Comparison of Research Ethics Committees (RECs) review of protocols reviewed by multiple ethics review committees.

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ABSTRACT

As high-impact diseases have increased, so have the collaborative efforts to alleviate their effects. These collaborative efforts have gone beyond borders, resulting in collaborative research between low- and middle-income countries (LMICs) and high-income countries (HICs). This collaborating factor has resulted in protocol review between the sponsor and host countries, resulting in multiple ethics review of a single site protocol.

This study discusses the issue of using a multiple research ethics committee (REC) model in ethics review. The study objectives were to investigate the similarity and/or variability in ethics review for a single-site protocol reviewed by multiple research ethics committees and to determine if protocols reviewed by both developing and developed countries were reviewed according to the ethical framework for clinical research proposed by Emanuel, Wendler, Killen, and Grady (2004). The study employed an exploratory qualitative design. For data collection, retrospective document review was used to review and compare REC responses.

Key findings were that there are major similarities in the ethics review process of RECs in developed and developing countries. Where variability was noted, this was negligible. The study highlighted that RECs in both developed and developing countries followed common research ethics principles and benchmarks as laid out in the ethical framework by Emanuel et al. Most researchers did not deviate from the protocols when carrying out their proposed studies as determined in the subsequent publishing of results.

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[1] My mother passed away in December 2013, a month before I undertook my ethics studies in South Africa.

CHAPTER 1: INTRODUCTION

Globally, there has been tremendous growth in health research, leading to increased collaborative research between developed and developing countries; this has the potential of exploitation of participants, which may also partially be caused by unequal expertise in research oversight (Ndebele, Blanchard-Horan, Shahkolahi & Sanne, 2014). The research ethics review process has become an inherent part of the research process for all research involving humans to ensure the safety, respect for, dignity and integrity of research participants The collaborative effort in research has led to multiple reviews of the same protocol for a single site (Ndebele, Blanchard-Horan et al., 2014). While most studies done to date have been looking at the number of applications submitted for ethics review and the process itself, there is lack of documented information regarding the degree of similarity and or variability in ethics review between multiple ethics review committees reviewing a single protocol in collaborative research between developed and developing countries. There is partial evidence that research ethics committees (RECs) review protocols, using similar international regulations and guidelines (Tsoka-Gwegweni & Wassenaar, 2014). Tsoka-Gwegweni and Wassenaar (2014) state that there is not enough evidence which evaluates whether international and local RECs review protocols in collaborative research use a similar ethics review framework such as described by Emanuel et al. (2004).

CHAPTER 2: LITERATURE REVIEW

2.1 Background

Macduff et al. (2007) report that procedures for ethical review of health care research vary considerably across, and sometimes within, different countries. Differences in cultural dynamics and geographical frameworks may also warrant that a protocol be reviewed by more than one research ethics committee. For example, when researchers from high-income countries (HICs) carry out health intervention studies in low- and middle-income countries (LMIC), it becomes a prerequisite that their protocols be reviewed and approved in both the country of origin and the host country (Ezzat et al., 2010; Studdert et al., 2010). This has resulted in the adoption of the multiple-REC review model, but there is a lack of information regarding the outcome of such multiple REC review.

2.2 History of ethics review guidelines

According to Macrae (2007) numerous bodies, including governmental regulatory bodies, research entities and medical professional bodies, have strived to provide guidance on how clinical trials are to be conducted ethically. All these guidelines had their roots in the post-war trials after World War II (Markman & Markman, 2007; Rice, 2008). From the Nuremburg trials emerged the Nuremburg Code, setting out vital principles to be observed when conducting research involving human participants, and this successively formed the foundation for other international research ethics guidelines regarding health care research such as the Declaration of Helsinki, the Belmont Report and later, the International Ethical Guidelines for Biomedical Research Involving Human Subjects of the Council for International Organizations and Medical Sciences (CIOMS) (Macrae, 2007; Schüklenk, 2000; Weindling, 2001). Research ethics committees that review according to these established research ethics guidelines have become a standard feature of the research environment internationally and are currently a prerequisite in the majority of countries (Guillemin, Gillam, Rosenthal & Bolitho, 2012).

2.2.1 The Nuremberg Code

The first historical guideline for research involving human participants was the Nuremberg Code, published in 1949 (Nuremberg, 1949; Quest & Marco, 2003). This stated the need for informed consent, but did not discuss any risk-benefit ratio or the need for independent review (Emanuel, Wendler, & Grady, 2000; Ghooi, 2011). This historical document was developed in

response to the Nazi atrocities during the Second World War, where research was conducted on people without individual consent. The Code, which is made up of ten principles, shifted priorities from investigator-centred decisions to participant involvement in decisions regarding research participation (Nuremberg Code, 1949; Quest & Marco, 2003). Despite the widespread adaptation of the code, unethical research studies continued, many of which used vulnerable populations without their consent, demonstrating no respect for their autonomy (Quest & Marco, 2003).

Unethical research continued after the development of the Nuremberg Code and one example is the Tuskegee Syphilis Study, between 1932 and 1972, in which the United States Public Health Service financed a study to assess the natural progression of untreated syphilis in human beings (Amdur & Bankert, 2010; Corbie-Smith, 1999; Rice, 2008). The premise of the study was considered ethical since there was no real treatment for the deadly disease at the initiation of the study; however, treatment subsequently became available with the development of penicillin. The study population was drawn from the most vulnerable population of society, namely uneducated African Americans living with the disease. According to Amdur and Bankert (2010), the study population did not comprehend their condition nor understand the essence of the study. Also, despite the discovery of penicillin, study participants were not offered the available beneficial treatment. Studies such as the Tuskegee Syphilis Study laid the foundation for the establishment of the ethics review system, especially the development of the principle of justice in the Belmont Report.

2.2.2 Helsinki Declaration

The Helsinki Declaration was developed by the World Medical Association (WMA) in 1964; since then, it has been updated several times with the latest update being in October 2013 (Lederer, 2004; Weijer & Anderson, 2001; World Medical Association, 2013a). The Helsinki Declaration was developed to address the gaps in the Nuremberg Code, especially in relation to physicians conducting research with patients, the need for a positive risk-benefit ratio and independent review of research protocols (Lederer, 2004). According to Lederer (2004) the Declaration is the most influential international ethics document governing the conduct of clinical research. The Helsinki Declaration developed a principle-based approach to ethics review and promotes ethical standards that ensure respect and protection, including protection of the human rights of the participants (World Medical Association, 2013a) Protection of research participants was usually seen as the responsibility of the researchers (Lederer, 2004).

The Helsinki Declaration focuses on issues that may pose harm to research participants (Goodyear, Krleza-Jeric, & Lemmens, 2007).

The Helsinki Declaration was the first ethical document that required RECs to review research protocols independently and to monitor on-going studies (Carlson, Boyd, & Webb, 2004; Rid & Schmidt, 2010.; Word Medical Association, 2013a). The emphasis on independent review of research is intended to abate conflicts of interest and safeguard the welfare of research participants by paying particular consideration to risks, benefits and informed consent (Kass et al., 2007). According to these principles, researchers also have an obligation to adhere to international and national regulatory standards (World Medical Association, 2013b). The document is holistic as it encompasses health research involving human participants, including identifiable human biological material and data (World Medical Association, 2013b).

2.2.3 CIOMS Guidelines

In 1949, the World Health Organization (WHO) and the United Nations Scientific and Cultural Organisation (UNESCO) co-founded the Council for International Organizations of Medical Sciences (CIOMS) with the mandate of maintaining collaborative research and especially to provide guidance to researchers in international contexts (Bhutta, 2002; Macrae, 2007; Weijer & Anderson, 2001). CIOMS, together with the WHO, developed guidelines on the application of ethical principles that govern the conduct of biomedical research involving human participants as laid down in the Helsinki Declaration. This was done to address socio-economic, legal and regulatory discrepancies between developed and developing countries (CIOMS, 2002).

CIOMS guidelines created a framework that seeks to address the challenges of modern-day research communities by addressing various multifaceted issues such as informed consent and its limitations; appropriate research participation compensation; research with vulnerable populations; and strengthening ethical and scientific review capacity for biomedical research (CIOMS, 2002). According to Weijer and Anderson (2001), CIOMS guidelines are more receptive to the health needs of the community in which research studies were to be conducted and they accord protection to study participants in developing countries. These protections entail developing ethics review resources in host countries to enable research review in both host and sponsor countries (Weijer & Anderson, 2001).

CIOMS guidelines require that countries develop national guidelines and regulations for ethics review of research involving human participants with due regard to local standards, socio-economic status and culture. International ethical regulations and guidelines focus more on addressing controversies surrounding collaborative research and pay less attention to context-specific issues such as cultural diversity (Bhutta, 2002). CIOMS guidelines also require that researchers obtain ethical approval before commencement of studies (CIOMS, 2002).

In its discussion of multi-site research, CIOMS (2002) makes reference to multiple ethics reviews. While it gives the RECs in host countries the power to review protocols with regard to inclusion and exclusion criteria (CIOMS, 2002), the guidelines do not provide sufficient ways of dealing with conflict that may arise from different RECs reviewing the same protocol. However, it recommends that changes to the protocol at one centre be made at all centres.

2.2.4 The Belmont Report

The Belmont Report was developed in response to unethical studies such as the Tuskegee Syphilis Study mentioned above (Benham & Francis, 2006; Greaney et al., 2012; Varmus & Satcher, 1997). This guideline, published in 1979 in the United States, provided a concise description of the mandate for review of research involving human research participants. The report is based on three distinct topics which demonstrates the boundaries between practices and research, basic ethical principles, and the application of basic ethical principles (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research Research, 1978).

According to Greaney et al. (2012) the Belmont Report recognises the existence of all the other guidelines. However, its principles are more comprehensive and generalisable, taking into consideration all stakeholders in the research process and making sure they understand the ethical issues essential in research. The document provides guidance to the work of RECs, including a framework for RECs to review protocols. This document defined the fundamental principles of ethical research, namely respect for persons, beneficence (and non-maleficence) and justice. These principles are applied through the need for informed consent, risk-benefit assessment and the need for inclusion/exclusion criteria in participant selection (Cassell, 2000).

2.2.5 The Common Rule

After international guidelines had been developed, individual countries started to produce and revise their own ethical guidelines, which were context specific (Guillemin & Gillam, 2004). In the beginning, the guidelines were meant for biomedical research but later on covered all research that includes human participants (Guillemin & Gillam, 2004). The United States of America developed the Federal policy for the protection of human participants, popularly referred to as the "Common Rule" (United States Department of Human and Health Services, 2014). The "Common Rule" was established in the wake following the Tuskegee Syphilis Scandal (Emanuel & Menikoff, 2011). The Common Rule was developed in 1981 and published in 1991. It was heavily influenced by the Belmont Report of 1978 and is codified in separate regulations by 17 Federal departments and agencies (Emanuel, Wood, et al., 2004; United States Department of Human and Health Services, 2014).

