

UNIVERSITY OF KWAZULU-NATAL

An evaluation of the ethical concerns of
Zimbabwean Research Ethics Committees (RECs),
using the Emanuel et al. (2004) principles and
benchmarks

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Abstract

The nature of concerns and issues raised by research ethics committees (RECs) during protocol review meetings can be informative about the principles which they apply in protocol review, yet little is known about the actual concerns they raise. This study sought to examine these local concerns in light of the internationally acclaimed Emanuel et al. (2004) framework and also describe the pattern of the ethical issues raised.

Protocol review meetings' minutes can provide a rich source of information and insight into the concerns that RECs raise during protocol review meetings. These concerns are central to the practice of research ethics: they shape the nature of research and sometimes even alter the knowledge it produces, and by doing so, contour what comprises ethical research and how this can be pursued. Nevertheless, these concerns have seldom been subject to scrutiny. Accordingly, this study carried out a qualitative analysis of minutes written during the review of protocols by a Zimbabwean REC overseeing biomedical, health and behavioural research. It sought to offer a description and analysis of the REC's concerns, using the Emanuel et al. framework. It is hoped that this study will provide a useful window into the REC's concerns.

Key findings were that 65% of concerns raised during REC review fitted into the Emanuel et al. (2004) framework. Of these, the most frequently raised concerns revolved around the principle of informed consent. The principle with the least number of concerns was social value. The study also noted a significant number of concerns which did not necessarily fit into the Emanuel et al. (2004) framework which seems to suggest the REC's preoccupation with routine, procedural concerns.

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Chapter 1

Introduction

Lately, as Moreno (1998) puts it, IRBs have been 'under the microscope'. A great deal has been published on the nature, capacity and functioning of RECs in developed and resource-poor settings. Though positive strides and progress have been noted in the capacity of RECs in African countries (Ndebele et al., 2014), little has been published in terms of the actual ethical concerns that African RECs raise during ethical review of protocols.

Health research is generally guided by international ethical codes and legislation derived from the basic moral research principles of autonomy, beneficence and justice (Macrae, 2007). The obligation for protection of participants lies with research ethics committees (RECs) and/or institutional review boards (IRBs), whose main function is to review research projects for their proposed ethical acceptability, clinical usefulness and scientific merit. Protection of study participants is at the core of ethics review of research study protocols. Failures in the review process itself may put the lives and welfare of research participants at risk, especially if the REC does not apply effort in reviewing ethical and scientific aspects of research protocols. Much has been proffered in terms of guidelines and policies, both internationally and locally, including capacity-building interventions targeting REC members and their secretariat (Nyika et al., 2009). This was all done with a view to enhancing the capacity of RECs or IRBs so that they can be able to offer a sound ethical review process of research projects in their settings.

The Emanuel, Wendler, Killen and Grady (2004) framework, which has until recently largely been applauded for its perceived universal nature, has been used as a tool to analyse the actual concerns that African RECs raise (Tsoka-Gwegweni & Wassenaar, 2014). While this framework is compatible with most settings, it must be highlighted that this study has shown that RECs may raise other issues outside of this framework. These issues are regularly evolving in line with the local socio-political situation, national policies and internal undercurrents within the RECs in question. These factors may thus give rise to other concerns that may not necessarily fit into the Emanuel et al. (2004) framework.

This study conducted a retroactive document examination of the records of a Zimbabwean REC's meeting minutes. The study endeavoured to identify the concerns that were raised by the REC. This may help to bring a better understanding of the ethical queries raised by the

REC and the applicability and universality of the Emanuel et al. (2004) framework. This study, thus aimed to identify and describe the pattern of ethical concerns and issues raised by the REC in their reviews of research protocols and also to analyse the ethical issues and concerns according to the principles of the Emanuel et al. (2004) framework, ranking these principles, and identifying concerns that did not fit the framework.

Chapter 2

Literature review

2. 1. Background

According to Beauchamp and Childress (2009), the concern about the moral status of research has grown out of concern about ostensibly vulnerable populations. The need to provide extra protection for populations perceived to be vulnerable forms the basis for both clinical and health research ethics. By 1953, the United States' National Institutes of Health required that all proposed clinical research studies at its Bethesda centre get approval from a 'protection of human subjects' review panel. In 1966, the United States Public Health Service published its first rules extending this review requisite to all 'extramural' research supported by the agency. These regulations were additionally reviewed in 1971 and 1974 and led to the setting up of institutional review boards (IRBs) at several institutions getting funding for research from the federal government.

Macduff, McKie, Martindale, Rennie, West, and Wilcock (2007) report that procedures for ethical review of health research differ substantially across, and sometimes even within, different nations. Differences in cultural dynamics, economic standing and geographical context may at times explain the differences. Despite the differences in context, the basic functions of RECs, as stated by Benatar (2002), are to: (i) assess the risk-benefit ratio of a research study; (ii) help and guide researchers on matters of research ethics and; (iii) monitor and audit the research. Hence, RECs fundamentally ensure that research carried out is ethically sustainable and complies with local specific regulations (Guillemin, Gillam, Rosenthal, & Bolitho, 2012).

Though still trailing behind these trends, Africa and the developing world in general have been making strides to keep up with international trends (Kass et al., 2007a). The field of health research ethics is at a transitional point in most African countries, where health research ethics and health RECs are changing from being a poorly regarded, albeit necessary element of doing research in developing countries to a fully integrated and respected aspect of all medical research in Africa (Kass et al., 2007a). 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). Though African RECs have developed their own guidelines for ethics review (Ateudjieu et al., 2010), they are basically informed by

international guidelines (Ndebele et al., 2014). To help RECs and researchers with the review of research protocols, Emanuel et al. (Emanuel, Wendler, & Grady, 2000, 2008; Emanuel, et al., 2004) undertook a careful analysis of several major international guidance documents and came up with a framework comprising eight principles and associated benchmarks to guide ethics review of biomedical research. The first version of the framework (Emanuel et al., 2000) did not include the principle of collaborative partnership and hence it had seven principles. While RECs are under no obligation to adopt the framework in whole or in part, the framework has received acclaim and reference in both international and national ethical fora (Tsoka-Gwegweni & Wassenaar, 2014).

Though the Emanuel et al. framework was essentially developed as a universally applicable tool for ethics review of health research study protocols, very little is known on whether the actual concerns raised by RECs in Africa during the review process of protocols demonstrate compatibility with this framework. Tsoka-Gwegweni and Wassenaar (2014) made the first attempt to extract minutes from REC meetings and analyse them utilising the Emanuel et al. (2004) framework. This project aims to complement that work. This study was motivated to investigate the concerns raised by a Zimbabwean REC, particularly considering the alignment of the concerns raised with the Emanuel et al. framework. The absence of elaborate information on the work of African RECs and how much their work reflects the relevance of the Emanuel et al. (2004) framework has motivated the conception of this study.

2.2 History of RECs in Africa and Zimbabwe

There are few studies that focus closely on the development of RECs in Africa. Silaigwana and Wassenaar (2015) found 4 studies that proffered a description of the history of African RECs: Henderson, Corneli, Mahoney, Nelson and Mwansambo (2007), Kass et al. (2007a), and Oyedeji (2011) and Rwabihama et al. (2010) (all in Silaigwana & Wassenaar, 2015). A study of 20 RECs in Africa reported that nine countries had formed RECs in the 1980s, whereas the other eleven were established during the 1995 to 2003 period (Rwabihama et al., 2010, in Silaigwana & Wassenaar, 2015). This clearly demonstrates the fact that RECs in Africa are recent but steadily growing establishments.

South Africa, which boasts the oldest African REC, had its first REC established in 1967 at the University of Witwatersrand. The Medical Research Council of Zimbabwe was formed soon thereafter in 1974 (Rwabihama et al., 2010; Kass et al., 2007a in Silaigwana & Wassenaar, 2015). The National Health Sciences Research Committee of Malawi was created in 1988 (Henderson et al., 2007). One more study cited by Silaigwana and Wassenaar (2015)

reported that six of eight Nigerian RECs had been formed in the previous five years (Oyedeji, 2011, in Silaigwana & Wassenaar, 2015). The requirement by international funders to have ethics approval for collaborative research in both in the sponsor country and the host nation is also credited for the formation of most RECs studied in one survey (Rwabihama et al., 2010, in Silaigwana & Wassenaar, 2015).

Silaigwana and Wassenaar's (2015) study found that one survey indicated that ten of 28 African nations did not have RECs at national level, though they noted that eight of those countries had what could be termed *ad hoc* mechanisms for ethical review of research protocols. This simply points to the fact that the establishment and development of RECs is still a work in progress for some countries in the developing world, and for many of them it is a very new and recent development, especially those in Africa which have generally operated under significant resource constraints (Mokgatla, Bahati & Jsselmuiden, 2017).

In Zimbabwe, as noted above, the REC of the Medical Research Council of Zimbabwe was established in 1974. However, it only functioned intermittently up to 1992, when it became more officially operational. Two further African RECs were established in the 1980s; eight were initiated within the most recent couple of years, including two (Democratic Republic of the Congo and Kenya) established by a trainee (Kass et al., 2007).

