised in the minutes were not coded correctly, as such it has a bearing on the frequencies of principles used. In addition, the years sampled my not adequately represent the work of the REC over many years.

6.4 Conclusion

This content analysis of a Malawian REC minutes has identified the most frequently raised ethical issues during protocol review meetings and the pattern of issues raised. Most of the issues frequently raised could be accommodated by the Emanuel et al. (2004, 2008) framework. Scientific validity and informed consent issues were frequently raised. The top ranked concerns were directed at the investigators to ensure appropriate study design, followed by consent-related issues. The quality of science in the protocols and the quality of information given to participants were prioritised. The Malawian and South African RECs studied so far have therefore put much weight onto these two principles of the Emanuel et al framework (2008), suggesting that these issues may warrant further careful attention by future research ethics applicants, and should be a focus of research and research ethics training.

6.5 Recommendations

1. Scientific peer review within research institutions should be promoted and encouraged before Protocol submission for REC approval. This may reduce the relatively high number of scientific validity queries raised by the REC.
2. Malawian Researchers who are self-funded should consider collaborating with experts in study design and analysis because employing an Epidemiologist or statistician may be expensive. If collaboration is challenging, the researchers must consider involving the services of the Research Support Centre at College of Medicine to strengthen the quality of science in the research protocol. This may also reduce the relatively high number of scientific validity queries raised by the REC.
3. Researchers should consider involving language editors to proof read their protocols before REC submission. This may reduce the relatively high number of typos and grammatical queries raised by the REC. In turn, REC members should be trained not to raise grammatical queries unless they obscure the meaning of the protocol.
4. The Malawian REC should consider developing a standard informed consent guidance template to ensure that researchers addressing all the legally and ethically required issues in the Malawian context. This may reduce the relatively high number of informed consent related queries raised by the REC

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APPENDICES

Appendix I: Request for permission to access protocol review minutes from UKZN thesis Supervisor

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

The Chairman
[redacted]
Blantyre
Malawi

18 July 2016

Dear Sir,

REQUEST FOR PERMISSION TO ACCESS [redacted] PROTOCOL REVIEW MINUTES: MS TIWONGE KUMWENDA-MTANDE

Ms Tiwonge Mtande is a Malawian student registered for a Master's Degree in Social Science (Health Research Ethics) at the University of KwaZulu-Natal (UKZN).

Ms Mtande was awarded a scholarship from the South African Research Ethics Training Initiative (SARETI) whose objective it is to train African scholars in the field of research ethics.

Ms Mtande is currently working on her dissertation and is interested in replicating the study by Tsoka-Gwegweni and Wassenaar, 2014 (article attached). Her study requires access to review minutes of research ethics committees and she hopes to use the [redacted] protocol review minutes from January 2012 to December 2013. Institutional and minuted data will be anonymized in reports on the project.

This letter therefore serves to seek your kind permission before the study proposal is submitted for review at the National Health Science Research Committee in Malawi and the Biomedical Research Ethics Committee (BREC) in South Africa.

Sincerely,

Douglas Wassenaar, PhD
Principal Investigator: SARETI

South African Research Ethics Training Initiative
SARETI
http://sareti.ukzn.ac.za/Homepage.aspx
Fogarty International Center, National Institutes of Health
Grant Number 5 R25 TW01599-16

School of Applied Human Sciences
University of KwaZulu-Natal
Private Bag X01
Scottsville 3209
Pietermaritzburg
South Africa
Phone: +27 33 260 6162
Fax: +27 33 260 5809

Appendix II: Support letter requesting for permission to access protocol review minutes

Blantyre 3
Malawi
Telephone: 01 871 911
01 874 107
Fax: 01 874 700

Our Ref.: comrectiwo1

Your Ref.:

6th November 2016

From:
Full Professor Joseph Mfutso-Bengo
Head, Health Systems and Policy Department
School of Public Health-College of Medicine
University of Malawi
Private Bag 360
BLANTYRE 3
Malawi
Email: josephbengo@gmail.com
+265999957805

To:
The Chairman,
College of Medicine Research Committee,
Private Bag 360,
Blantyre,
Malawi.

Dear Sir,

A letter of support for by Tiwonge Mtande.

This is to advise your office that Tiwonge Mtande research project is being co-supervised by me.

I wish to send the letter of support to conduct a research ethics study.

The study aims to identify the main ethical issues raised during ethics review of research proposals submitted to [redacted] and assess their relative weight using Emanuel et al.'s (2004;2008) recommended principles of ethical review of clinical research.

This is a very important study and the results will could contribute to the understanding of [redacted] ethical decision-making and review process.

Yours faithfully,



Prof Joseph Mfutso-Bengo PhD
Head Health, Department of Systems and Policy
Director, Center of Bioethics for Eastern and Southern Africa (CEBESA)
UNESCO Bioethics Unit

Appendix III: Certificate of Ethics Approval from COMREC



CERTIFICATE OF ETHICS APPROVAL

This is to certify that the College of Medicine Research and Ethics Committee (COMREC) has reviewed and approved a study entitled:

P.10/16/2051 – Ethical issues raised by a Malawian research ethics committee by Tiwonge Mtande

On 1st December 2016

As you proceed with the implementation of your study, we would like you to adhere to international ethical guidelines, national guidelines and all requirements by COMREC as indicated on the next page

Dr. C. Dzamalala- Chairperson (COMREC)

Approved by College of Medicine
01 DEC 2016
(COMREC)
Research and Ethics Committee

1st December, 2016
Date

Appendix IV: Protocol Amendment Approval from COMREC

COLLEGE OF MEDICINE

Principal
M. H. C. Mipando MSc PhD

College of Medicine
Private Bag 360
Chichiri
Blanytre 3
Malawi

Our Ref:

Telephone: 01 871911 Your Ref: P.10/16/2051 01 874107

Fax: 01 874 700

1st February 2017

Ms. Tiwonge Mtande
C/O Mr. Sunganani Mtande
Times Group
P/Bag 39
BLANTYRE

Dear Ms. Mtande,

RE: P.10/16/2051 – Ethical issues raised by a Malawian research ethics committee version 1.2 dated 05/09/2016

I write to inform you that COMREC reviewed the amendment to the above captioned proposal which you submitted for review. I am pleased to inform you that COMREC **approved** the following amendment:

1. To change duration of minutes to be studied from (2012-2013) to (2013-2014)

As you proceed with implementation, please adhere to the college requirements per attached page.