According to the United States Department of Human and Health Services (2014), Rule 45 CFR Part 46 is made up of four sub-parts; (1) protection of human research subjects; (2) protection for pregnant women, foetuses and neonates; (3) protection for prisoners; and (4) protection for children. The Common Rule requires as its basic elements: (1) assurance of compliance by institutions; (2) researchers to obtain and document informed consent from human participants; and (3) composition of ethics review committees. It also outlines basic ethical provisions for RECs and stipulates that all research studies undertaken or supported by Federal departments abide by it (Emanuel, Wood, et al., 2004).

2.3 Guidelines for REC review process

While multiple ethics review is now common, the current guidelines provide no guidance regarding the process to be followed when multiple RECs are involved in the review of a single protocol. Gupta (2014) reported on several studies which looked at the relevant issues RECs should evaluate and guidelines to be followed. Gupta (2014) reported that the main problems faced by ethical reviews in health systems research were challenges on how to separate research from practice and how intercultural research practices have the power to influence the review and conduct of research. Challenges include ethics review delays, especially when clinical research and clinical practices are combined. These delays were attributed either to the under-

protection or over-protection of the participant by the RECs (Gupta, 2014). Of all the guidelines that were stipulated, none made any reference as to how multiple RECs should operate.

2.3.1 Research ethics committees in Africa

With the huge burden of disease in Africa, there is an increased volume and intricacy of protocols that need to be reviewed to ensure the protection of human research participants (Nyika et al., 2009). Nyika et al. (2009) carried out a comprehensive study to determine the ethics review capacity of RECs in sub-Saharan Africa. While the majority of the countries in Africa now have a REC in place, ethical review of health research may be limited by lack of resources, inadequate training of committee members, as well as weak participation by committee members (Nyika et al., 2009). In addition, in Africa, most RECs are constituted by members from the same institution, which may be problematic for independent review with potential bias (Nyika et al., 2009).

Research ethics review in Africa has improved in the last decade with only 36% of WHO regional members not having an established REC (Kass et al., 2007). Kass et al. (2007) reported that, because of challenges synonymous with RECs in Africa, such as inadequate financial and personnel resources, research ethics protocol review varied tremendously, sometimes leaving research participants unprotected and their welfare depending on the researchers. RECs may also be inclined to provide approval without adequate ethics review, which may be exacerbated by corruption in Africa (Kass et al., 2007). Besides the poor socio-economic environment, RECs also had to deal with politicians who were meddling in the running of the RECs (Kass et al., 2007). The study reported gross abuse of review procedure by researchers, for example, unwarranted expedited review of more than minimal risk protocols.

Collaborative research between developed and developing countries is now common and this has led to concerns regarding the possible manipulation of participants in developing countries (Hyder et al., 2004). Ndebele, Blanchard-Horan et al., (2014) posit that, without robust research oversight, ethical principles might be ignored, be it unintentionally or deliberately, thereby jeopardising the welfare of the research participants. As noted by Gilman and Garcia (2004) collaborative research involves approval by RECs in the sponsoring country and also in the developing county. Collaborative research between developed and developing countries is usually conducted under the auspices of the international regulatory frameworks of the

developed or sponsor country (Milford, Wassenaar, & Slack, 2006). In most cases, these frameworks from the developed country do not take into consideration the socio-economic and cultural environment of the developing country, where the research will be conducted.

There is documented proof of limited ethics review capacity in parts of Africa, which may increase the potential for varied ethics review responses (Milford et al., 2006), as noted above. In trying to establish the availability of institutional ethics review policies and mechanisms, Zielinski et al. (2014) identified gaps within health research institutions in terms of research guidelines and practices in sub-Saharan Africa. A third (34%) of their respondents were offered some ethics training, including staff not involved in ethics review. Of 847 research institutions, fewer than 50% had links with a national or regional ethics organisation. This lack of research ethics capacity in most African countries may translate into failure to adequately review protocols ethically. The sponsor REC is often the approving REC, but may be unable to reconcile cultural diversities with the aims of the study. However, despite acknowledgement of ethical standards of the developed countries, there is a need for international guidelines for collaborative research studies which will guide the review process in both the host and sponsor countries (Hyder et al.,2004). Hyder et al. (2004) calls for a framework where the nature and type of guidelines in collaborative research are governed by the host country. The contradiction between (Nyika et al., 2009) that REC members tend to work for the implementing institutions and the assertion by (Milford et al., 2006) that there is lack of research ethics capacity in Africa is augmented by Hyder, Zafar et al. (2013) in their ethics capacity study in LMICs. They found out that there is general lack of a plausible framework for evaluating research ethics capacity and suggested for an adoption of a more holistic and external process of evaluating ethics capacity rather than to rely on internal processes which they assumed tend to "sugar-coat" reality.

2.3.2 South African research ethics guidelines

According to Coleman and Bouësseau (2008), international guidelines are not legally binding in countries that have not ratified them. South Africa, adhering to the international ethics guidelines both in the conduct of research and the ethical review process, also has legislation regulating research involving human subjects in terms of the National Health Act 61 of 2003 (Department of Health, 2004). The National Health Act made provision for the establishment of a National Health Research Ethics Council, whose sole mandate is to govern the operations

of local RECs in accordance with the terms of the National Health Act (NHA) 61 of 2003[2] (Parliament South Africa, 2004). To complement Act 61, the South African government produced additional guidelines such as the South Africa Good Clinical Practice (GCP) guideline, as well as guidelines for ethics review committees (Department of Health, 2015a). According to the (Department of Health, 2015a) all 'health research' proposals should be independently reviewed by registered research ethics committees registered with the National Health Research Ethics Committee (NHREC) as guided by s73 (2) of the NHA. The guidelines, according to Moodley and Myer (2007), specifies the structure of RECs, but lacks significant information on how the multiple-REC system should function.

2.4 RECs' functions, roles and challenges in developing countries

Despite the numerous difficulties faced by RECs, their main obligation is to improve research participants' protection (Coleman & Bouësseau, 2008). This ethical oversight of research involving human participants is vital to safeguard the principles of justice, beneficence and justice (Green, Lowery, Kowalski, & Wyszewianski, 2006). As stated by (CIOMS, 2002) REC review is the epicentre of guidelines for both international and local research. International and local research both compel RECs to ensure that the risk-benefit analysis is applied favourably in research studies and that research studies are implemented in accordance to ethical guidelines (Coleman & Bouësseau, 2008). It is the function of RECs to make sure that ethical principles such as justice are amply addressed. Thus the main function of RECs is providing oversight to research studies. Arguably, one can view the role of RECs in two ways (Ross & Athabassoulis, 2014). In the first way, as stated by Coleman and Bouësseau (2008) RECs monitor the risk-benefit ratio of research studies and secondly, they ensure that participants give informed consent prior to their participation in research studies. The general function of the REC is to preserve research ethics and, since their introduction, RECs have been tasked with reviewing the ethical suitability of research studies (Guillemin, Gillam, Rosenthai, & Bolitho, 2012).

Studies done the world over have shown that RECs continue to encounter challenges despite the availability of national and international ethical guidelines. With the growth of health research, there is need for strong and sound ethics review (Ijsselmuiden et al., 2012) and the importance of ethical review cannot be understated. In developing countries, on the African

[2] s73 (2) No 61 of 2003, National Health Act, 2004 (NHA).

continent to be specific, where competing socio-economic challenges prevail, RECs continue to be underfunded but they are expected to uphold international research ethics guidelines in such situations where there are stark power inequalities and discrepancies (London, 2002).

According to Nyika et al. (2009) and Ijsselmuiden et al. (2012), RECs in Africa are fraught with poor financial and human resource capacity, the training is insufficient and if operating procedures exist, they are often inadequate. REC members frequently also have multiple tasks, and their roles are poorly acknowledged (Ijsselmuiden et al., 2012). Ateudjieu (2010) state that, despite their independence being questionable, some RECs in developing countries may tend to 'rubber stamp' approvals in an effort to lure and secure international funding. REC members usually work for the institution that will be implementing the research or there is over-dependence on international organisations for financial support, thereby bringing the independence of the committee into disrepute (Nyika et al., 2009).

Benatar (2002) reported that in developing countries, REC's shortcomings range from self-appointed private committees (which are lacking in expertise) to lack of dialogue and public deliberations, leading to undisclosed conflict of interest. A study by Schuppli and Fraser (2007) found out that one of the RECs' shortcomings was group-decision making. The authors attributed the shortcomings in group decision-making to factors such as REC structure, social influence and how the members of the committees are selected. Shortcomings in group decision-making usually result in biases and polarisation of the review process (Schuppli & Fraser, 2007).

2.5 Multiple REC review

Ethics review by multiple RECs is often a parallel process based on the expectations that the model will reveal different aspects of the research environment (Ravina, Deuel, Siderowf, & Dorsey, 2010). While most research has been done on the effects of multi-site ethical review of studies and the variability on the RECs' outcome listed, little has been documented on multiple review of a single protocol by different RECs. Gilman and Garcia (2004) note the complex procedures collaborative studies have to negotiate in obtaining the necessary dual ethical approval. This difficulty, as pointed out by Gilman and Garcia (2004) has contributed to a maze of ethical challenges which researchers are supposed to navigate, where all the RECs

involved have an assumption that the researchers are aimed at exploiting the research participants.

The basic functions of the RECs as stated by Benatar (2002) are to evaluate the risk-benefit ratio of a study; assisting and guiding the researchers on research ethics and; monitoring and auditing the research; thus the fundamental function of multiple research ethics review is to protect their local institutions. Thus they ensure research carried out by their institutions is ethically sustainable and complies with local specific regulations (Guillemin et al., 2012). Gilman and Garcia (2004) also point out that another function of the multiple review system is for respective RECs to safeguard the economic status and liability of their institutions, though this usually results in the review process resembling a legal process. While multi-centre studies follow one protocol at many sites, each local REC has the mandate to review and approve the protocol before participants are enrolled at its site (Caulfield, Ries, & Barr, 2011; Greene & Geiger, 2006; Stair, Reed, Radeos, Koski, & Camargo, 2001). Multiple review entails one protocol for a single-site study being bounced back and forth between more than one REC. Usually it is between the REC of the sponsor country and host country. The multiple review system is also employed to reinforce the protection of research participants by bringing ethical matters related to intricate studies to the surface (Caulfield et al., 2011). This parallel process is intended to ensure protection of human subjects and assist with issues pertaining to the local cultural context.