Research ethics review in Africa has been improving steadily in the last decade. Only 36% of WHO African regional members did not have an established REC by 2007 (Kass et al., 2007a). According to Kass et al. (2007a), due to the challenges commonly associated with RECs in Africa, such as inadequate financial and personnel resources (Mokgatla et al., 2017), research ethics protocol review has varied tremendously, sometimes leaving research participants with little or no protection and their welfare solely depending on the researchers. Some RECs may also be inclined to provide approval without adequate ethics review (Silaigwana & Wassenaar, 2015), which may be a function of rampant corruption in Africa (Kass et al., 2007a). Thus, besides the poor socio-economic environment (Nyika, 2009), African RECs also have to deal with politicians who are sometimes found meddling in the running of the RECs (Ateudjieu et al., 2010; Kass et al., 2007a). The Kass et al. (2007a) study reported gross abuse of review procedures even by researchers, for example, unwarranted expedited review of more than minimal risk protocols. Therefore, this highlights the need to understand what concerns African RECs raise and how much these concerns reflect internationally acclaimed standards (Mokgatla et al., 2017)

2.2.1 Current governance of health research in Zimbabwe

While in most African countries there may be fragmentation in terms of how research with human participants is regulated (Nyika, 2009), in Zimbabwe, review and regulation of medical and health research projects is carried out by the Medical Research Council of Zimbabwe (MRCZ) which also doubles as the National Ethics Committee (NEC). The Medical Research Council of Zimbabwe (MRCZ) National Ethics Committee was established in 1974 under the *Research Act* of 1959 and Government Notice Number 225 of 1974 (MRCZ, 2016). This was done to give health researchers and institutions in which health research is done, independent ethical oversight of research carried out by those researchers or within those institutions. The REC is generally composed of ethicists, medical experts, scientists, a lawyer, religious and community representatives, to make a sum of fourteen members. The Medical Research Council of Zimbabwe (MRCZ) is a specialised Council of the Research Council of Zimbabwe (RCZ). Though the MRCZ is supported and established by the government of Zimbabwe through the Ministry of Health and Child Care, it is independent in its reflection, advice and decisions

Another regulatory body, the Medicines Control Authority of Zimbabwe (MCAZ), is responsible for regulating all clinical research of drugs conducted in Zimbabwe in terms of Part III of the *Medicines and Allied Substances Control Act* (Chapter 15:03). There are also other specific laws dedicated to research on specific issues in Zimbabwe, for example the *Anatomical Donations and Post-Mortem Examinations Act* which says: "Replacement tissue may be removed from the body of a living person for scientific purposes or therapeutic purposes". This is another piece of legislation that deals with the conduct of research involving human participants.

To receive ethics approval for research in Zimbabwe, the applicant must apply to the Medical Research Council of Zimbabwe (MRCZ – see Medical Research Government Notice Act (1974) and the Research Act (1986) and MRCZ (2016)). Requirements may vary slightly depending on whether the applicant is a student, local researcher or foreign researcher, but in all cases the initial stage would be to complete an ethics application form. In all cases the researcher must submit their completed application form together with: a) Research proposal summary; b) Full research proposal and an electronic version; c) Informed consent forms: (English & vernacular versions – in appropriate vernacular); d) CVs for the Principal and Co-Investigators; e) Drug brochure or supplementary information if applicable; f) Permission letter from head of institution where data is to be collected (for research in schools, a letter from the Ministry of Education is also required; g) Proof of funding on sponsor's letterhead.

While there has been some research on what the RECs should be doing and on their resource needs, there is little information available on what sort of concerns these committees raise when reviewing protocols (Tsoka-Gwegweni & Wassenaar, 2014). According to Kass et al. (2007a), most of the studies examining RECs is from developed nations. There has, however, been some effort to examine RECs in Africa's resource needs in light of HIV vaccine trial readiness (Milford, Wassenaar & Slack, 2006). However, no studies have really looked at the sort of concerns that RECs in Zimbabwe raise in the review of protocols. While there is information on the capacity and infrastructure for research protocol review in Zimbabwe (Ndebele et al., 2014), there is no information on what concerns RECs in Zimbabwe raise, and how those concerns might conform to international standards and guidelines. Kass et al.'s (2007a) study provides some data on how African RECs operate in general, and this includes their weaknesses, operating procedures, staffing, strengths and challenges, which is very valuable for international and African researchers working within Africa, and for increasing efforts to boost ethics capacity on this vast continent. However, there are international guidelines for ethics review and these guidelines should inform the review process of health research protocols in Africa and developing countries in general.

2.3 History of ethics review guidelines

History demonstrates that terrible atrocities in health research can occur if proper ethical guidelines and enforcement are absent or are not followed. According to Macrae (2007), several international bodies, including local governmental regulatory bodies, research entities and medical professional bodies, have striven to proffer guidance on how clinical trials should be conducted ethically. All these guidelines are rooted in the criminal trials at Nuremberg, following the Second World War (Markman & Markman, 2007; Rice, 2008). In an effort to avoid a repeat of such atrocities, the Nuremberg Code (which emerged from the trials at Nuremberg) set out vital principles that were to be observed when conducting research involving human subjects. This became the foundation for other international health research ethics guidelines such as the Belmont Report, the Declaration of Helsinki, and also the International Ethical Guidelines for Biomedical Research Involving Human Subjects of CIOMS (Macrae, 2007; Schüklenk, 2000; Weindling, 2001). RECs across the globe probably review protocols in line with these established research ethics guidelines and these have become a standard feature of the research environment internationally (Guillemin et al., 2012).

Many of these guidelines are often viewed as flawed because they were generally born out of atrocities and research scandals. They are perceived as responding to specific controversies,

thus they tend to focus on what was perceived as the transgression in the scandal (Emanuel et al., 2008). For example, the Nuremberg Code directly addresses the atrocities committed by the Nazi physicians, while the Belmont Report was a reaction to the Tuskegee Syphilis Study. It is in this light that these guidelines are often focused not on the entirety of research ethics, but somewhat on a definite practical issue needing to be addressed.

2.3.1 The Nuremberg Code

The Nuremberg Code, published in 1949, was the first historical guideline for research involving human subjects (Nuremberg Code, 1949; Quest & Marco, 2003). This code outlined the need for informed consent, but it did not discuss any issues to do with risk-benefit ratio or even the need for independent ethics review (Emanuel et al., 2000; Ghooi, 2011). This historical document was basically developed as a response to the Nazi atrocities committed during World War II, where in the name of research, horrific research was conducted on people without their individual consent. The Code, which is comprised of ten principles, shifted the focus from researcher-centred decisions to participants' empowerment and involvement in decisions regarding their participation in research (Nuremberg Code, 1949; Quest & Marco, 2003).

Despite the successful international acknowledgment and adoption of the code, vulnerable populations continued to be exposed to unethical research studies. In many cases, such people were used as research subjects without their consent, thereby demonstrating no respect for their autonomy (Quest & Marco, 2003). An example is the Tuskegee Syphilis Study of 1932 to 1972, in which the United States Public Health Service financed a research project that was assessing the natural progression of untreated syphilis in human beings (Amdur & Bankert, 2010; Corbie-Smith, 1999; Rice, 2008). The research study was initially considered ethical on the premise that there was no cure for syphilis at the inception of the study; however, treatment subsequently became available during the course of the study but was withheld from participants.

The Tuskegee study population was primarily drawn from the most vulnerable sector of American society, the barely educated 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 research study. Consequently, despite the discovery of penicillin as an effective treatment for the disease, study participants were not offered the available treatment. Studies such as the Tuskegee Syphilis Study gave the impetus to the establishment of ethics review systems, especially the promulgation of the principle of justice in the Belmont Report.

Some of the strong statements in the Nuremberg Code were also viewed as wrong; worth noting here is the statement that “*The voluntary consent of the human subject is absolutely essential*”. This statement has been perceived as prohibiting paediatric research (Emanuel, Wendler et al., 2004). These criticisms show how the Nuremberg Code is inadequate and lay the ground for further guidelines.

2.3.2 The Declaration of Helsinki

In addition to the Nuremberg Code, there is also the Declaration of Helsinki which was developed by the World Medical Association (WMA) in 1964; this has been revised several times, with the latest revision being the update of October 2013 (Lederer, 2004; Weijer & Anderson, 2001; World Medical Association, 2013a). The Declaration of Helsinki was mainly designed to ‘plug the gaps’ in the Nuremberg Code, with special focus on physicians doing research with patients. The need for a positive risk-benefit ratio and independent ethics review of research protocols are some of the issues at the core of the declaration (Lederer, 2004).

Lederer (2004) argues that the Declaration of Helsinki is the most prominent international ethics document governing the conduct of clinical studies. The Declaration of Helsinki developed a principle-based approach to ethics review that promotes ethical standards to ensure respect and protection, including observing the human rights of the participants (World Medical Association, 2013a). Protection of research participants was previously viewed as the responsibility of the researchers (Lederer, 2004). The Declaration of Helsinki focuses on issues that may pose harm to research participants (Goodyear, Krleza-Jeric, & Lemmens, 2007). The Declaration of Helsinki became the first ethical guidelines that required RECs to review research study protocols independently and also to monitor ongoing studies (Carlson, Boyd, & Webb, 2004; Rid & Schmidt, 2010; World Medical Association, 2013a). The emphasis on independent review of research is based on the need to deal with conflicts of interest and also safeguard the welfare of research participants by putting particular focus on informed consent, benefits and risks (Kass et al., 2007a). Based on these principles, researchers have an obligation to abide by the international and national regulatory standards (World Medical Association, 2013b).

The Declaration of Helsinki takes a holistic approach as it deals not only with health research involving human participants, but includes identifiable human biological material and data (World Medical Association, 2013b). According to Emanuel et al. (2004), these guidelines tend to emphasise what they term the ‘procedural safeguards’ of informed consent and independent review by a REC or IRB, principally so that they leave a paper trail that can

subsequently be audited. However, this renders these guidelines 'piecemeal' or lacking a comprehensive and systematic outlook.

2.3.3 CIOMS Guidelines

The World Health Organization (WHO) and the United Nations Scientific and Cultural Organisation (UNESCO) established the Council for International Organizations of Medical Sciences (CIOMS) in 1949. CIOMS was given the mandate to maintain collaborative research and also to provide guidance to researchers at an international level (Bhutta, 2002; Macrae, 2007; Weijer & Anderson, 2001). CIOMS, together with the WHO, developed guidelines based on the application of ethical principles that govern the conduct of biomedical research involving human participants as laid down in the Declaration of Helsinki. This was premised on the need to deal with socio-economic, legal and regulatory differences between developed and developing countries (CIOMS, 2016).