Yours Sincerely,

Dr. YB Mlombe
COMREC CHAIRMAN

YM/ck

REQUIREMENTS FOR ALL COMREC APPROVED RESEARCH PROTOCOLS

1. Pay the research fees as required by College of Medicine for all approved studies.

2. You should note that the follow-up committee will monitor the conduct of the approved protocol and any deviation from the approved protocol may result in your study being withdrawn.

3. You will provide an interim report in the course of the study and an end of study report.

4. You are required to obtain a continuation approval after 12 months from the date of approval.

5. All investigators must be fully registered with the Medical Council of Malawi.

Appendix V: UKZN BREC Approval

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

17 March 2017

Ms Tiwonge Mtande (Student No: 215078234) (Malawi)
c/o Prof D Wassenaar (PI of Study)
Discipline of Psychology
School of Applied Human Sciences
wassenaar@ukzn.ac.za

Dear Ms Mtande

CLASS APPROVAL

Protocol: Ethical issues raised by African Research Ethics Committees.
***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*). Your response dated 08 February 2017 in response to BREC letter dated 26 September 2016 has been noted by BREC.**

This approval is valid for one year from **17 March 2017.** 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 **11 April 2017.**

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

Yours sincerely

Professor V Rambiritch
Deputy Chair: Biomedical Research Ethics Committee

cc: **Ms Tiwonge Mtande**
Postgraduate officer: khanyilet@ukzn.ac.za

Biomedical Research Ethics Committee
Professor J Tsoka-Gwegweni (Chair)
Westville Campus, Govan Mbeki Building
Postal Address: Private Bag X54001, Durban 4000
Telephone: +27 (0) 31 260 2486 **Facsimile:** +27 (0) 31 260 4609 **Email:** brec@ukzn.ac.za

Appendix VI: Data collection sheet

REC Codename: _____

Protocol no: _____

Instruction: Review recorded minutes of each protocol reviewed, code the frequency with which the following issues were raised. Some issues can occur several times in the review of a single protocol, these must be included.

1. Collaborative Partnership
    a. Community representatives
    b. Responsibility sharing
    c. Respect for local context
    d. Fair research benefits for community
    e. Sharing research products
2. Social Value
    a. Research beneficiaries
    b. Research benefits
    c. Enhancing research benefits
    d. Impact on health systems
3. Scientific Validity
    a. Appropriate design and methods
    b. Applicability of results
    c. Impact on provision of health care services
    d. Study design feasibility
4. Fair Participant Selection
    a. Suitable study population
    b. Risk minimization
    c. Benefits to participants
    d. Vulnerability
5. Favourable risk–benefit ratio
    a. Risks identification and minimization
    b. Type, probability and magnitude of benefits
    c. Comparison of risks and benefits
6. Independent Ethics Review

    a. Regulatory compliance
    b. REC members conflict of interest
    c. Transparent review
    d. Minimization and reconciliation of multiple reviews
7. Informed Consent
    a. Recruitment & incentives applicability to local context
    b. Appropriate disclosure documents and processes
    c. Presentation and accuracy of information
    d. Legally authorized representatives
    e. Gatekeeper's permission
    f. Context of consent process
    g. Respect for autonomy
8. Ongoing respect for participants
    a. Monitoring health and well-being
    b. Confidentially and privacy
    c. Voluntariness
    d. Research results dissemination
    e. Post-research obligations
9. Other 1
10. Other 2
11. Other 3

Appendix VII: REC A Review Of Research Protocols

TITLE OF STUDY:_____

PRINCIPAL INVESTIGATOR:_____
REVIEWER:_____
DATE OF REVIEW:_____
OVERALL RECOMMENDATION: _____

1. Briefly summarize proposed research. What is the research about, how will it be done and why is it important to do the study. Comment on its strength and/or weakness

SCIENTIFIC SECTION:

1. Comment on the objective (s) and design of study

2. Comment on the proposed methods to address the objectives

3. Comment on the setting, study population, recruitment process

4. Comment on sample size calculation and selection of sample

5. Comment on data collection method and statistical analysis

6. Comment on factual accuracy or error in the protocol

ETHICAL SECTION

1. Comment on the risks involved, have they been all identified?

2. Comment on the informed consent, have all the risks been explained in the consent form. **Have they been adequately addressed?**

3. Comment on any other risk that may occur as a result of participation in the study/standard of care issue

4. Comment on whether the confidentiality, direct benefits, indirect benefits

5. Comment on possible Adverse Events and how they will be addressed

6. Comment on sample collection, storage and testing/shipping samples outside the country. Justification of, or shipment of sample

7. Comment on randomization/use of placebo if applicable

ADMINISTRATIVE SECTION

1. Comment on the adequacy of budget to conduct study

2. Comment on the personnel including the qualifications of the investigation team

3. Comment on presentation format errors: indicate page, paragraph and error

4. Comment on any direct benefit to College, Department, etc

DECISION – Give reasons for approval/not approved or any other recommendations