2.5.1 Advantages of multiple-REC review

The study carried out by Stair et al. (2001), showed that multiple-REC review helps to reinforce protection of participants. With regard to changes that are requested by local RECs, Stair et al. (2001) noted that many of the changes requested by RECs were as a result of a thorough review. Requested changes to the informed consent forms included all elements required by Federal regulations and forms to be simplified into languages best understood by the study participants. Multiple-REC reviews may therefore complement and enhance each other in their duty to safeguard the rights and welfare of study participants, pointing out issues which can easily be overlooked in a single-REC model. Stair et al.'s (2001) study showed that the growth in number and complexity of clinical trials overwhelms the single model of REC review which may compromise human participant protection whereas multiple REC reviews may improve the protection.

According to Hicks et al.(2009) multiple-REC review does not reduce the turnaround time of protocol review, it adds to the duplicating of administrative roles, which thereby promote consistency of research documentation. While there is a perception that multiple-REC review is inefficient, it should be noted that its mandate is to protect human participants and to facilitate the research process (Master, Ries, & Caulfield, 2011). However, concerns of inefficiency should be balanced with the committee's role of protecting participants' welfare. According to Master et al. (2011), redundancy of multiple-REC review can be an integral part that promotes human protection; furthermore, the process becomes beneficial if one REC identifies and proffers solutions to ethical issues not raised by others.

Yassi, Breilh, Dharamsi, Lockhart and Spiegel (2013) looked at the ethics of ethics reviews in global health research. In their study, they focused on how researchers are often overwhelmed by ethical challenges in the absence of coherent guidelines to guide their actions. They called for a robust approach to ethical reviews of research projects (Yassi et al., 2013). This study in particular looked at the guidelines which can guide researchers from HICs when collaborating with LMICs (Cash, Capron, Saxena, & Wikler, 2009; Yassi et al., 2013). The study by Yassi et al. (2013) highlighted challenges of collaborative research to researchers. Some of the challenges noted were the difficulties researchers face working in socio-economic and cultural settings different to their own (Yassi et al., 2013). According to Yassi et al. (2013), these ethical challenges could be mitigated by use of multiple RECs.

Multiple RECs can provide complementary oversight of each other in that important ethical issues within the protocol can be noticed and corrected before the research can cause harm to participants. Where one REC may miss a valid reason for increased risk and approve the protocol, another may identify the potential for risk and reject the protocol. Another rationale for using the multiple-REC model of review is the fact that one of the RECs may be site-specific and details such as local regulations may only be known through guidance to the distant REC (Enzle & Schmaltz, 2005). Henderson, Corneli, Mahoney, Nelson and Mwansambo (2007) report on how the involvement of multiple RECs in a collaboration helps with defining benefits, with RECs in host countries assisting in understanding the local culture. Local RECs in collaborative research help with the interpretation of local regulations, customs and norms. Involving multiple RECs in collaboration also guarantees that competing interests are

balanced. According to Edwards, Ashcroft and Kirchin (2004), it becomes the duty of the REC to reconcile conflicting interests, which is best achieved by the use of multiple RECs.

2.5.2 Disadvantages of multiple-REC review

As stated by Yassi et al. (2013), with the increasing call for global research, there is a growing concern regarding the ethical challenges encountered by researchers from high-income countries working in low- or middle-income countries. This has arisen either by research collaboration between high-income countries (HIC) and low- to middle-income countries (LMICs) or regionally by a founding agency and the agency conducting the research.

According to McIntosh et al. (2008), collaborative research especially between developed and developing countries continues to be burdened by controversies, mainly because of the lack of, or unclear, ethical structures to govern the RECs. RECs in developing countries are expected to adhere to international standards, which may not be compatible with the local regulatory environment or respect local culture (Enzle & Schmaltz, 2005; McIntosh et al., 2008). Despite the local RECs being familiar with their communities and more likely to offer their communities more protection, RECs in developed countries tend to be more authoritative, with low regard for the quality of the review done by RECs in developing countries (Gilman & Garcia, 2004). As stated by Gilman and Garcia (2004), at times studies fail to be approved for fear of affecting the institution's image though the risks to the institution would be negligible; this is due to the over-protectiveness RECs tend to exhibit in multiple reviews. This view is also supported by Salman et al. (2014) they state that research due to the overprotective of RECs, research might be conducted too late to matter or sometimes insufficient sample size of participants is retained to enable the research question to be addressed. This result in less sustainable of independent researches as compared to commercially sponsored ones (Salman et al., 2014).

Taljaard et al. (2014) carried out a scenario-based survey in three countries on variability in research ethics review of cluster randomised trials (CRT). Though the study was looking at inconsistences across several ethics review committees' responses to ethical challenges faced in conducting CRT, it is relevant to the proposed study in that it solicited responses from several RECs reviewing a number of similar studies. Despite the geographical distances between the three countries (Canada, United States and the United Kingdom), Taljaard et al. (2014) tried to create a scenario that could be faced when conducting a multi-site research study which would

require a study to go through more than one REC. Their idea was to get responses from different RECs reviewing the same protocol.

In Taljaard 's study (2014) all the committees under study had an inclusive view, that the degree of protection required for participants was subject to the protocol itself (Taljaard et al., 2014). However, most of the committees involved showed there was a lot of uncertainty within the RECs when reviewing projects, and usually personal experiences influence decision-making. While the study attributed the small disagreements in the types of review required among the countries concerned to regulatory differences, reasons for differences within countries could not be ascertained. In conclusion, Taljaard et al. (2014) state that the type of review may have implications with respect to the level of scrutiny a protocol will receive during the review process, number of reviewers and the time required to complete the review process. There were also inconsistencies among the REC chairs with regard to subject selection. Chairs tended to combine the identification of research participants with the need to seek informed consent. Though the study was limited to the review of CRT and was based on hypothetical scenarios, it is congruent with the present study in that it looked at studies hypothetically carried out in a multi-site setting.

Tully, Ninis, Booy, and Viner (2000) carried out a prospective study trying to evaluate the role of the new 'system of review' by multi-site RECs. This was done in six regions in England and prospective data reviewed was in relation to administration, financial implications and turnaround time, as well as the non-local changes in the application demanded by RECs of the whole review process. According to Tully et al. (2000) less than one-third of the RECs reacted within the predetermined 21 days. These were RECs which acted by executive subcommittees. Variability in RECs' decisions prevent studies from being implemented promptly and this results in increased study costs (Tully et al., 2000).

The study by Tully et al. (2000) highlighted the problems caused by use of multi-centre RECs from an administrative, financial and turnaround time perspective, and their effects on research participants. Monetary cost is a great challenge posed by multiple-REC reviews to research as studies will require additional funding to cover application costs (Jamrozik & Kolybaba, 1999; Tully et al., 2000). This additional funding may not represent the best use of research funds as the research suggests that funds are mis-spent on redundant multiple ethics review processes. At the same time, the additional administrative costs do not contribute to the additional

protection of study participants; rather, they slow the improvement of health care services by delaying study commencement (Gold & Dewa, 2005; Jamrozik & Kolybaba, 1999).

Hyder et al. (2014) presented a conceptual exploration of ethical review of health systems research (HSR) in low- and middle-income countries. HSR presents a myriad of challenges to RECs, especially in terms of the inability to differentiate the research subjects in HSR due to its use of different units for intervention and observation. RECs may find it difficult to conduct a risk-benefit assessment when multiple levels of research participants are involved as primary (unit of intervention) and secondary research subjects (data collected but no intervention) (Hyder et al., 2014). This further highlights another challenge often met by RECs when reviewing HSR: how matters of risk-benefit analysis and informed consent are dealt with. McWilliams, Hoover-Fong, Hamosh, Beck and Beaty (2003) posit that protection of human participants within research studies is an evolving process, while the use of a multiple-REC review system results in high variability, mainly on the risk-evaluation criteria. While the need for human protection is fundamental, lack of uniformity in the review process generates uneven human participant protection, resulting in significant inefficiency.

Gold and Dewa (2005), point out that multiple REC review leads to a waste of time and resources spent on documentation, resulting in delays to commencement of the study. Multiple-REC review also causes reduced financial resources being committed to the objectives of the research when resources are channelled to ethical review (Gold & Dewa, 2005). This is attributed to a lack of standardised forms used by RECs, differences in expectations and background of the RECs and to the degree of influence of institutional or professional culture within a REC (Gold & Dewa, 2005). For example, Burman et al.'s (2003) study showed that use of a multiple-REC review system tended to increase the reading grade level of consent forms, as changes to consent forms by different RECs resulted in them becoming more complex and longer.

In contrast to some views presented earlier, unless reforms are implemented, the use of the multiple-REC review model offers little or no benefit to the study participants and research studies, and will continue to impede discovery of avoidable threats to participants. Gilman et al.(2002) state that multiple review of a single protocol does not enhance the ethical standard; rather, it impedes the ethical review process resulting in delays in implementing the much-needed health research.

2.6 Ethical principles and operational research

As the studies analysed in this dissertation are operational research (OR), it is important to define what OR is and how such studies are affected by ethics. From a public health perspective, OR is research into approaches, interventions, tools or information in order to improve the quality, efficiency or performance of health systems (Bissell et al., 2014; Edginton et al., 2012; Harries et al., 2011; Ramsay et al., 2014). It has origins in the military and is identified as the science of formal decision-making, giving it relevance for adaptation for health research studies (Zachariah et al., 2009). While OR is ideal for health research and its immediate results can influence policy, it has its own ethical challenges. Edginton et al. (2012) documented the challenges which affect OR as including the inability by researchers to accept that confidentiality of participants may be compromised through identifying characteristics other than demographic data. Edginton et al. (2012) also state that researchers often neglect the right of participants to receive study results. These ethical concerns should be addressed in all research studies for them to be deemed ethical and appropriate. Edginton et al. (2012) state that the ethical approval process for operational research should not be lengthy, cumbersome or present a barrier to research. Ways should be devised to avoid lengthy review processes without compromising the ethical review process (Edginton et al., 2012).

2.7 Harmonisation of REC review

Emanuel et al. (2000) and Emanuel, Wendler, et al. (2004) proposed an ethical framework for guiding the conduct of clinical research in developing countries. This framework consists of eight principles and their benchmarks to guide researchers and RECs in research ethics review. The authors of these principles and benchmarks acknowledge the complexity of their proposed framework due to the problems inherent in the ethical evaluation process of research; however, by following this comprehensive framework, RECs should be able to carry out the review process in a harmonised way.