The CIOMS guidelines incorporate a framework which is meant to inform the challenges posed by modern-day research communities through dealing with multifaceted issues such as informed consent and its potential limitations; appropriate compensation for research participation; research with vulnerable populations; and general strengthening of ethical and scientific review capacity for biomedical research (CIOMS, 2016). Weijer and Anderson (2001) opine that the CIOMS guidelines are receptive to the health needs of the community in which research studies are to be conducted and they place an emphasis on protection of study participants in developing countries. Such protections include developing ethics review resources in host countries to enable research protocol review in both host and sponsor countries (Weijer & Anderson, 2001).

The CIOMS guidelines encourage countries to develop their own national guidelines and regulations for ethics review of research involving human participants, including consideration of local standards, socio-economic status and culture. International ethical regulations and guidelines are oriented more toward addressing controversies facing collaborative research and they pay less attention to local context-specific issues such as cultural diversity (Bhutta, 2002). The CIOMS guidelines also require that researchers obtain ethical approval before commencement of studies (CIOMS, 2016). While CIOMS guidelines give the RECs in host countries the power to review protocols with regard to inclusion and exclusion criteria (CIOMS, 2016), the guidelines do not provide sufficient ways of dealing with contextual issues that may arise from different RECs when they review protocols.

2.3.4 The Belmont Report

The Belmont Report was promulgated in response to unethical studies that continued to be conducted even after Nuremberg, including the Tuskegee Syphilis Study described above (Benham & Francis, 2006; Greaney et al., 2012; Varmus & Satcher, 1997). This report, which was published in the United States in 1979, provided a concise guideline and description of the mandate for review of research involving human participants. This report is premised on three distinct areas; this validates the boundaries between practice and research, basic ethical principles, and the application of basic ethical principles (National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research, 1978).

The Belmont Report acknowledges the existence of all the other guidelines (Greaney et al., 2012). However, its principles are more comprehensive and generalisable, valuing all stakeholders in the research process and ensuring they understand the pertinent ethical issues in the research. The document provides guidance to the work of RECs, including a framework for RECs to review protocols. This document laid out the fundamental principles of ethical research, that is, respect for persons, beneficence (and non-maleficence) and justice. These principles are actualised through the need for informed consent, risk-benefit assessment and the need for inclusion/exclusion criteria in participant selection (Cassell, 2000).

2.3.5 The US Common Rule

The international guidelines in their various forms did set the general tone for RECs but each country had to develop its own set of guidelines. For some developed nations, it was merely a case of reviewing their existing guidelines (Guillemin & Gillam, 2004). Other countries began producing and revising their own ethical guidelines, which were context specific (Guillemin & Gillam, 2004). Initially, the guidelines were generally meant for biomedical research but later on covered all research that includes human participants (Guillemin & Gillam, 2004). It is very important to highlight some of the guidelines in the United States because some of their guidelines do affect all research that is funded by the American Government internationally.

The United States developed the federal policy for the protection of human participants, which became popularly known as the 'Common Rule' (Office for Human Research Protections, 2014). The Common Rule was established in the aftermath of the Tuskegee Syphilis scandal (Emanuel & Menikoff, 2011). The Common Rule was developed in 1981 and it is encapsulated in the 1991 revision to the U.S. Department of Health and Human Services Title 45 CFR 46 (Public Welfare). The Common Rule is the baseline standard of ethics by which any government-funded research in the US is held; nearly all U.S. academic institutions hold their

researchers to these statements of rights regardless of funding. It was mainly informed by the Belmont Report of 1978 and was codified in separate regulations by 17 federal departments and agencies (Emanuel, Woods et al., 2004; Office for Human Research Protections, 2014).

According to the Office for Human Research Protections (2014), Rule 45 CFR Part 46 is made up of four sub-parts: (1) protection of human research subjects; (2) protection for pregnant women, fetuses 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) attention to the 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).

As described above, a number of international guidelines for ethical research have been established. In order to simplify and harmonise these international guidelines, Emanuel et al. (2004) proposed a system of seven principles that draw from all the major international guidelines, so that for local RECs, this might be simpler to use in the process of reviewing research protocols. The next section will look at the functions, roles and challenges of RECs in developing countries before a more detailed review of these principles in Section 2.5

2.4 RECs' functions, roles and challenges in developing countries

Notwithstanding the numerous challenges faced by RECs especially in developing countries, their major obligation is to improve protection of research participants (Coleman & Bouésseau, 2008). This fundamental role of ethical oversight of research involving human participants is crucial in order to safeguard the principles of justice, beneficence and justice (Green, Lowery, Kowalski, & Wyszewianski, 2006). As required by the Council for the International Organizations of Medical Sciences (CIOMS) (2016), International guidelines are the backbone of many REC reviews governing both international and local research (Macklin, 2001). International and local research both require RECs to ensure that the risk-benefit analysis is applied favourably in research studies and that research studies are carried out in line with the ethical guidelines (Coleman & Bouésseau, 2008).

It is also the function of RECs to make sure that ethical principles such as justice are fully adhered to. Hence, the general function of RECs is to provide ethical oversight of research studies. According to Ross and Athabassoulis (2014), one can arguably be tempted to

perceive the role of RECs in two ways; one of which is monitoring the risk-benefit ratio of research studies while the second is ensuring that participants give informed consent prior to their participation in research studies. Thus, the general function of the REC is to preserve research ethics (Guillemin et al., 2012).

Many studies that have been carried out around the world have demonstrated that RECs continue to encounter challenges despite the availability of national and international ethical guidelines (Kass et al., 2007, Mokgatla et al., 2017). With the global growth of health research, there is a much greater need for strong and sound ethics review (IJsselmuiden, Marais, Wassenaar, & Mokgatla-Moipolai, 2012); hence, the importance of ethical review cannot be overstated. However, in developing countries, and with particular emphasis on the African continent where a myriad of competing socio-economic challenges prevail, RECs continue to be poorly resourced, yet they are expected to uphold international research ethics guidelines in such situations where there are stark power inequalities and discrepancies (London, 2002, Silaigwana and Wassenaar, 2015). The same notion has been supported by Nyika et al. (2009) and IJsselmuiden et al. (2012), who reported that RECs in Africa are fraught with poor financial and human resource capacity. In addition, the training is insufficient and if institutional operating procedures exist, they are often inadequate. REC members frequently also have multiple tasks, and their roles are poorly acknowledged (IJsselmuiden et al., 2012). Thus, many African RECs struggle with issues of being poorly resourced.

Apart from issues of lack of resources, Ateudjieu et al. (2010) state that the independence of RECs is sometimes questionable; some RECs in developing countries have been viewed as having a tendency to 'rubber stamp' ethics approvals in an effort to attract and secure international financial support. In some cases, REC members work for the institutions that will be carrying out the research or there is an over-dependence on international organisations for financial support, thereby bringing the independence of these committees into question (Nyika et al., 2009).

Benatar (2002) points out that, in developing countries, the weaknesses of RECs range from being self-appointed private committees (which are lacking in expertise) to a lack of dialogue and public deliberations, leading to undisclosed conflicts of interest. In addition, a study by Schuppli and Fraser (2007) found 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).

Collaborative research between developed and developing countries, which has now become very common, (Yassi, Breilh, Dharamsi, Lockhart & Spiegel, 2013) has led to concerns about the possible manipulation of participants in developing countries (Hyder et al., 2004, Ateudjieu, 2010, Yassi et al, 2013). According to Ndebele, Blanchard-Horan, Shahkolahi and Sanne (2014), without robust research ethics oversight, ethical principles might be deliberately ignored or even unintentionally overlooked, thereby putting the welfare of research participants in jeopardy. Gilman and Garcia (2004) argue that collaborative research should involve approval by RECs in the sponsoring country and also in the developing country. Collaborative research between developed and developing countries is sometimes done under the auspices of the international regulatory frameworks of the developed or sponsor country (Milford et al., 2006). However, in some instances, these frameworks from the developed country do not necessarily take into account the socio-economic and cultural context of their developing country partner, where the research will be conducted.

In developed nations, the work of RECs is often shrouded in privacy and secrecy, which has often caused alarm in various sections of the research community (Clapp, Gleason, & Joffe (2017). In the developed world, taking the American context, for instance, RECs have been accused of 'mission creep' (Gunsalus, Bruner, Bubules, Dash, Finkin, Goldberg & Pratt, 2006) and of utilising their *ethico-regulatory* muscle well over and above what was initially intended, in so doing becoming a "virtual police force in the service of liberal humanism" (Nelson, 2004, p. 210). In the view of critics, the most critical evidence that REC authority has outstripped its obligation is the empirical literature (reviewed in Abbott & Grady, 2011) which demonstrates a clear variation within and between RECs with regard to their application of regulations, commentary, time to complete review, decisions and determination of which protocols should be expedited or exempted (Ndebele et al., 2014).

There is documented evidence of limited ethics review capacity in some parts of Africa, which may increase the potential for manipulation of local communities participating in research (Milford et al., 2006), as noted above. In a study aiming at establishing 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. Their study reported that about a third (34%) of their respondents were offered some ethics training, including staff not involved in ethics review. However, of the 847 research institutions surveyed, fewer than 50% had links with a national or regional ethics organisation. This points to a lack of research ethics capacity in most African countries and this may translate into poor and or inadequate ethical review of research study protocols.

Furthermore, as noted above, the sponsor country's REC is often the approving REC, but may be unable to reconcile local cultural diversities and context with the aims of the study. Despite acknowledgement of the 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) call for a framework where the nature and type of guidelines in collaborative research are governed by the host country.