The principles are: (1) *collaborative partnership* which aims to lessen disparities between researchers and sponsors from developed and host countries. Collaborative partnership entails a sense of ownership within communities while demonstrating an awareness of, and respect for, cultural diversities; (2) *social value*; the research must be responsive to the health needs or priorities of host communities; (3) *scientific validity*; the research has to be scientifically and

ethically sound; (4) *fair selection of participants*; (5) *risk-benefit ratio*; there must be favourable balancing between risks and benefits of research; (6) *independent review* of research in order to protect the rights and welfare of study participants; (7) *informed consent*; obtaining individual consent, with due regard to cultural, socio-economic and literacy disparities; (8) *respect for recruited research participants and communities* through the protection of confidentiality and the availability of unconditional withdrawal of consent (Emanuel et al., 2000; Emanuel, Wendler, et al., 2004).

The ethical framework by Emanuel et al. (2000) and Emanuel, Wendler, et al. (2004) provides guidance in a coherent and systematic way for determining whether research is ethical. The sole purpose of the ethical framework is to provide guidance for the ethical development, implementation and review of research protocols. According to Emanuel et al. (2000), the framework takes into consideration all of the deep-seated protections rooted in all of the ethical guidance documents and is not related to any prior research scandal. The ethical framework was built on the basic premise of helping RECs to offer protection to research participants and should be used as a guiding framework when reviewing research protocols (Dhai, 2005; Emanuel, Wendler, et al., 2004). The principles of the framework are described below.

2.7.1 Collaborative partnership

According to Minkler (2004) and UNAIDS/AVAC (2011) Good Participatory Practice Guidelines for Biomedical HIV Prevention trials, collaborative partnership involves a holistic approach to research which includes cooperation in a joint venture among communities, researchers, academia and other stakeholders. Collaborative partnership, according to Zeanah et al. (2006), entails the involvement of communities and other partners at all stages of the research. Central to collaborative partnership is transparency, which includes community consultations (Zeanah et al., 2006). It recognises capacity development of the local populace. Thus, collaborative partnership constitutes the working together of different parties to achieve common goals and ideologies. As pointed out by DeCamp (2011), collaborative partnership is not only an ethical principle but it also guarantees that research is successfully realised by eliminating the sense within the local community of just receiving aid while instilling that of ownership. It ensures that challenges in contextualising and applying other ethical principles are limited (Quinn, 2004).

Goals of collaborative partnership are: (i) protection; (ii) respect; (iii) empowerment; (iv) mutual understanding- which includes social-cultural competency and research competency; (v) integrity- encompassing both scientific and ethical integrity; (vi) transparency; (vii) accountability; (viii) partnership-building; and (ix) community stakeholder autonomy – which gives community stakeholders the right or refusal to participate in a research study based on their interests and desires (Dickert & Sugarman, 2005; UNAIDS/AVAC, 2011). Therefore, collaborative partnership becomes the guiding principle for all the other ethical principles (DeCamp, 2011). Finally, through collaborative partnership, research does not seek to marginalise or exclude communities; rather, it seeks to improve on existing services (DeCamp, 2011). It brings about a shared understanding which reinforces the research process (Marsh et al., 2008).

2.7.2 Social value

While this ethical principle, according to Emanuel, Wendler, et al. (2004), measures the importance of the health problems under study, it also seeks to improve the value of research for each beneficiary through actions such as product development, collaborative research and improvement to health systems. Research with social value prevents displacing the existing systems; rather, it builds onto them. As pointed out by Emanuel, Wendler, et al. (2004), research which lacks social value introduces participants to risks without valid reasons and is a waste of scarce resources, especially in developing countries. In their outline of the ethical benchmarks of clinical research, Emanuel, Wendler, et al. (2004) point out that while priorities of research change, determinants of social value become ambiguous and this calls for judgment with regard to the usefulness of a research study.

Despite such problems, social value is integral to the success of a research study and is enhanced by four benchmarks (Emanuel, Wendler, et al., 2004). These are: (i) beneficiaries - it is imperative to point out the beneficiaries of the intended research (be it participants or those in host communities); (ii) the assumed research value for each beneficiary should be well outlined, taking into cognisance that each beneficiary might view or perceive the health problem differently; (iii) procedures to promote social value should be devised and these should be done through collaborative partnership; and (iv) research should not subvert the community's existing health care services; rather, it should complement or enhance them (Emanuel, Wendler, et al., 2004). Basically, the premise that research should have social value

in order to be considered ethical rests solely on the need to avoid exploitation of research participants and to ensure responsible use of limited resources (Dhai, 2005).

2.7.3 Scientific validity

Emanuel et al. (2000) and Emanuel, Wendler, et al. (2004) pointed out that when considering the principle of scientific validity, there are three benchmarks which should be considered. Firstly, the study design should be appropriate to the health problem of the host community of the research (Emanuel, Wendler, et al., 2004; Macklin, 2001). Secondly, the study design should have the capacity to realise the research objectives without "subordinating the participants' welfare to the study objective"(Angell, 1997). Lastly, the design should be feasible within the socio-cultural and political environment of the host community, which includes sustainable capacity and infrastructure development (Emanuel, Wendler, et al., 2004). According to Dhai (2005), not only should the scientific design of a research study be sound but also the study itself should be implemented in an accurate manner, in accordance with the research design. RECs should not render protocols unworthy without reflecting on adjustments that can make the protocol scientifically valid (Dhai, 2005). Thus, this principle stipulates that poor science is parallel to poor ethics; this is because research participants would be exploited and exposed to needless risks and scarce resources would be used on research that produces uncertain results (Dhai, 2005).

2.7.4 Fair selection of study population

This principle stipulates that the selection of people to participate in research should be done to enhance the scientific validity of the research and that potential risks to such participants is minimised (Emanuel, Wendler, et al., 2004). Selection of the potential study population should recognise other ethical principles which contribute to research being implemented in an ethically sound manner. For example, where there is collaborative partnership, there is a guarantee that social value of research will be realised (Emanuel, Wendler, et al., 2004). Emanuel, Wendler, et al. (2004) further suggest that selection of the study population should not be done based on social subjugation; rather, it should be based on the ability of the population to address the research objectives. While vulnerable populations can be selected for research studies, measures should be put in place to accord them confidentiality and assure them voluntariness. As stated by (Gostin, 1991), the principle of fair selection of study population rests on the ethical principle of justice. Research burdens and benefits should be

equitably distributed; thus, study populations should be selected on the factors relevant to the problem under investigation (Gostin, 1991).

DeCamp (2011) reiterates that selection of the study population should be clear and bear a justifiable rationale. According to Emanuel, Wendler, et al. (2004), inclusion criteria, recruitment strategies and selection of study populations should not be based on the availability or vulnerability of participants, but should be ethically justifiable. Selection of study population should be done in accordance with the scientific goal of the research (Dhai, 2005). While guided by the principle of justice, the principle of fair selection of participants entails that equals should be treated equally, and benefits and burdens of research should be equitably distributed (Dhai, 2005).

2.7.5 Favourable risk-benefit ratio

Emanuel, Wendler, et al. (2004) state that clinical research should provide participants with a positive risk-benefit ratio. This obligation is central to the ethical principle of beneficence and non-maleficence (Gostin, 1991; Weijer, 2000). This is further supported by research ethics regulatory frameworks such as the Common Rule, which helps RECs to carry out their mandate of protecting research participants (Weijer, 2000). Furthermore, Weijer (2000) points out that proper analysis of risk is required to ascertain the magnitude of harm which research can pose to participants. It should be noted that there is a possibility of participants being exposed to a number of risks as well as potential benefits; thus, benefits cannot always be instant in research (Weijer, 2000). However, Emanuel, Wendler, et al. (2004) outline that the risk-benefit ratio must be favourable to participants in the context in which they exist and it is their prerogative to accept the risks posed by research vis-a-vis the potential benefits.

Thus, this benchmark works hand-in-hand with other ethical benchmarks such as collaborative partnership, social value and respect for study populations (Emanuel, Wendler, et al., 2004). The principle demands that, for research to be ethically justifiable, it has to address three aspects: (i) potential risks to participants are limited; (ii) potential benefits are maximised; and (iii) potential benefits to individual participants and communities are over and above the potential risks (Dhai, 2005). According to Emanuel et al. (2000) and Emanuel, Wendler, et al. (2004) the principle exemplifies the essential values of research, namely beneficence and non-maleficence.

2.7.6 Independent ethics review

Emanuel, Wendler, et al. (2004) and Dhai (2005) suggest that independent review should be done as a measure for assuring social accountability. This is in line with the Declaration of Helsinki World Medical Association (2013a) guideline number 23 which states that "research protocols should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee". This benchmark safeguards against the exploitation of research participants by researchers who might have competing interests (Dhai, 2005). To ascertain that the protocol does not entail any conflicts of interest, this review should be done by a committee independent from the sponsor and the investigator; at the same time, the committee should abide by the laws and regulations of the host country. The World Medical Association (2013a) stated that the committee also has the obligation to monitor on-going research studies for ethical compliance. To facilitate this review, researchers should disclose information such as the sponsors, affiliate institutions, potential conflicts and any incentives they intend to give to the research participants (Emanuel et al., 2000; Emanuel, Wendler, et al., 2004).

2.7.7 Informed consent

This principle is still regarded as the cornerstone and centrepiece of health research (Mystakidou, 2009; Tangwa, 2002). According to Emanuel, Wendler, et al. (2004) the principle requires engagement with the community to help institute recruitment procedures and incentives. The principle aims to ensure that individual participants have control over their participation in research and that their participation is in line with their individual values, interests and preferences (Dhai, 2005) and, furthermore, they are not viewed as a means to an end (Dhai, 2005; Emanuel, Wendler, et al., 2004). The principle also demands that research information be disseminated and disclosed in a culturally and linguistically suitable way (Emanuel, Wendler, et al., 2004).

As proffered by Emanuel et al. (2000) and Emanuel, Wendler, et al. (2004) the informed consent principle is based on five benchmarks: (i) engagement with the community to ascertain recruitment procedures and incentives relevant to the socio-political and cultural context of the community; (ii) use of appropriate language when soliciting and disseminating study information to participants; (iii) issuing the participants with the correct type of consent; for example, in some cultures there is a need to obtain familial consent before individual consent; (iv) participants should voluntarily participate in research. Voluntary participation as a need

for informed consent is also advocated by Mystakidou (2009) lastly, (v) measures for withdrawal from the study should be observed; this is also dependent on understanding the research design. The principle also calls for collaborative partnership (Emanuel, Wendler, et al., 2004).

2.7.8 Respect for recruited participants and study communities

The obligations of the researchers to the participants do not end when informed consent is obtained, but they have the duty to treat current, former and host communities with respect (Dhai, 2005; Emanuel et al., 2000; Emanuel, Wendler, et al., 2004). (Dhai, 2005) and Emanuel, Wendler, et al. (2004) delineated five key aspects in relation to this principle: (i) respecting the privacy of the participants through development of procedures to hold the information collected in confidence; (ii) upholding the participants' right to withdraw from research studies without consequences; (iii) provision of new study information to the participants and host communities; (iv) providing care to the participants and monitoring their welfare during the research study; and lastly (v) development of clear procedures by researchers to disseminate research results to the participants and host communities. This principle is based on the ethical principles of beneficence, non-maleficence and autonomy (Emanuel, Wendler, et al., 2004).

The eight principles are all essential for the planning and review of research protocols and, if properly followed, RECs can ensure that research which is of social value is achieved without exploiting the participants and that the participants and host communities share the rewards of the research equitably in a justifiable manner (Dhai, 2005).

2.8 Summary

Quite a number of issues have been discussed in relation to multiple REC review, from the international ethics guidelines to the South African guidelines. Advantages and disadvantages of multiple-REC review have been highlighted; however, literature on multiple-REC review in Africa is lacking. This study aims to investigate the similarity and/or the variability in ethics review for research protocols reviewed by more than one REC and to establish how variabilities can be harmonised, using the Emanuel, Wendler, et al.'s(2004) framework on clinical research.

CHAPTER 3: RATIONALE

3.1 Introduction

Increased multi-national and collaborative research has led to multiple RECs reviewing the same research protocol for a single site study. While the challenges faced by RECs in Africa are documented, little is known about research involving multiple RECs in the review process in South Africa. There is also a lack of literature on how different RECs interpret the ethical framework for clinical research for developing countries proposed by Emanuel, Wendler, et al. (2004). This study seeks to determine the similarity or variability of ethics review between different RECs and analyse the ethics review, using the ethical framework for clinical research described by Emanuel, Wendler, et al. (2004). The use of such an ethics review framework may assist in harmonising the ethics review of multiple ethics review committees, ensuring that study participants are adequately protected from harm without unnecessary delays in approval of research that may benefit them.

3.2 Research questions

The present study sought to answer the following question(s):

1. What is the similarity and/or variability in ethics reviews for operational research protocols subjected to multiple-REC review?
2. Are collaborative operational research protocols implemented in developing countries reviewed according to the ethical framework delineated by Emanuel, Wendler, et al. (2004)?

3.3 Objectives

The study set out to address the following objectives:

1. To investigate the similarity and/or variability in ethics review for research protocols subjected to multiple-REC review.
2. To determine whether the protocols were reviewed according to the ethical framework for clinical research as proposed by Emmanuel, Wendler et al. (2004).

3.4 Expected impact

This study will indicate whether protocols for collaborative research reviewed by international and local RECs return similar or variable reviews. In addition, research findings will focus on the need for RECs to adhere to the more comprehensive ethical framework for clinical research proposed by Emanuel, Wendler, et al. (2004). Information gained may influence policy formulation on collaborative research should be ethically reviewed and/or the development of a new ethics review model, which does not warrant multiple reviews for collaborative research.

CHAPTER 4: METHODOLOGY

4.1 Introduction

Methodology occupies an important place in the research because it guides the collection and analysis of data. This chapter focuses on the research design, sampling and analysis procedure.

4.2 Research design

An exploratory qualitative research design was employed to meet the objectives of the study. The basis for using a qualitative design in this study was that meaning is a social construct reached by individuals in interaction with their world. Therefore, data sources for exploratory research include interviews, observations and or documents (Polkinghorne, 2005). According to Merriam (2002), reality is not static nor agreed upon, neither is it a measurable entity. Rather, it changes constantly and the interpretations of reality are in flux and change with time. The decision to use a qualitative research design in this study was informed by the researcher's need to understand different interpretations within a specific framework at a particular time.

4.3 Sampling

In order to collect the richest data, the study used purposive sampling. This is a technique which exemplifies some structures or procedures that are pertinent to the study (Silverman, (2000, in De Vos, Delport, Fouché & Strydom, 2011). According to Marlow (2010), purposive sampling is a technique which is suitable for specific cases. It is used to enhance understanding of selected group experiences (Devers & Frankel, 2000). Teddlie and Yu (2007) state that purposive sampling is used for the selection of explicit cases based on purpose rather than casual or arbitrary selection. Marlow (2010) defines purposive sampling as a 'typical case' sampling, where typical cases are sought and selected for a particular inquiry. Purposive sampling was used to select reviews of twelve protocols of operational research studies conducted between the years 2010 and 2014, which have had more than one REC involved in their ethics review and which were readily available. Quality was thus substituted for quantity; hence, a small number of protocols were reviewed, which might pose a limitation in generalising research findings. Purposive sampling selected operational research protocols from the Desmond Tutu Tuberculosis Centre (DTTC) within in the Department of Paediatrics and Child Health, Stellenbosch University, rather than a random selection of research protocols conducted within the department. The proposed research studies were to be conducted in

different health care settings in different provinces of South Africa, but were centrally funded by the International Tuberculosis Union and DTTC at Stellenbosch University. As such, all these protocols had to have ethics review by both the International Union against Tuberculosis and Lung Diseases (IUATLD) Ethics Advisory Group, the Stellenbosch University Health Research Ethics Committee, and University of Free State Ethics Committee. Six other local institutional RECs provided local oversight for the studies.

4. 4 Data analysis

This was a retrospective document review of the documented reports of RECs after ethics review regarding the protocols selected. Data analysis used the ethical benchmarks described by Emanuel, Wendler, et al. (2004) to compare the reviews by different RECs for the same selected protocols. In reviewing the ethics review responses, the study aimed to establish the degree of agreement or variability per protocol within the ethics reviews by different RECs.

Data from the above-mentioned documents were reviewed and evaluated, classifying the responses from the different RECs involved. The responses were coded into respective themes. Categorising the data into themes was done through intense reading and re-reading of the documents under review and grouping similar information together. The coding of the information and grouping were done according to the ethical framework for clinical research as proposed by Emanuel, Wendler, et al. (2004). The eight principles of the framework as stated by Emanuel, Wendler, et al. (2004) were used as the framework for the themes and these were: collaborative partnership, social value, scientific validity, fair subject selection, favourable risk-benefit ratio, independent review, informed consent, and respect for recruited participants and study communities.

Responses from RECs review were read, after which the researcher began the coding of the data set. Though the researcher manually identified the codes and basic themes, coding of the data set was based on Attride-Stirling's (2001) thematic network analysis (Attride-Stirling, 2001). Data coding was done manually and entered into a word processing document. According to Attride-Stirling (2001), phrases in the collected data summarise the main themes in the data set. Thematic analysis seeks to unravel the themes prominent in a text at diverse levels, and thematic networks analysis aims to enable the organising and portrayal of these themes (Attride-Stirling, 2001).

4.5 Ethical considerations

The study was of minimal risk as no human participants were recruited. However, because of the sensitivity of the documents that were reviewed, anonymity and confidentiality of the information was maintained. Waiver of informed consent was granted by the custodian of the data, namely the DTTC director at Stellenbosch University, as well as the sponsor of the studies, namely the International Tuberculosis Union (Appendix 1). Precautionary steps, such as de-identifying the documents, were taken; names of participating institutions were not used anywhere in the documents or this dissertation and thus not revealed. The KwaZulu-Natal's Biomedical Research Ethics Committee (BREC) approved the study (approval number BE344/16) (Appendix 2).

4.6 Variability, Reliability and generalizability

Retrospective document review is now a widely applicable methodology in qualitative research, however, there are still misunderstandings about the methodological approach (Marshall, 1996; Matt & Matthew, 2013). According to Bashir, Afzal, and Azeem (2008) while validity, reliability and rigour are most applicable in quantitative designs they are also still applicable qualitative designs. According to (Noble & Smith, 2015) while reliability, validity and generalisability are concepts synonymous with quantitative there are terms used for qualitative research (terms such as true value, consistency and applicability). True value, consistency and applicability of qualitative research sits with the researcher (Bashir et al., 2008). According to Bashir et al. (2008) reliability and validity in qualitative research cannot be separated, however they offer a more encompassing terminology, credibility, transferability and trustworthiness to be used instead. In order to achieve validity and reliability the researcher adopted a number of strategies to self-correct the data during collection and analysis. The review of documents was guided by the principles set forth in the framework proposed for clinical research by Emanuel, Wendler et al. (Emanuel, Wendler, et al., 2004) and used as a topic guide. The researcher made sure documents under review were of high quality. Though objectivity is impossible to achieve in qualitative research, the researcher tried not to explicitly allow personal beliefs or theoretical predispositions to impact on the conduct of neither the research nor the findings derived from it. The researcher also tried to promote trustworthiness of the research findings by ensuring that consistent and transparent data was methodologically recorded. According to Noble and Smith (2015) meticulous record keeping is one of the strategies which guarantees that validity and reliability is achieved in qualitative research. This

then results in the research findings being reproducible and applicable to other settings (Noble & Smith, 2015).

CHAPTER 5: FINDINGS

5.1 Structure of data

A total of twelve protocols were reviewed by both the international and local RECs. Two major local RECs were involved with the protocol review and six institutional provided oversights. Half of the protocols aimed to study tuberculosis-related health issues (TB) (*n*=6), one-third to study concomitant HIV-TB infections (*n*=4) and one-sixth to study Human Immunodeficiency Virus-related health issues (HIV) (*n*=2) (see table 1).

Table 1: *Types of research for protocols reviewed*

TB	HIV	TB-HIV co-infections	Total
6	2	4	12

The majority of the planned studies were cross-sectional studies (9 studies; 75%), while the rest were either a time series study (1 study), or a comparative study (1 study) or a case control study (1 study). Table 2 gives an outline of the aims and objectives of the reviewed protocols. The evaluation of the scientific validity of the studies was derived mainly from the study aims and objectives.