The point raised by 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 et al. (2013) in their ethics capacity study in low- and middle-income countries (LMICs). Though the latter authors found that there is a general absence of a plausible framework for assessing research ethics capacity, more recent studies (Ndebele et al., 2014; Silaigwana & Wassenaar, 2015) tend to point to a trend where capacity has been improving, though slowly.

2.5 REC review process and the Emanuel et al. framework

McWilliams et al. (2003) posit that protection of human participants within research studies is an evolving process, where the use of the REC review systems is an initiative to ensure human subjects are protected as well as to allow for research to be done, mainly ensuring risk is minimised. While the need for human participant protection is fundamental, lack of uniformity in the review process generates uneven participant protection, resulting in significant inefficiency. However, the Emanuel et al. (2004, 2008) framework was an attempt to make the review process more universal, thereby providing for more systematic and fair protection for participants.

The Emanuel et al. (2004, 2008) framework can assist the REC process by giving guidance on what reviewers can look out for during the review of research protocols. There is currently no universal standardised approach to the review of protocols. This framework provides a potentially universally applicable guide any REC can use. Each REC seems to have its way of doing business during the review of research protocols. 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).

In line with increased capacity and professionalisation of RECs in Africa and other resource-poor settings, the use of internationally acclaimed ethical guidelines has been noted. However, there are still challenges in some settings. Emanuel et al. (2004) and Emanuel et al. (2008) proposed an ethical framework for guiding the conduct of clinical research in developing countries. This framework, which consists of eight principles and their associated benchmarks, is intended 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 of research. However, by following this comprehensive framework, RECs should be able to carry out the review process in a standardised fashion.

The principles are: (1) collaborative partnership, which aims to lessen discrepancies between researchers and funders 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 a favourable balance between the risks and benefits of a research study; (6) independent review of research in order to protect the rights and welfare of study participants; (7) informed consent; individual consent must be obtained, 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 et al., 2004).

The ethical framework by Emanuel et al. (2000) and Emanuel 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 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). The principles of the framework are described in more detail below.

2.5.1 Collaborative partnership

Clinical research is not supposed to be done ‘*to*’ people but ‘*with*’ people (Weijer & Emanuel, 2000). The collaborative partnership principle is premised on the notion that meaningful involvement and partnerships with relevant community representatives should be part of the research study at all stages. It also requires that at all phases of the research, responsibilities, benefits and risks be shared, as well as ensuring that local context is respected. According to Minkler (2004) and UNAIDS/AVAC’s (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 between 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; this occurs through instilling a sense of ownership while eliminating the sense within the local community of just receiving aid. 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 socio-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 of 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 facilitates a shared understanding which reinforces the research process (Marsh, Kamuya, Rowa, Gokonyo, & Molyneux, 2008). Generally, collaborative research projects are required to have ethical approval from their funding country as well as the host nation institutions where the proposed study is to be carried out. This brings into consideration ethical standards from

different socio-cultural backgrounds. RECs in both the sponsor country and the host country carry the responsibility of ensuring scientific and ethical review, as well as the authority to deny approval of research protocols that do not meet their scientific or ethical requirements (Diekema, 2006).

Collaborative partnerships can be achieved through multiple formal and informal means which may include establishing community advisory boards, public engagement meetings with members of the community, or consultations with advocacy groups. Which approach is used will usually depend on the nature of the particular research study (Guillemin & Gillam, 2004).

2.5.2 Social value

Clinical research should not be an end in itself; it has instrumental value because it has the potential to generate knowledge that leads to improvements in health and health care (Emanuel et al., 2008). It is such improvements in health and its delivery system that should constitute social value. In general, this principle calls for the research to be of value to the community, participants, society and research community or health system, rather than a mere waste of time and scarce resources. This entails avoiding the exposure of participants to unnecessary risks through research which has no social value. Apart from evaluating the importance of the health problems under study, according to Emanuel et al. (2004), this ethical principle 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 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 studies, Emanuel et al. (2004) point out that as priorities of research change, this may make determinants of social value ambiguous; this calls for sound discretion 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, et al., 2004). These are:

- (i) 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 account 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;
- (iv) Research ought not to subvert the community's prevailing health care services; rather, it should complement or enhance them (Emanuel et al., 2004).

In effect, 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).

The important questions to ask in the pursuit of fulfilling this principle are: Who stands to benefit from the conduct and outcomes of the research study? What is the potential importance of the research for each of the potential research potential beneficiaries? How will the social value of the research study be improved? How can the negative social effects, if any, of carrying out the research study be lessened? In addressing these questions, the research study will be properly fulfilling the principle of social value.

2.5.3 Scientific validity

Valid science is considered a fundamental ethical requirement (Emanuel et al., 2004). Research need to be designed in a way that ensures valid and reliable data are generated, otherwise the participants will be prone to risk for no benefits. This principle requires that the research be premised on sound, valid and reliable research designs and proven scientific methods of getting data. The research methods should be relevant to the objectives of the study; the results obtained must be related to the health problem being researched; and the study design does not have to negatively affect but should rather complement provision of health care services.

According to Emanuel et al. (2000, 2004, 2008), when considering the principle of scientific validity, there are four benchmarks which should be considered:

- (i) The scientific, statistical design and methods must be crafted in a way that would allow the researchers to realise the objectives of the study. The objectives must be clear and justifiable, and the sample size must be adequate, and unbiased and reliable outcome measures and analysis must be employed;
- (ii) The study design should be appropriate to the health problem of the host community of the research (Emanuel et al., 2004; Macklin, 2001);
- (iii) The study design should have the capacity to realise the research objectives without subordinating the participants' welfare to the study objective (Angell, 1997);

- (iv) The design should be feasible within the socio-cultural and political environment of the host community, which includes sustainable capacity and infrastructure development (Emanuel et al., 2004).

According to Dhai (2005), not only should the scientific design of a research study be sound, but the study itself should also be implemented in accordance with the stated research design. RECs should not deem protocols unworthy without reflecting on adjustments that can be done to make the protocol scientifically valid (Dhai, 2005). Thus, this principle stipulates that poor science is equivalent to poor ethics. This is because research participants would be exploited and exposed to needless risks and scarce resources would be wasted on research that produces invalid results (Dhai, 2005).

2.5.4 Fair selection of study population

History has repeatedly shown that populations that were poor, uneducated, underprivileged and powerless were often the target for high-risk research studies, whilst promising studies with more benefits were often offered to the privileged communities (DeCamp, 2011). This principle stipulates that the selection of the study population should be in line with research objectives; harm minimisation, and maximising participant benefits and safeguarding of vulnerable groups, are key to this principle. Selection of study participants should be done to enhance the scientific validity of the research and so that potential risks to such participants be minimised (Emanuel 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 greater likelihood that social value of research will be realised (Emanuel et al., 2004).

Emanuel 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 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 based on the factors relevant to the problem under investigation (Gostin, 1991).

According to DeCamp (2011), the selection of the study population ought to be based on a clear justifiable rationale. According to Emanuel et al. (2004), the 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 the study population should be done in accordance with the scientific goals 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).

Emanuel et al. (2004) came up with four benchmarks under this principle:

- (i) The study population should be selected in a way that ensures scientific validity;
- (ii) The selection of participants should be done in a way that minimises risk;
- (iii) Participants must be selected in a way that enhances the social value of the study and the possibility of benefits to participants, for example, ensuring an adequate number of adolescents participate in a study of a disease largely affecting adolescents enhances benefits to them;
- (iv) Factors such as age, cognitive ability, familial relationships, clinical status, social marginalisation, economic deprivation and political powerlessness should also be taken into consideration when determining the vulnerability of individuals and their communities. Researchers need to ensure that the study population has been selected for good reasons, for example, a high incidence of the disease under study. If the study population has been identified as vulnerable, specific safeguards must be put in place, for example, monitoring the informed consent process.

2.5.5 Favourable risk-benefit ratio

Emanuel et al. (2004) state that clinical research should afford participants 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 IRBs to carry out their mandate of protecting research participants (Weijer, 2000).

In terms of ensuring a favourable risk-benefit ratio, there is a need to identify the risks and benefits associated with the research. Emphasis should be on minimisation of all forms of likely risks to research participants in terms of type, probability and magnitude; quantification and identification of all types of potential benefits; and harmonising the likely risks and benefits to the participants. 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 several risks as well as

potential benefits. Thus, benefits in research cannot always be instant (Weijer, 2000). However, Emanuel et al. (2004) outline that the risk-benefit ratio need to 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 principle works in a complementary fashion with other ethical principles such as collaborative partnership, social value and respect for study populations (Emanuel et al., 2004). The principle demands that, for research to be ethically justifiable, it has to fulfil three benchmarks:

- (i) Potential risks to participants are limited. This benchmark calls for the researchers to delineate and minimise risks, and these risks should not just be limited to the physical risks but should also include foreseeable psychological, social and economic risks. These should be based on empirical data, not just intuition or speculation. This also requires that researchers must use consistent procedures based on sound research design to avoid unnecessary exposure of participants to risk, and such procedures must be performed by trained personnel;
- (ii) Potential benefits are maximised. This requires identification of the type, magnitude and probability of the benefits. These benefits may include the potential benefits to individual research participants, like health improvements. However, the benefits must only include health-related benefits derived from the research intervention. As a general rule of beneficence, an effort should be made to enhance benefits to participants and communities, especially if provision of such benefits can be easily achieved without compromising the scientific validity of the research study (Emanuel et al., 2008);
- (iii) Potential benefits to individual study participants and communities are greater than the potential risks (Dhai, 2005). According to Emanuel et al. (2000) and Emanuel et al. (2004), this principle is a clear demonstration of the essential values of research, namely beneficence and non-maleficence.