Table 2: *Summary of protocols reviewed by local and international RECs*

Protocol Number	Aim(s)
1	The study aimed to determine why symptomatic patients with respiratory symptoms were not tested for TB when attending primary healthcare facilities.
2	To determine if there was an association between health clinic workload and identification of under-one-year-old patients with TB, as stipulated by the HIV AIDS STI TB (HAST) protocol[3].
3	Evaluation of outcomes of co-infected participants starting ART in a TB facility who received different models of on-going care.
4	Evaluation of the proportion of people living with HIV in pre-ART and ART care and factors associated with retention in pre-ART and ART care in a community cohort.
5	Determine if equitable access to HIV counselling and testing was increased through the availability of Community HIV Counselling and Testing (HCT)
6	To determine if the Antiretroviral Therapy (ART) policy of 2012 reduced mortality amongst TB patients.
7	To measure to what extent missing reported TB cases in electronic registers impacted on the reduced TB caseload reported.
8	To find out if the absence of secondary or higher level care in districts has a relationship with reported cases of child TB and if there are other factors contributing to lower proportions of children diagnosed.
9	The aim of the study was to find out if there is an association between two-month sputum smear non-conversion on newly diagnosed TB patients and a number of factors, including their HIV status and disease severity.
10	Find to what extent poor adherence to TB diagnostic protocols contributes to low bacteriological coverage in health facilities.
11	Investigation of association between HIV infection and TB mortality in children.
12	Explore reasons why there are low rates in Multiple Drug Resistance-TB (MDR-TB) treatment initiation in public health facilities.

[3] HAST Protocol as contained in the South African National Strategic Plan (2012-2016) committed to reversing the HIV and TB epidemics through four objectives: (i) address social and structural drivers of HIV & TB prevention and care; (ii) prevent of new HIV, STI and TB infections; (iii) sustain health and wellness; and (iv) ensure protection of human rights and improve access to justice.

Table 3 shows the characteristics of the study populations selected as participants. Five of the twelve protocols intended to recruit adults, representing the majority of the studies. Three studies were going to use clinical records, while three studies would recruit children only, and one study involved both adults and children as research participants.

Table 3: *Study population per protocol*

Protocol Number	**Study Population**	**Total Number**	**Percentage**
2; 8; 11	Children	3	25%
1; 3; 4; 5; 9	Adults	5	41.66%
12	Adults and children	1	8.33%
6; 7; 10	Stored records	3	25%

5.3 Submitted proposals versus published manuscripts

Of the twelve protocols reviewed by the international and local RECs, seven had been published at the time of data analysis of this study and are therefore in the public domain. Protocols 1, 2, 3, 4, 5, 9 and 10 published their research findings, constituting 58% of the total number of the protocols reviewed (see table 4). Most of the publications correlated with the reviewed protocols with the exception of protocols 1 and 5. There was an additional research site reported in the results from protocol 1. Protocol 5 study deviated from the approved protocol, which stipulated as one of its inclusion/exclusion criteria the geographical residence of the participants, while the publication reported that enrolled participants were from various places of residence. Despite these minor deviations to the protocol, most of the studies, when compared to the publications, appeared to have adhered to the ethics approved protocols.

Table 4: *Protocols versus published studies*

Protocol Number	**Status of the Study**	**Total**	**Percentage**
1; 2; 3; 4; 5; 9; 10	Completed and data available in the public domain	7	58.33%
6; 8; 11; 12	In progress	4	33.33%
7	Not completed	1	9%

5.4 Local and international REC reviews

Table 5 demonstrates reviews done by both local and international RECs respectively and the responses are tabulated as per the ethical principle, delineated in the framework proposed by Emanuel, Wendler, et al. (2004) for clinical research in developing countries.

Of the twelve protocols reviewed, nine protocols received critique from one or both of the ethics review committees. Queries concerned scientific validity (*n*=2), fair selection of study population (*n*=1), respect for participants and communities (*n*=2) and other issues (*n*=4). Seven out of nine queries were raised by the international REC, which constituted 77.78% of the total issues, while the local REC raised 22.22% of the issues. Descriptions of REC similarities and variability for each principle are outlined in descending order in Table 5 below.

Table 5: *Responses by local and international RECs*

Basic Themes/ Principles	Protocols																								Comments
	1		2		3		4		5		6		7		8		9		10		11		12		
	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2	
Collaborative partnership	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	Both local and international RECs agree there existed elements of collaborative partnership in all twelve studies reviewed.
Social value	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	All the reviewed studies were of social value, according to the local and international RECs.
Scientific validity	√	√	√	**x**	√	√	√	√	√	√	√	√	√	√	√	**x**	√	√	√	√	√	√	√	√	**Protocol 2**: International REC had concerns about the scientific validity of the study. They pointed out that the objectives were not specific and measurable; the study sample was not indicated; method of data collection was not well explained and neither was the research staff clearly outlined. **Protocol 8**: International REC had issues with the scientific validity of the protocol. The REC pointed out that the sampling procedure was not outlined and the sample size was also not defined.
Fair selection of study population	√	√	√	**x**	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	**Protocol 2:** International REC had issues with the selection of the study population. The inclusion/exclusion criteria of the protocol were vague.
Favourable risk-benefit analysis	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	All RECs (international and local) were satisfied with how the risk-benefit analysis was addressed in all the protocols.
Independent review	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	All RECs (international and local) were satisfied with how the principle of independent review was addressed. All protocols had adhered to the Helsinki Declaration guideline which stipulates that a statement about the ethical considerations be incorporated in protocols.
Informed consent	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	International and local RECs were satisfied with the application of the informed consent principle in all the protocols.
Respect for recruited participants and study communities	√	√	√	**x**	√	√	√	√	√	√	√	√	**x**	√	√	√	√	√	√	√	√	√	√	√	**Protocol 2**: International REC had concerns about how the principle of respect for recruited participants and communities was going to be maintained. The study had not addressed how confidentiality of participants was going to be upheld. **Protocol 7**: Local REC had ethical issues with the study concerning the respect for recruited participants and study communities. Local REC had issues with confidentiality being maintained due to the misuse of the word 'anonymised'.

1: Local Research Ethics Committee
2: International Research Ethics Committee
Key:
√ **No issues**
X Have issues

5.4.1 Collaborative partnership

Most of the protocols demonstrated a collaborative partnership between international organisations, local communities, health departments and the academic institutes. As illustrated in Table 5, both the local and the international RECs were in agreement that all twelve protocols demonstrated collaborative partnership.

5.4.2 Social value

Table 5 demonstrated that the reviews conducted by both the international and local RECs with regard to the principle of social value agreed that all protocols had social value. Besides outlining the benefits of the study to the host communities, the protocols also accommodated the four benchmarks that ensure social value, namely identifying the beneficiaries, outlining the actual benefits, enhancing mechanisms of social value through collaborative partnership and demonstrating the intention to disseminate the results, as well as involving partnerships with the existing health systems in the conduct of the research (Emanuel, Wendler, et al., 2004). Protocol 2, for example, stated that they "hoped to address the knowledge gap in the identification of children at risk". Both the local and international RECs noted that all protocols had no intention of disrupting normal access to health services.

5.4.3 Scientific validity

Variability between the local and international REC was noted for scientific validity, where the international REC raised concerns for two of the protocols, although the local REC was satisfied. The international REC queried the objectives and sample size in one protocol and was concerned with the use of a single location for justifying the sampling strategy in another protocol. Their queries contributed 22% of the total queries for scientific validity.

5.4.4 Fair selection of study population

The international REC queried the fair selection of the study population in one protocol, which contributed 11% of the total dissimilarities between the international and local RECs with regard to the ethical framework of Emanuel, Wendler et al. (2004). The international and the local RECs clearly approved the fairness of study population selection for the remaining eleven of the twelve protocols (89%).

5.4.5 Favourable risk-benefit analysis

Evaluation of the protocols according to the risk-benefit principle had a 100% similarity rate between the local and international RECs. This principle explicitly entails that RECs should ensure that risks are minimised (Emanuel, Wendler, et al., 2004). The risks in studies presented for review were outweighed by the potential benefits envisioned. Some of the benefits included (1) immediate direct health care services to participants found to be affected and (2) changes or modification of health policy to enhance equal health care delivery. Though most of the studies did not have direct benefits to the community and/or participants, there was potential benefit to the whole health care system. Studies without direct benefits showed that they could influence larger studies, which in turn had the potential of benefitting the whole country without putting the participants from non-participating communities at risk.

5.4.6 Independent ethics review

In Table 5 above, both RECs agreed that the protocols reviewed had satisfied the independent review principles. No regulatory concerns were raised by either the international or local REC. According to the reviews, all the proposals adhered to the international guidelines. The international and local RECs agreed that measures had been put in place to guarantee transparent application of this principle and its benchmarks.

5.4.7 Informed consent

Table six shows the proposals reviewed for the principle of informed consent by both RECs. A quarter (25%) of the proposals had no changes suggested by either REC to the consent forms. All the proposals had either informed consent forms reviewed which supplied satisfactory scientific, ethical and legal knowledge, or they requested waiver of consent. The majority (75%) of the protocols, reviewed by both the international and local RECs, applied for waiver of consent or gatekeeper's permission because they would be using routine data without human participant contact. In Table 6, protocols 1, 4, 5 and 9 provided detailed informed consent forms that would be given to the participants. Protocols 2, 3, 6, 7, 8, 10, 11 and 12 stipulated that, due to the nature of the studies, which were mainly retrospective, a consent waiver was applied for.

Protocols, which were going to be administering informed consent clearly outlined potential risks, risks and methods which the studies were going to employ to extract the information. Participants were given the option to withdraw from the study at any given time, implying

participation in the study was voluntary and enough information was given to participants to make an informed decision. Studies using telephonic interview, for example protocol 12 (phase two), assured the RECs that consent forms were going to be sent to participants prior to these telephonic interviews. As the studies were going to be carried out within local communities, Table 6 summarises that the gatekeepers or custodians of data in terms of retrospective studies were notified and their permission would be sought. Both RECs agreed with each other on their review of this principle. There were no disparities in review of the informed consent principles between the RECs and they allowed the waiver of consent when requested (Table 6).

Table 6: *Protocols with consent waiver against those requiring consent*

Protocol Number	Administering Consent	Consent Waiver
1	The study indicated that it would only enrol participants after they had given their written consent to take part in the study. Participation was voluntary and without consequences to those who withdrew later on.	
2		Review of documents with no human contact participant. Study applied for consent waiver.
3		The study was to use routine patient data without getting into contact with the actual patients. Records were going to be de-identified, hence the application for consent waiver.
4	Participation in the study was based on the provision of written informed consent.	
5	Participation in the study was guaranteed by completion of informed consent. The consent was obtained through both written and verbal means (for the illiterate).	
6		Not feasible to obtain informed consent from individual participants, thus the application of consent waiver.
7		The study is to be a programmatic evaluation of health facilities with no contact with human participants, hence application for waiver of informed consent.
8		Data to be used will not contain any individual participant names and will be collected from national database - no contact with human participants, thus the application for consent waiver.
9	The qualitative component of the study required a written consent from its participants.	The quantitative component was a retrospective analysis of documents. The study had no contact with human participants; hence they applied for a consent waiver.
10		The study would use routinely collected, retrospective data; thus, it qualifies for a consent waiver as it is difficult to obtain individual consent.
11		Project will make use of routine data on ETR - applicable for consent waiver as there is no contact with human participants.
12		Waiver of individual consent will be used, as routine data on ETR will be used.

5.4.8 Respect for recruited participants and study communities

The proposed ethical framework by (Emanuel, Wendler, et al., 2004) specifically requires respect for study communities and participants (Lidz et al., 2012). Regarding the principle of respect for participants, there were concerns raised in two protocols (22 %) (Table 5). The main concern raised was how confidentiality was to be maintained; each REC raised this issue in one protocol each. For the rest of the protocols, there were no issues raised, with a similarity of 78% with regard to this principle.

5.4.9 Other issues

Table 7 demonstrates protocols which had other issues besides concerns with the eight ethical principles outlined by (Emanuel, Wendler, et al., 2004).

Table 7: *Non-ethical issues raised by RECs*

Protocol	RECs	Issues Raised
1	1	Both the local and the international RECs had no ethical concerns with the protocol.
	2	
2	1	No concerns regarding ethical issues were raised by the local REC.
	2	The REC had concerns with the administration issues. Research staff were not specified, especially for data collection.
3	1	No issues
	2	
4	1	No issues
	2	
5	1	No issues
	2	
6	1	No Issues
	2	
7	1	The local REC had budgetary issues. They felt the budget for some equipment was overstated.
	2	No issues
8	1	No issues
	2	International REC had concerns with the study timeline, which made it appear as if the study had already begun (without ethical approval).
9	1	No issues
	2	The international REC had concerns with the study title which they pointed out to be too long and confusing.
10	1	No issues
	2	
11	1	No issues
	2	
12	1	No issues
	2	

Key: 1: Local REC; 2: International REC

Most of the queries raised by the RECs (44.44%) (see Table 5) were regarding other issues which could not be coded under the eight principles of the ethics framework proposed by Emanuel, Wendler, et al. (2004). The local REC raised 25% of these queries and the international REC 75%. Concerns were mainly regarding study administration (25%), research budget (25%), study timelines (25%), document format and study titles that were too long (25%). While the international REC queried the study administration, study timeline and too long a study title, the local REC was concerned with budgetary issues. While these queries raised by both the international and local RECs were not ethical in nature, they had a bearing on how the studies under review would be ethically implemented. Such issues have the potential to derail the implementation of studies beneficial to participants.

5.5 Summary

In summary, the international and local RECs similarity in ethics review was found for the majority of protocols (78%), while there was a difference in ethics review for 22%. There was a clear indication that RECs (both local and international) adhered to the ethical principles proposed by Emanuel, Wendler, et al. (2004), confirming the Emanuel et al model in analysing ethics process.

CHAPTER 6: DISCUSSION, CONCLUSIONS AND RECOMMENDATIONS

6.1 Discussion of findings

The study objectives were to investigate the similarity and/or variability in ethics review for research protocols subjected to multiple-REC review and also to determine if local and international RECs review protocols according to the ethical framework for clinical research outlined by Emmanuel, Wendler et al. (Emanuel, Wendler, et al., 2004).

Research regulations concerning oversight differ from country to country and research in developing countries is often cited as problematic (Rugemalila, 2001). Findings in the current study revealed that local RECs have been able to apply the ethical regulations in the same way as the international REC, notwithstanding the minor differences identified. Discretion has been given to RECs to translate and employ country-specific and federal regulations to protect human participants in research (Silverman, Hill, & Sugarman, 2001). This study found that both the international and local RECs adhered to the ethical framework for clinical research review, proving that the framework offers an integrated and coherent ethical guideline (Emanuel, Wendler, et al., 2004).

Major variability noted was on other issues besides the eight principles of the framework. The international REC raised two-thirds of those issues. In terms of scientific validity, the international REC raised queries about the study objectives and sample size. According to Freedman (1987), for a study to be scientifically valid it should be designed and managed in a manner which enables valid data to be generated. Freedman (1987) also posits that a study with too large or too small a sample size is considered unethical. Thus, omitting to indicate a sample size in the protocol fails to present an opportunity for RECs to ethically review the proposals. A study sample which is poorly controlled can neither confirm not disconfirm hypotheses (Freedman, 1987).

Concerns were also raised by the international REC on the principle concerning fair selection of study participants; this was, however, was not an issue for the local REC. In accordance with Miller, Emanuel, Rosenstein, and Straus (2004), selection of study participants should be done in line with the study objectives in order to avoid unnecessary participation of vulnerable

populations. Selected participants should receive, if possible, direct or potential benefits of the study (Wassenaar & Rattani, 2016). Therefore, a study should contain clear and justifiable inclusion and exclusion criteria (Wassenaar & Rattani, 2016). A study by Labrique, Kirk, Westergaard, and Merritt (2013) on injection drug users (IDUs) living with human immunodeficiency virus (HIV) clearly outlines the importance of this principle, fair selection of participants, more so if the study is an interventional one where there is possibility of participants benefitting from it (Labrique et al., 2013).

Similarities were observed regarding collaborative partnership, social value, informed consent, independent review and favourable risk-benefit analysis. Studies done to date on REC variability, such as Abbott and Grady (2011) and Tsoka-Gwegweni and Wassenaar (2014), found out that a major source of variation concerned the informed consent principle; however, the present study demonstrated consensus between the RECs in this regard. The majority of studies requested waiver of consent to use available clinical data. Application for consent waiver has become synonymous with operational research, as these studies are mainly quality improvement research or research with stored samples, making it impracticable to obtain informed consent (Miller & Emanuel, 2008).

Research without consent is justifiable when research does not interfere with the participants' rights, when it poses minimal risk and when it is not feasible to obtain consent (Gelinas & Miller, 2016; Miller & Emanuel, 2008). Gelinas and Miller (2016) state that it is also acceptable when research interference with the right of the participants to privacy is outweighed by the social value derived from the research (Gelinas & Miller, 2016). Operational research often deals with retrospective data or data already in the public domain in which case there is no interaction with human participants and it is arguable that this data is available for research purposes without consent (Sixsmith & Murray, 2001). The need for individual informed consent was clearly addressed within the proposals reviewed, where this was appropriate.

Though the variability was minor (and could be considered negligible), a number of issues could be attributed to those differences. These minor differences between the RECs' reviews could easily be attributed to a number of factors, including the composition and the structure of RECs. According to Klitzman (2014) variability in review can stem from the idea that some RECs feel they have a role to play in the scientific design of a protocol; at the same time, the

similarities could also be attributed to the 'need' by local RECs to lure researchers to their institutions.

Most studies of RECs done to date focussed primarily on the REC's structure and variation in RECs' responses to a protocol for a multi-site study (Dziak et al., 2005; Ferguson & Master, 2016; Kass et al., 2007). The current study tried to focus on the application of the framework's principles and their benchmarks by international and local RECs. Findings from the current study show that it is possible to use the framework as a guiding principle in proposal review and this is supported by the study done by Tsoka- Gwegweni and Wassenaar. While the study by Tsoka-Gwegweni and Wassenaar (2014) was based on the application of the framework by one REC, it validates that the ethical principles of the framework can be used in review of research protocols in developing countries. Though the multiple review model has a number of advantages, including reinforcement of the protection of study participants and balancing conflictual ethical issues (Stair et al., 2001), the results of this study showed that the minor dissimilarities in the review outcomes of the involved international and local RECs were not sufficient to warrant the multiple review process. This lack of variability in the RECs' review outcome highlights the potential disadvantages of the use of multiple RECs in terms of leading to unnecessary delays (Klitzman, 2014). This practice thus brings about redundancy to the research oversight process, especially when all the involved RECs arrive at more or less the same decision in their protocol reviews.

The difference in research ethics review by the international RECs (77.78%) compared to the local RECs (22.22%) could actually represent the over possessiveness of the international RECs earlier on stated in literature. On the other hand it could either support the theories that research ethics review capacity in LMICs is still lagging behind with the trainings offered so far focusing on individual RECs. Supporting the view by Hyder, Zafar et al. (2013) that there is need for a framework to evaluate research ethics capacity in LMICs.

The lack of major dissimilarities question the assertion by Yassi et al. (2013) that there is a need for more ethical guidelines for researchers in HICs when they are collaborating with LMICs. While it cannot be disputed that multiple-REC review provides site-specific review, ways should be devised to harmonise the process and mitigate the disadvantages of the multiple-REC process which have become synonymous with it. According to Edwards et al. (2004) it is the duty of the multiple-REC review process to balance competing ethical

principles. This can be attained by the use of a single REC, in consultation with stakeholders, thereby calling upon the principle of collaborative partnership. This would mean that the principle is not only limited to research implementation but also encompasses the ethical review process.

The similarities in the review process outcome by both the international and the local RECs demonstrated that, if guidelines are adhered to in the review of collaborative research, it becomes unnecessary to employ the multiple-REC review model. Though it is still a fact that RECs in developing countries grapple with the interpretation of international guidelines which are deemed not compatible with their local regulatory environments (Enzle & Schmaltz, 2005; McIntosh et al., 2008; Ndebele, Wassenaar, et al., 2014), more should be done to align and simplify the guidelines so that there is a globalised standard ethical review framework (McIntosh et al., 2008). The similarities in ethical review of protocols shown in this study reflect that despite lack of standardised forms being used by RECs, highlighted by Gold and Dewa (2005) as a major pitfall of multiple-REC review model, the process is also a waste of resources earmarked for research and continues to impede the ethical review process. Following a laid-down ethical framework has shown that RECs in developing countries are equally capable of providing research oversight. Having protocols reviewed by one REC can eliminate the administrative and financial costs, as well as slow turnaround time (Tully et al., 2000), which is common when multiple RECs are reviewing the same protocol. It seems clear that this does not provide enhanced protection to the study participants as it delays them from receiving research benefits in good time (Gold & Dewa, 2005; Jamrozik & Kolybaba, 1999).

In view of the minor dissimilarities in ethical review between the international and local RECs' reviews in this study, RECs in host countries should be responsible for the protocol review of proposed studies (Hyder et al., 2004). This should enable them to control the nature and type of guidelines suitable for research in their countries (Hyder et al., 2004). The view is shared by Bhutta (2002) who asserts that local research ethics review models should be developed as this is linked to actual research implementation. According to Hyder, Dawson, Bachani and Lavery (2009), use of international guidelines is not practical in developing countries but the framework has meritorious goals sufficient to address ethical problems inherent in the multiple REC review model (Killen & Fauci, 2002).