2.5.6 Independent ethics review

This principle is important for two reasons: one is to minimise concerns around researchers' conflict of interest and secondly, to ensure public accountability (Emanuel et al., 2008). This principle concerns RECs themselves and indicates that their standard operating procedures must guarantee independence from manipulation and external meddling, and must be directed by law and recognised ethical guidance. It stipulates that RECs must be properly constituted, and their members need to be suitably skilled and must declare any conflicting interest. It

further requires that the review process should be transparent and all decisions should be justified; it should also ensure a rational handling of decisions from multiple reviews.

Emanuel et al. (2004) and Dhai (2005) suggest that independent review should be done as a means of ensuring 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 principle seeks to safeguard against exploitation of research participants by researchers who might have competing interests (Dhai, 2005). For the review process, researchers are also expected to disclose information such as the sponsors, affiliate institutions, potential conflicts and any incentives they intend to give to the research participants (Emanuel et al., 2004). To rid the protocol review process of any conflicts of interest, this review should be done by a committee independent of the sponsor and the investigator. At the same time, the REC should abide by the laws and regulations of the host country. This principle also requires RECs to monitor ongoing research studies. The World Medical Association (2013a) also supports this notion that the REC has an obligation to monitor ongoing research studies for ethical compliance.

Emanuel et al. (2004) listed four benchmarks under this principle:

- (i) Procedures stipulated by law and regulation should be followed; this means that prevailing laws and regulations dictate the standards that are to be followed. Thus, while international guidelines are available, the actual review procedures are generally determined by local laws and regulations.
- (ii) Whatever the process, the review must be independent and competent. This benchmark ensures that members of the review committee are free of any common interests with the researchers or the research study; hence, reviewers must not be collaborators in the study they are reviewing. Some settings separate scientific review from ethics review, making them two separate processes whilst others integrate both into a single assessment. The key issue is that the reviewers should have sufficient expertise to review the protocol;
- (iii) The review must be transparent. This benchmark requires that all the reasons for the decisions of the independent review committee be explained, so that even an independent observer can clearly assess if the reasons were appropriate and relevant considerations were appropriately addressed;
- (iv) Multiple independent review might be necessary for multisite studies. This is very important, especially in view of the increasing number of complex multisite studies that are conducted by researchers from multiple institutions

2.5.7 Informed consent

No principle has received as much attention as informed consent (Tsoka-Gwegweni & Wassenaar, 2014). The main function of informed consent is generally to honour the autonomy of individuals. By allowing participants to decide 'if' and 'how' they can contribute to research, informed consent respects persons in terms of their autonomy (Emanuel et al., 2008). This principle is basically concerned with recruitment procedures and incentives. These must be suited to the local setting; thus, all consent procedures and documents should be tailor-made to suit participants' local situation. Informed consent also entails disclosure of accurate, complete, and enough information to potential research participants. This principle also covers provision for getting consent from legally authorised representatives, if needed; provision for getting authorisations from relevant community leaders; consent within the local site and it also clearly confirms participants' right to join, decline, or pull out from research.

This principle is commonly viewed as the bedrock and pivot of health research (Mystakidou, Panagiotou, Katsaragakis, Tsilika, & Parpa, 2009; Tangwa, 2002). According to Emanuel 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). Furthermore, it ensures that participants are not viewed as a means to an end (Dhai, 2005; Emanuel et al., 2004). The principle also demands that research information be disseminated and disclosed in a culturally and linguistically suitable way (Emanuel et al., 2004).

According to Emanuel et al. (2004, 2008), the informed consent principle is based on seven 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 permission before individual consent. This may refer to what Emanuel et al. (2008) termed 'spheres of consent', which range from spouses to household heads, to school heads, to village heads to chiefs, to other community leaders and gatekeepers whose permission may be necessary before researchers can talk to potential individual participants. However, the family or community can only give

permission for the researchers to approach potential individual participants; the individual still holds the right to decide to either participate or refuse to participate;

- (iv) Participants should voluntarily participate in research. Voluntary participation as a need for informed consent is also advocated by Mystakidou et al. (2009);
- (v) Measures for withdrawal from the study should be observed; this is also dependent on understanding the research design. Special attention should also be given ensure that participants are cognisant of their right to decline to participate or to pull out from a research study at any time without any penalty.

The principle also involves collaborative partnership (Emanuel et al., 2004). This principle often brings to the fore the debate that individual decision-making characterises the informed consent procedure in developed nations, unlike the family and community involvement in some African and Asian nations (Shaibu, 2007). Research should try to utilise consent procedures that are acceptable within the local context while ensuring that voluntary participation is verifiable by an independent observer. For example, the US regulations (Office for Human Research Protections, 2014) require a written signature, which has become the norm in many other settings as well. Other known methods of consent are handshakes, embracing, or sharing a meal, which sometimes pose challenges in terms of how to document such, with suggestions of audio and/or video recording as an alternative documentation option.

2.5.8 Ongoing respect for participants

Respect for participants should be shown during and even after the study, and this is achievable through monitoring the health status of participants, minimising risks, upholding confidentiality, giving participants room to pull out without losing access to their entitled health care services, and planning for dissemination of research findings and post-research obligations (Emanuel et al., 2008). The obligations of the researchers to the participants do not stop when informed consent is gained; researchers have a duty to treat current and previous study communities with respect (Dhai, 2005; Emanuel et al., 2000, 2004).

Dhai (2005) and Emanuel 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; this means that pledges of confidentiality must be honoured and measures must be taken to ensure that databases, coding specimens and data forms are secure. This also means making provision for participants to be interviewed in private spaces;

- (ii) Upholding participants' right to withdraw from research studies without consequences; this benchmark focuses on ensuring that participants are allowed to change their minds, and even to pull out from the study at any time without attracting any disadvantages or losing any of their benefits;
- (iii) Provision of new study information to the participants and host communities
- (iv) Providing care to the participants and monitoring their welfare during the study, with a view to intervention and prevention or treatment of any harms from the adverse effects, or untoward events associated with the study;
- (v) Lastly, development of clear procedures by researchers to disseminate research results to the participants and host communities. This principle is premised on the ethical principles of beneficence, non-maleficence and autonomy (Emanuel 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 study communities and participants share the rewards of the study equitably in a justifiable manner (Dhai, 2005). The eight principles of the framework are not weighted, and it is not known how they are distributed in typical REC functioning. Unfortunately, there is no algorithm to balance and/or weigh these principles.

2.5.9 Overview of the Emanuel et al. (2004) framework

Due to the inadequacies and deficiencies of existing guidance on research ethics, Emanuel et al. (2008) saw the need to proffer a more extensive, systematic and complete framework that would include ethical justification and specification on how every principle can be applied in actual practice. These principles should not be seen as adding ethical guidelines or requirements, but rather as distilling and coherently presenting the ethical norms that underlie prevailing international ethical guidelines. These eight principles focus more on what is required to evaluate research protocols but not necessarily on the enforcement side of the research process. The eight principles, according to Emanuel et al. (2008), are not independent of all other ethical guidelines; they are meant to be compliant with general moral norms, such as honesty and keeping one's promise.

According to Tsoka-Gwegweni and Wassenaar (2014), the principles and benchmarks of the Emanuel et al. framework are viewed as all-inclusive and applicable to all settings and contexts. Many more scholars point to the fact that the framework is extensively referenced in the literature and has been utilised to develop ethics review frameworks or training courses on research ethics, in various settings, or in the review of both published and anticipated

research (Miller & Brody, 2003; Wassenaar, 2006; Fakruddin, Chowdhury, Hossain, & Mannan, 2012; Budin-Ljosne, 2012; Union Graduate College & Vilnius University, 2012; Shaw & Elger, 2013). Mark (2014) portrayed it as a comprehensive framework, with ethical requirements listed in sequence from the beginning of research to implementation and conclusion; it is also described as universal while depending on the culture, economy and disease burden of each research setting.

The Ethics Review Committee (ERB) of Médecins Sans Frontières has utilised the Emanuel et al. (2004) framework to develop its own standard operating procedures and indicated that the framework was useful and applicable to both its ERB and researchers, while improving the quality of research proposals submitted to ERB (Médecins Sans Frontières, 2013). Hyder et al. (2014) also described the framework as relevant in terms of public health, in particular the collaborative partnership principle, as it links ethics to health systems and is seen as a tool for promoting decision makers' involvement in research programs and dissemination of research results. Chen, Jones and Gelberg (2006) utilised the framework for community-based participatory research framework (CBPR) and indicated that it was easy to adapt to their community-based work.

According to Hyder et al. (2014) the framework's principle of independent ethics review has led to the formation of a National Bioethics Committee in Pakistan. Labrique, Kirk, Westergaard and Merritt (2013) used the framework to assess ethical issues in mobile health (mHealth) research involving human participants living with HIV/AIDS and substance abuse in a Johns Hopkins University-based research project. The framework is also viewed as useful for reviewing research in social sciences (Wassenaar & Mamotte, 2012) and health systems (Wassenaar & Rattani 2016). The Emanuel et al. framework is said to have been influential in configuring the major Joint United Nations Programme on HIV/AIDS ethics guidance documents for HIV prevention trials (UNAIDS, 2012). Apart from health research settings, the same framework was also used by the U.S. Environmental Protection Agency in reviewing a published study that examined environmental exposure to chromium (Carley, 2006).

A short comment about South African RECs might be useful here. South African health law necessitates that all health research be reviewed by a REC which is nationally registered. In South Africa, all RECs are required to be registered with the National Health Research Ethics Council (NHREC), which audits RECs for compliance, composition and structure (Langlois, 2013). Several South African RECs are also registered with the U.S. Office for Human Research Protections (OHRP) and have Federal Wide Assurance (FWA) status. Given the diverse cultures, socio-economic and political environments, disease burden, and educational

backgrounds, under which South African RECs operate, a better understanding of the ethical issues that South African RECs consider during the review of research protocols is needed, although some such studies have been carried out in South Africa.

This Southern African data would likewise inform an understanding into the appropriateness of the Emanuel et al. (2004) framework to the Zimbabwean setting in particular and possibly the African context in general. Although the Emanuel et al. (2004, 2008) framework was intended for use in all environments including resource-poor nations, it is not yet known whether the work of African RECs is attuned with this framework. Furthermore, the lack of any normative or empirical weighting of the Emanuel et al. (2008) principles suggests that different RECs are more likely to raise some ethical issues more frequently than others when reviewing protocols. It is also not immediately known whether the frequency of the issues raised is consistent with the importance ascribed to ethical issues. This point will be revisited later in this study.

This study aimed to assess the ethical concerns raised by a REC in Zimbabwe by identifying ethical issues that were frequently raised during the protocol review process, using the principles and benchmarks recommended for review of biomedical research proposed by Emanuel et al. (2008). To the best of our knowledge, this is the first study attempting to apply the Emanuel et al. (2008) framework to describe and analyse issues raised by a REC in its routine work in Zimbabwe. This study is thus an examination of the applicability of the Emanuel et al. framework for examining REC outputs in an African context.

2.5.10 Review of related studies that have Examined REC review outcomes

Despite the dearth of studies analysing REC review outcomes in the developing world, there are a few recent studies that have examined REC review queries. One study by Tsoka-Gwegweni and Wassenaar (2014) which was linked to this current study, is one of the few known attempts to study REC review queries. Apart from that study there are also a few other international studies for Dixon-Woods et al. (2016).

Studies examining REC outcomes have not necessarily yielded a typology of distribution of concerns using the Emanuel et al. (2004) principles. A common trend amongst such studies is the finding that informed consent related queries constituted the greatest proportion of all queries. Informed consent constituted a significant proportion of all queries raised by RECs according to a number of studies conducted in the developed world (Cleaton-Jones, 2011,

Lidz et al., 2012, Abbott & Grady, 2011) and was reported to be the main reason cited for protocol rejection. A South African review of a biomedical REC reported that informed consent was the most frequently considered ethical issue during protocol reviews, amounting to 27.4% of all the queries raised (Tsoka-Gwegweni & Wassenaar, 2014).

In their study Tsoka-Gwegweni and Wassenaar (2014) found that queries relating to the principle of social value were a paltry 4.1% of all the queries. In the same study scientific validity accounted for 21.4% of queries raised and had the second highest number of queries. Collaborative partnership related queries accounted for 3% of all the queries in their study (Tsoka-Gwegweni & Wassenaar, 2014).

Tsoka-Gwegweni and Wassenaar (2014) found that 9% of the queries in their study were related to risk-benefit ratio. In an analysis of twenty protocol reviews by one REC, a risk-benefit comparison was not considered in as many as 60% of the cases (Lidz et al. 2012). Another US study reported the total number of queries raised relating to risks and benefits was considerably high, and these were raised in as many as 37 % of the protocols (Adams et al., 2013). These differences may be explained by Happo, Halkoaho, Lehto and Keränen's (2016) study which found that a biomedical REC was more likely to raise concerns relating to the risk/benefit ratio in reviewing studies involving clinical drug trials compared to studies involving clinical trials with medical devices, studies with other invasive interventions, studies with non-invasive physical procedures, and non-physical procedures only. This seems to suggest that the nature of the protocol may have an overbearing effect on what ethical concerns RECs raise (Happo et al., 2016). While the spotlight cast by the nature of the study under review is helpful in directing RECs' attention towards the most likely ethical issue the study may confront, it may well obscure other ethical concerns.

Queries relating to fair selection of participants were also commonly raised, being the most frequently raised in the Happo et al. (2016) study and accounting for 13.9% of all queries in the Tsoka-Gwegweni and Wassenaar (2014) study. Independent review related constituted 7.3% of all queries in Tsoka-Gwegweni and Wassenaar (2014) study.

Some studies reviewing IRB/REC letters have cast a negative light on the ethics review process. It was reported that reasons for IRB stipulations often left ethical issues implicit, or used generic, standardised language in elaborating actual ethical and scientific concerns, which may amplify the danger of RECs acting as mere bureaucratic gatekeepers whose review processes are arbitrary at best (Dixon-Woods et al., 2016). Such reservations are also amplified by Cleaton-Jones (2011) who indicated that concerns about typing errors and

application forms that were incomplete constituted 15% of queries. Some scholars argue that typological errors should not be raised in ethics review except when meaning becomes obscured by them (Amdur & Bankert (2011)). Dixon-Woods et al. (2016) found that 87% of applications not approved at first review had issues that included missing information, procedural violations, slip-ups such as errors in spelling and grammar, and inconsistencies between different parts of the application. These studies suggest a preoccupation with routine, perfunctory concerns in ethics review meetings. One scholar, Schneider (2015), characterises REC reviews as chronically arbitrary and capricious. In addition, ethics oversight committees tend to arbitrarily request changes to study design even where protocols have been scientifically peer reviewed (Dixon-Woods et al., 2016).

2.6 Summary

The eight principles and their benchmarks are viewed as necessary, and hence are all expected to be fulfilled for a research protocol to be considered ethical - there should not be any picking or choosing (Emanuel et al., 2008). The benchmarks under each principle do provide the practical concerns in a very clear and systematic fashion. Several issues have also been discussed in relation to REC review guidelines and gold standard procedures, from the international ethics guidelines to the Zimbabwean guidelines. There is, however, limited information on the applicability of the Emanuel et al. framework to the actual review process, and hence this study looked at the concerns raised in actual review meetings. Some related studies have reviewed REC review outcomes, but some of them have been carried out in developed countries. These studies have documented the dominance of informed consent related concerns. Some of the studies noted a tendency by RECs to act as bureaucratic gatekeepers, effectively providing little ethical justification for their stipulations. The next section will outline the rationale for the current study.

Chapter 3

Rationale

3.1 Introduction

Until recently, there was no literature or research that looked closely at what RECs raise as their ethical concerns and queries during research protocol review meetings. Furthermore, there are very few studies that have looked at the concerns that African RECs raise during their review process. Very little is known about whether these concerns align with what Emanuel et al. (2004) proposed as the international framework incorporating the eight principles and benchmarks. This study sought to identify, describe and analyse the ethics review concerns raised by a Zimbabwean REC, using the ethical framework proposed by Emanuel et al. (2004). The use of such an ethics review framework may assist in ascertaining the relevance and determining the applicability of the framework in ethics review of research protocols in African settings.

3.2 Research questions

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

- What concerns do RECs in Zimbabwe raise when reviewing protocols?
- Is there a systematic prioritisation of some ethical issues over others?
- Is there an observable pattern to the ethical concerns raised by committee members?
If so, what is the pattern?
- Are the concerns raised consistent with the framework developed by Emanuel et al. (2004)?
- Does any feature of the Emanuel et al. (2004) framework dominate the concerns? If so, which one?
- Are there other concerns raised by RECs which are not consistent with the framework discussed by Emanuel et al. (2004)?

3.3 Objectives

The study set out to address the following objectives:

- To study the minutes of the Zimbabwean REC's review meetings to identify and describe the pattern of ethical concerns and issues raised in their reviews of research proposals;
- To analyse the ethical issues and concerns using Emanuel et al.'s (2004) framework, ranking them and identifying how they do or do not fit the framework.

3.4 Expected impact

This study aimed to identify the type of concerns that the REC raised with a view to analyse whether the concerns raised fitted in the framework developed by Emanuel et al. (2004). This study also analysed other concerns that might not necessarily fit in the framework by Emanuel et al. (2004). This study also may provide knowledge and information on what issues RECs in Africa consider important during ethical review of research protocols. The information gained may help in shaping guidelines and policies on ethical review of research protocols in African settings. It also provided information to researchers who have research interests in African settings. The study methods are outlined in the next section.

Chapter 4

Methodology

4.1 Introduction

The methodology chapter seeks to lay out the methods and describe in detail the research strategy, the research setting, the research approach, the methods of data collection, the selection of the sample, the research process, the type of data analysis, the ethical considerations and the research limitations of the project.

4.2 Research design

The researcher used a mixed methods approach to meet the objectives of the study. The main characteristic of qualitative research is that it is mostly appropriate for small samples, while its outcomes are not easily measurable and quantifiable. Its main strength, which also constitutes its basic difference with quantitative research, is that it provides a more thorough description and analysis of a subject being studied, without limiting the scope of the research (Collis & Hussey, 2003). However, the effectiveness of qualitative research is heavily based on the skills and abilities of the researcher, while outcomes may sometimes not be perceived as reliable, because they mostly come from the researcher's personal judgments and interpretations.

The idea of employing a qualitative component was premised on the fact that meaning is a social construct reached by individuals as they interact with their world; hence, data sources for exploratory research include interviews, observations and/or documents (Polkinghorne, 2005). The decision to use a qualitative research component for this study had its basis in the researcher's desire to understand different interpretations within a specific framework at a particular time.

The researcher also employed quantitative techniques in the capturing and analysis of data. The data obtained was captured using Microsoft Excel and analysed. The counts of issues per proposal were considered as scores and conventionally analysed. How frequently particular issues (whether Emanuel's system or otherwise) arose were also analysed using conventional categorical data analysis. This then qualified the research design of the study as a mixed methods.

4.3 Sampling

A purposive sampling method, which belongs to the category of non-probability sampling techniques, was used for this study. Freedman et al. (2007) define purposive sampling as 'typical case' sampling, where typical cases are sought and selected for a particular inquiry. Marlow (2010) further explains that 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 generally useful for the selection of explicit cases based on purpose, rather than casual or arbitrary selection.