The secondary aim of the present study was to determine if the protocols were reviewed according to the ethical framework for clinical research as delineated by Emanuel, Wendler, et al. (2004) for collaborative research in developing countries. The study by Tsoka- Gwegweni and Wassenaar (Tsoka-Gwegweni & Wassenaar, 2014) analysed the REC minutes for a single REC according to the ethical framework of Emanuel et al. Tsoka-Gwegweni and Wassenaar (2014) focused on one only and confirmed that RECs adhere to Emanuel, Wendler et al.'s framework. The present study has shown that both the international and local RECs, in their review of collaborative research protocols, adhered to the principles outlined in the ethical framework by Emmanuel, Wendler et al. (Emanuel, Wendler, et al., 2004).

Literature has advocated for adoption of all the eight principles when reviewing protocols for conducting research in developing countries, to ensure participants are protected from exploitation and research is responsive to the health needs of the community (Lairumbi et al., 2008.). Studies by Truog (2008), Lidz et al. (2012) and Luseno et al. (2014) have evaluated how RECs employ at least one of the principles outlined in the framework in proposal reviews. More comparable to the current study is the study by Lidz et al. (Lidz et al., 2012) which evaluated RECs' adherence to the Common Rule. Some of the Common Rule principles are similar to Emanuel et al.'s framework (Khanlou & Peter, 2005). However, a study done in a developed country found that elements of the Common Rule were not applied uniformly across the RECs, while there were only minor disparities documented in the present study (Lidz et al., 2012).

While ethics is cross cultural and should be governed by the norms and values of the research participants (Christakis, 1992), the ethical framework by Emanuel et al. (Emanuel, Wendler, et al., 2004) is sensitive to cross-cultural issues, making it easy to be adopted by different RECs in their reviews of research protocols (Tilburt & Kaptchuk, 2008). Despite minor differences in their reviews of research protocols, the similarity between the international and local RECs' reviews shows that the ethical framework is not static but can be used and adapted to suit the different developmental levels of the RECs. The versatile character of the ethical framework enables RECs in developing countries to review protocols similarly to international RECs. The ever-increasing adaptation and application of western ethical considerations by developing and developed RECs has enabled the framework to be cross cultural (Christakis, 1992). Thus, when properly applied as was witnessed in the current study, the framework enables the RECs to satisfy both the investigators' and the participants' cultures without major ramifications (Killen

& Fauci, 2002; Shapiro et al., 2001), reducing the '10/90' gap (Davey, 2004). The framework, with its eight principles and associated benchmarks, facilitates dialogue between diverging individuals, enabling them to reach a compromise thereby bridging gaps in research ethics review (Molyneux, 2009).

Studies done to date, whose protocols were reviewed using the Emmanuel et.al ethical framework include the study on autism in LMICs by Daley, Singhal, and Krishnamurthy (2013); the Bucharest Early Intervention Project (BEIP) and the analysis of ethical considerations related to experimental drugs by Rid and Emanuel (2014), as well as a community-based research study with vulnerable children in Rwanda by Betancourt et al. (2016). All the three studies were able to fulfil the dictates of the framework, highlighting the need for a collaborative partnership among communities, researchers, international organisations and the academia. In following the framework, RECs (international and local) made sure the collaborative partnership was not about the researchers gaining access to participants but that their proposed research has a positive impact (Betancourt et al., 2016; Daley et al., 2013; Rid & Emanuel, 2014). By using the ethical framework, researchers were able to build protocols which promote safety of participants and adequately allocate resources (Betancourt et al., 2016). The framework was also used in the ethical analysis of Alzheimer's disease (Peters, Beattie, Feldman, & Illes, 2013), and was found to be helpful.

While there is relatively little published literature on experiences of RECs reviewing protocols based on the framework in developed countries, the use of the framework in research ethics review - if adopted as a guiding framework - has shown the capacity to demystify myths such as therapeutic misconceptions and misunderstandings which have the potential of derailing the ethical aspects of a research study (Marsh et al., 2008). Principles such as collaborative partnership help minimise internal risks such as social identity and equilibrium and lessens local viewpoints such as stigmatisation (Marsh et al., 2008). This also creates a conducive environment for communities and recruited participants to receive their fair share of benefits from the research study (Emanuel, Wendler, et al., 2004) and enhances all the other principles.

There is the notion that RECs in developing countries still need training in research ethics capacity (Ndebele, Wassenaar, et al., 2014); this has been made possible through various training initiatives in research ethics training programmes made available by the National Institutes of Health (NIH) (Ndebele, Wassenaar, et al., 2014). Therefore, adopting the multiple-

REC review model for a single-site study may be a mere duplication of effort and waste of resources which can be channelled into the actual implementation of research to benefit participants. This is in line with Benatar and Landman (2006) assertion that ethics in South Africa has developed in several stages, responding to evolving forces similarly to other developing countries. As pointed out by Tsoka-Gwegweni and Wassenaar (2014), it is the RECs' obligation to use existing national regulations and guidelines, but if they adopt the framework for protocol review in developing countries, there will be little or no variability between REC reviews as the principles of the ethical framework are shaped by cultural norms and values. RECs are made aware of these norms and values through the principles and benchmarks of the framework when they use it for providing research oversight (Luseno, 2014).

6.2 Limitations

The study had a small sample; hence, it is not necessarily representative of all protocols reviewed by multiple RECs. It also focussed only on operational research, making generalisations to other fields of health care research not possible. However, the limitations were outweighed by the fact that useful local and specific information regarding the multiple RECs review process was collected which could be used to design larger, more generalisable studies and the small sample collection represented quality rather than quantity. The researcher was not made aware of the RECs' structure and composition, and therefore was not able to ascertain how they based their decisions, nor how they calculated the risk-benefit ratio.

6.3 Key conclusions

The present study sought to investigate the similarity and/or variability in ethics review for research protocols subjected to multiple-REC review. It also set out to determine if protocols were reviewed according to the ethical framework for clinical research as suggested by Emanuel Wendler et al. (Emanuel, Wendler, et al., 2004) in collaborative studies. While the sample size was generally too small to reach conclusive results, the researcher considered the high quality of data such a sample size would present. Variability and similarities were noted in the responses to protocol reviews of the international and local RECs and it was also noted that both international and local RECs adhered to the ethical framework when reviewing protocols.

The research findings have shown that uniformity exists when local and international RECs apply the Emanuel, Wendler, et al. (2004) ethical framework when reviewing study protocols. Findings suggest that while variability between reviews by international and local RECs in collaborative research exists, it is outweighed by the similarities observed, hence can be considered insignificant. The dissimilarity between reviews does not necessitate protocols to be reviewed by multiple RECs as this exacerbates delays in the implementation of the research studies which could be beneficial to host communities while also wasting finite resources which could be channelled towards the actual implementation. However, disregarding the multiple review model can only be done after a new model which addresses the concerns of the sponsor country and host country has been put in place. The research findings also noted that, despite the notion that RECs in developing countries are still under developed, they are now capable of providing research oversight in complex studies, resulting in no protocol deviations. There was a consistency in protocols reviewed by the international and local RECs when compared to the published articles for those protocols. This showed that there was little or no deviations from the protocols by the researchers when implementing the studies.

The current study also found that the ethical framework by Emanuel, Wendler et al. (2004) managed to produce a methodical and far-reaching framework for reviewing protocols in developing countries. The results showed that the proposed framework by Emanuel, Wendler et al. (2004) can be used by all RECs as a major guiding principle as it simplifies the international codes and regulations and is applicable in different cultural settings. With the framework in use, different countries are able to review protocols following the same benchmarks, taking into cognisance diverse cultural backgrounds and arriving at very similar conclusions. The findings also highlighted that the framework can be used in different types of biomedical research and no principle of the framework is superior to any other; rather, they complement each other and produce a sequence which is interlinked.

RECs have no formal guidance in review of collaborative research; hence, there is an impetus to adopt the framework for collaborative research between developed and developing countries. The envisioned ethical framework can be a tool for both the local and the international RECs in review of protocols for collaborative research

6.4 Recommendations

This study recommends the expansion of the use of the Emanuel et al.(2004) framework for protocol review in collaborative research. In addition, roles to be played by the international and local RECs should be clearly outlined rather than having the duplicated effort currently being witnessed. From the research study it was not clear if the similarities witnessed in the reviews were as a result of the local RECs 'rubber stamping' what the international RECs had done. Therefore, it is advised that a pilot study be carried out to ascertain the capability of the local RECs to review protocols on their own without the influence of the developed countries' RECs. Bearing in mind that ethical protocol review is still a relatively new phenomenon, coupled with the various pitfalls that RECs in developing countries still grapple with, there is a need to monitor that RECs not only in South Africa but in other developing countries are adhering to the principles and benchmarks of the framework. Future research should assess the success of protocol review using the ethical framework. Ascertaining the knowledge, attitude and perceptions of REC members in developing countries towards the ethical framework proposed by Emanuel, Wendler, et al. (2004) is imperative to guarantee appropriate tailoring of basic understandings of the ethical framework.

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APPENDIX 1: GATEKEEPER'S PERMISSION

10 June 2015.

Prof M Kruger

Department Paediatrics and Child Health

Stellenbosch University

Dear Prof Kruger

Ms Florence Mutevedzi

It is with great pleasure that I give permission for Ms Florence Mutevedzi, a Masters of Social Science student of Health Research Ethics at the University of KwaZulu-Natal, to do a retrospective analysis of protocols submitted by the Desmond Tutu TB Centre to multiple ethics review committees as part of her research on the **"Comparison of Research Ethics Committees (RECs) review in protocols reviewed by multiple ethics review committees".**

I wish the candidate well with her research

I forward an email from Dr Rick O'Brien, chairperson of the Ethics Advisory Group at the Union, the other organisation approving the Operational Research Assistance Programme sub-studies.

Kind regards

Nulda Beyers

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APPENDIX 2: ETHICS APPROVAL LETTER (BREC)

UNIVERSITY OF
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21 June 2016

Ms F Mutevedzi (214580938)
Discipline of Psychology
School of Applied Human Sciences
vim_bai@yahoo.com

Dear Ms Mutevedzi

Protocol: Comparison of Research Ethics Committees (RECs) review in protocols by multiple ethics review committees.
Degree: M Soc Sci
BREC reference number: BE344/16 (HSS/0108/015M)

I wish to advise that your application dated 31 May 2016 has been noted by the Chair of the Biomedical Research Ethics Committee (BREC).

The chair has granted reciprocity to the approval letter from HSSREC dated 16 September 2016.

This approval will be noted at the next Biomedical Research Ethics Committee meeting to be held on 12 July 2016.

Yours sincerely

Ms Anusha Marimuthu
Senior Admin Officer: Biomedical Research Ethics Committee

cc postgraduate officer: Khanyile@ukzn.ac.za
cc supervisor: Prof Mariana Kruger