Purposive sampling was employed to select the research site of a REC in Zimbabwe. The REC was located within the country and written approval from relevant authorities was obtained to access and analyse the data. For the purpose of data collection, the minutes of the REC ethics review committee meetings of January 2012 to December 2013 were accessed. Concerns raised on all new protocols that were submitted during that period were sampled. The inclusion criteria specified only minutes recorded on all newly submitted applications, without any consideration of the type of study (e.g. clinical trial, biomedical, epidemiological, social research, behavioural, implementation research, or operational research or studies). Continuing reviews, annual reports, expedited reviews and final reports were excluded. The sample size for the research was unlimited and depended on the workload of the REC under study within the stipulated time frame.

4.4 Data collection

This research was part of an international collaboration involving the 2013 South African Research Ethics Initiative (SARETI) Master's degree students from the University of KwaZulu-Natal, South Africa. These countries and partners included: Ghana (Hannah Frimpong and Pamela Selormey), Malawi (Abdallah Chilungo) and Zimbabwe (the present author). The study also partially complements some studies that were in progress or in press, in particular Tsoka-Gwegweni and Wassenaar (2014).

For the purposes of this research, all archived records of the REC's protocol review meetings within the stipulated time frame were accessed. These archived documents are confidential organisational documents which were recorded for different purposes than this study. The main advantage of a retrospective document review is that it allows researchers to get the information in its original state which addresses issues of social desirability, as well as eliminating non-response rates. The following steps outlined below were followed by the researcher for data collection:

- A REC that is within the country (Zimbabwe) was identified and written approval from the relevant authorities was obtained to access and analyse the data (REC minutes) for the period January 2012 to December 2013. Ethics approval for the study was obtained from the UKZN BREC; (approval number BCA 342/16)
- All records of the minutes for the protocols reviewed by this REC during the period 2012 to 2013 were accessed and the researcher read through all the REC minutes records for the period under study;
- Summary review comments were extracted and categorised; these were captured on an Excel spreadsheet using the eight principles and benchmarks of the Emanuel et al. (2004) framework. This was to record the observable pattern in ethical concerns raised during ethical review of research proposals. A standard data capture sheet (Appendix 1) was developed on which simple frequency counts for each type of ethical issue raised were coded. There was also provision for 'other' categories of review comment not covered by the Emanuel et al. framework;
- The number of comments per category per proposal was also recorded.
- The frequencies of occurrence per category or principle per minutes were also recorded;
- The analysis also identified issues raised by the REC that did not fall within the categories of the proposed framework; the frequencies of occurrence of these other issues were also recorded.

4.5 Data analysis

Content analysis was used to analyse the data which was gathered from REC's review meeting minutes. According to Moore and McCabe (2005), in content analysis, the qualitative data gathered is categorised into themes as well as sub-themes, so as to be able to be comparable. A major advantage of content analysis is that it is very useful in reducing and simplifying the collected data, while at the same time producing results that may then be analysed using quantitative techniques. Moreover, content analysis allows researchers to structure the collected qualitative data in a way that satisfies the accomplishment of research objectives. However, human error may occur in content analysis, since there is a risk that researchers may either misinterpret the gathered data or be subjective, thereby generating false and unreliable conclusions (Krippendorff & Bock, 2008)

This present study was what is called a retrospective document review. This study was basically a review of the documented minutes of RECs of the ethics review of new protocols submitted for review during the prescribed two-year period. For data analysis, the researcher

used the framework of eight ethical principles and associated benchmarks described by Emanuel et al. (2004). The eight principles of the framework 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, as described in Section 2.5.9

Data from the review minutes were reviewed and evaluated, classifying responses from the different concerns raised using the framework described above. Responses were coded into the respective themes (principles) or benchmarks. Categorising the data into themes was done through intense reading and re-reading of the concerns under review and grouping similar information together. The grouping and the coding of the information were done according to the ethical framework for clinical research as proposed by Emanuel, Wendler et al. (2004).

4.6 Ethical considerations

The study was of minimal risk as no human participants were recruited. REC's minutes of ethics review meetings do constitute sensitive and confidential organisational documents, however, hence there was the need for the researcher to anonymise all the protocol concerns. The researcher was asked to sign a confidentiality agreement before access to the minutes was granted. 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 University of KwaZulu-Natal's Biomedical Research Ethics Committee (BREC) approved the study (approval number BCA 342/16) (Appendix 2) and the Medical Research Council of Zimbabwe also approved the study (approval number MRCZ/ B/1299).

4.7 Validity, reliability and generalisability

According to Hammersley (1990, p. 57), validity in research is defined as "truth: interpreted as the extent to which an account accurately represents the social phenomena to which it refers". Cook and Campbell (1979) developed a taxonomy of threats to research validity, namely: statistical conclusion validity; construct validity; external validity and internal validity. Internal validity refers to whether the inferences made from the collected data are accurate (i.e. valid) and external validity refers to the ability to generalise from the results of the study to other environments and populations.

For both practical and logistical reasons, it was not possible for the researcher to incorporate all of the above strategies into this study. However, the strategies of peer review of methods (with fellow researchers doing the same topic), as well as clarifying researcher bias were considered in the design and conduct of this study from the outset. Furthermore, the researcher identified the specific problem of ‘anecdotalism’ as a potential threat to the overall validity of the study. This refers to the inclination of some researchers to convince both themselves and their readers that the findings of their study are genuine results, based on a critical unbiased analysis of the data collected and not based on a few ‘well-chosen examples’.

Other threats to both the internal and external validity of this study have been identified by the researcher during the design process. The researcher acknowledges Cook and Campbell’s (1979) taxonomy of threats to validity and recognises that firstly, because the research is a desk review, carried out on specific documents kept for specific purposes by a specific group of people working in a specific environment, it is possible that the study will not return results that are high in external validity (i.e. that it will not be possible to generalise the results to other populations and/or to other environments). Secondly, because the sample population was primarily selected using purposive methods, the element of randomness is not present in the selection process. This may, therefore, impact upon the internal validity of the study’s results.

This study is hopefully significant because when these principles are found to be adhered to, this implies protection for research participants and their respective communities. On the other hand, if the principles are not adhered to during proposal review, recommendations will be made to RECs in Zimbabwe to be aware of this issue so that it can be corrected if necessary to ensure protection for prospective participants and communities who participate research, especially in developing countries. Though objectivity is sometimes elusive in qualitative research, the researcher made an explicit effort to prevent personal beliefs or theoretical predispositions impacting on the conduct of either the research process or the results derived from it. The researcher also tried to promote trustworthiness of the research findings by ensuring that consistent and transparent data were methodically recorded. The results are presented in the next section.

Chapter 5

Results

5.1 Introduction

In this chapter the results of the data analysis are presented. The data were collected and then processed and analysed in line with the research questions posed in Chapter 3 of this dissertation. Two fundamental objectives drove the collection of the data and the subsequent analysis. Those goals were: 1) to study the REC's protocol review meeting minutes to identify and describe the pattern of ethical concerns and issues raised in their reviews of research proposals, and 2) and to analyse ethical issues and concerns using the Emanuel et al. (2004) framework, ranking them and identifying how well they did (or did not) fit the framework.

The findings presented in this chapter demonstrate the pattern of the concerns raised during a period of two years. A total of twenty local REC's protocol review minutes records were reviewed. The REC under study held one meeting per month except in December when they do not hold any meeting. In addition, minutes from May 2012 and November 2012 were missing from the data set. In those meetings, new research protocols and other continuing studies are also reviewed. For the purposes of this study, only concerns on new protocols submissions were considered excluding expedited reviews because they are not tabled at full meetings.

5.2 Structure of data

A total of 232 ethical concerns and issues were identified and extracted from 109 studies. Of the 230 concerns, 81 (35%) were issues that did not fit into the Emanuel et al. (2004) framework, while 65% of all the concerns did fit in the framework. The bar graph in Figure 1 below shows the distribution of all the concerns that were identified.

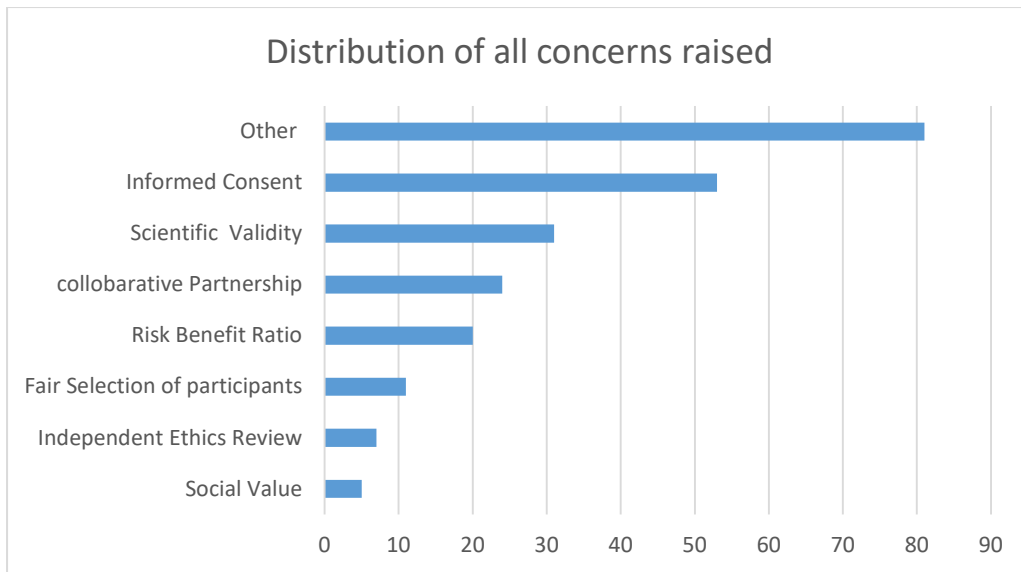


Figure 1: Distribution of all the concerns raised

Figure 2 provides the percentages of issues raised under each category, while Table 1 indicates the rank order of the various principles, according to the proportion of concerns that were classified under each principle.

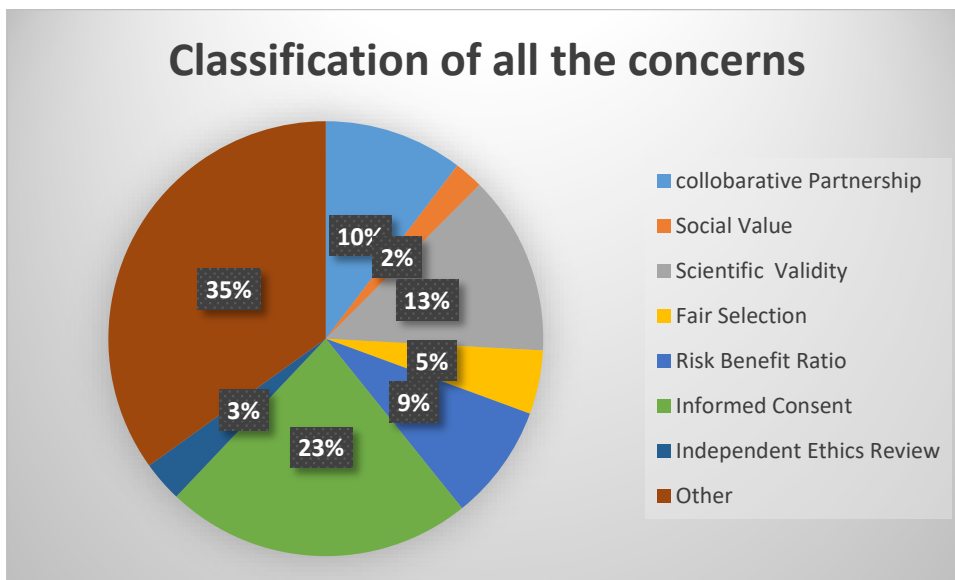


Figure 2: Proportion of all the identified concerns

The highest proportion of concerns were classified under 'other' concerns which could not be fitted in to the Emanuel et al. (2004) eight principles. Concerns which were captured under other concerns constituted 35% of all the concerns that were extracted from the minutes. It should be noted that other concerns included an array of different concerns, some of which

can be viewed as administrative or procedural in nature. For example, one issue was that the principal investigator had not used the appropriate application forms. This category also included issues to do with handling and shipment of samples.

Table 1: Rank order of concerns raised

Rank order based on the number (percentage) of concerns			
Rank Order	Principle	Principle Number	Number (Percentage of concerns)
i)	Other		81(35%)
ii)	Informed Consent	7	53(23%)
iii)	Scientific Validity	3	31(13%)
iv)	Collaborative Partnership	1	24(10%)
v)	Risk Benefit Ratio	5	20(9%)
vi)	Fair Selection	4	11(5%)
vii)	Independent Ethics Review	6	7(3%)
viii)	Social Value	2	5(2%)
TOTAL			232(100%)

Table 1 illustrates the rank order of proportion of concerns found to fit under each principle. “Other” concerns were ranked first because this category constituted the highest number (81) of the concerns. Informed consent ranked second with 23% of all the concerns that were analysed, third was scientific validity with 31 (13% of the entire sample), fourth was collaborative partnership with 24 (10%) of concerns, and fifth was risk-benefit analysis with 20(9%) of the concerns. Fair selection of participants 11 (5%) and social value 5 (2%) were ranked sixth and seventh amongst the concerns raised respectively.

5.2.1 Collaborative partnership

Concerns related to collaborative partnership comprised 24 out of the total of 232 concerns that were identified in the minutes. This translates to about 10% of all the concerns that were identified in the minutes and fourth rank order. Excluding the concerns that did not fit in the Emanuel et al. (2004) framework, this number constitutes about 13.2% and the third rank order out of all the concerns that did fit in the framework. The most common concern that was classified under this category was that “*The study doesn’t show any involvement of local researchers*” and “*Too little involvement of local researchers*”.

5.2.2 Social value

Analysis of the 232 concerns that were raised showed that a concern on social value was only raised five times, constituting 2% of all concerns raised and the least frequent concern. Excluding the subcategory “other”, this category constituted 3.3% of concerns in the Emmanuel et al. (2004) framework, making it the least frequent concern.

5.2.3 Scientific validity

Concerns related to scientific validity appeared relatively more frequently than some other principles. Concerns that queried the research design, and whether the chosen approach would answer the research questions, appeared 16 times. This translated to 13% and was the third most frequently raised concern, and this was also 20.5% of all the concerns that fitted into the Emanuel et al. (2004) framework. Of these 31 times that concerns appeared, four instances were on one protocol, three were on one other protocol. The rest were spread over ten protocols.

Some of the concerns that were classified under this principle were: “*Need to revisit sampling procedures*”, “*Sampling procedure unclear*”, “*Sampling strategy and recruitment criteria not clear*”, “*Objectives cannot be adequately realised using the proposed methodology*” and “*Sample size inconsistency*”. The data has also shown that the REC does pay attention to this principle. In most of the concerns under this principle, the reviewers queried issues to do with the research design, while very few of the concerns were related to feasibility of the study.

5.2.4 Fair selection of study population

This principle requires that the study population be of relevance to the study objectives. There were 11 concerns raised in relation to fair selection of study participants. Thus, 5% of all the concerns identified fitted in this category, making it the third least frequently raised concern. Some of the comments classified as fitting in this category were: “*No justification for selection of study population*”, “*Exclusion of Ndebele speaking from the study unjustified*”, while another comment read: “*How were the study participants going to be selected?*” Issues raised under this principle showed that the reviewers had concerns about why a particular tribe was being left out of the study. There are also concerns they were raising about why the study was leaving out a certain age group. Though the frequency of this concern might not be very high, the data seem to point to the fact that the REC is vigilantly looking at this aspect in the research protocols which they review.

5.2.5 Risk-benefit analysis

This was the fifth most frequent concern (20) raised by the REC and the queries were generally about the risk or potential risks being unclear and also benefits being either exaggerated or

not even mentioned. This constituted about 9% of all the concerns. This also translated to 13.2% of the concerns that fitted into the Emanuel et al. (2004) framework. Some of the comments that were common were: "*Risk underestimated*" and there were three comments that said: "*Benefits exaggerated*". This may suggest that the REC is alert about researchers who either try to overstate the benefits of the research study and/or who downplay the risks that will be associated with participation in the study. Of the 19 times that concerns related to this principle, three instances appeared on one protocol. The 19 concerns were spread over 13 different protocols. Most concerns classified under this principle showed that the reviewers were looking at whether all the risks were being clearly outlined and how such risks were justified.

5.2.6 Independent review

Concerns related to independent ethical review appeared 7 times and this was the second lowest number of concerns. This translates to 3% of all the concerns that were identified. It was 4.6% of the concerns that fitted into the Emanuel et al. (2004) framework. Some of the concerns that were classified under this principle were: "*Research has been started prior to obtaining ethical approval from any REC*". All of the 7 concerns that were classified under this category appeared in different protocols

5.2.7 Informed consent

The most frequent concerns raised that fitted into the framework were related to informed consent. These were issues where consent procedures were viewed as lacking important information or where the study processes were not explained in simple terms. There were 53 concerns related to informed consent. This constituted about 23% of all the concerns identified and formed 35% of all the concerns that fitted into the Emanuel et al. (2004) framework. A close analysis of the area of the informed consent concerns revealed that most of the queries identified alluded to the fact that the consent document needed to clarify participation (30%), and that the consent document needed to adopt lay language so that an ordinary person could understand it. The latter comprised 26% of the informed consent-related concerns. The other common concern in the informed consent area was the need to accommodate illiterate participants who may be unable to read the informed consent documents. The 53 concerns that were classified under this category appeared in 35 different protocols. The highest number that this concern appeared in one protocol was five times.

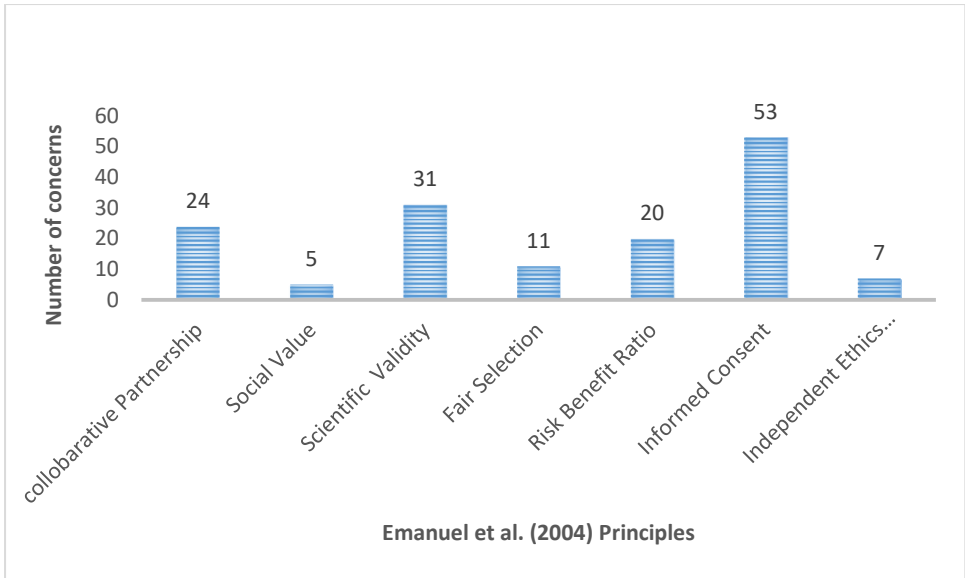


Figure 3: Distribution of concerns that fitted the Emanuel et al. (2004) framework only

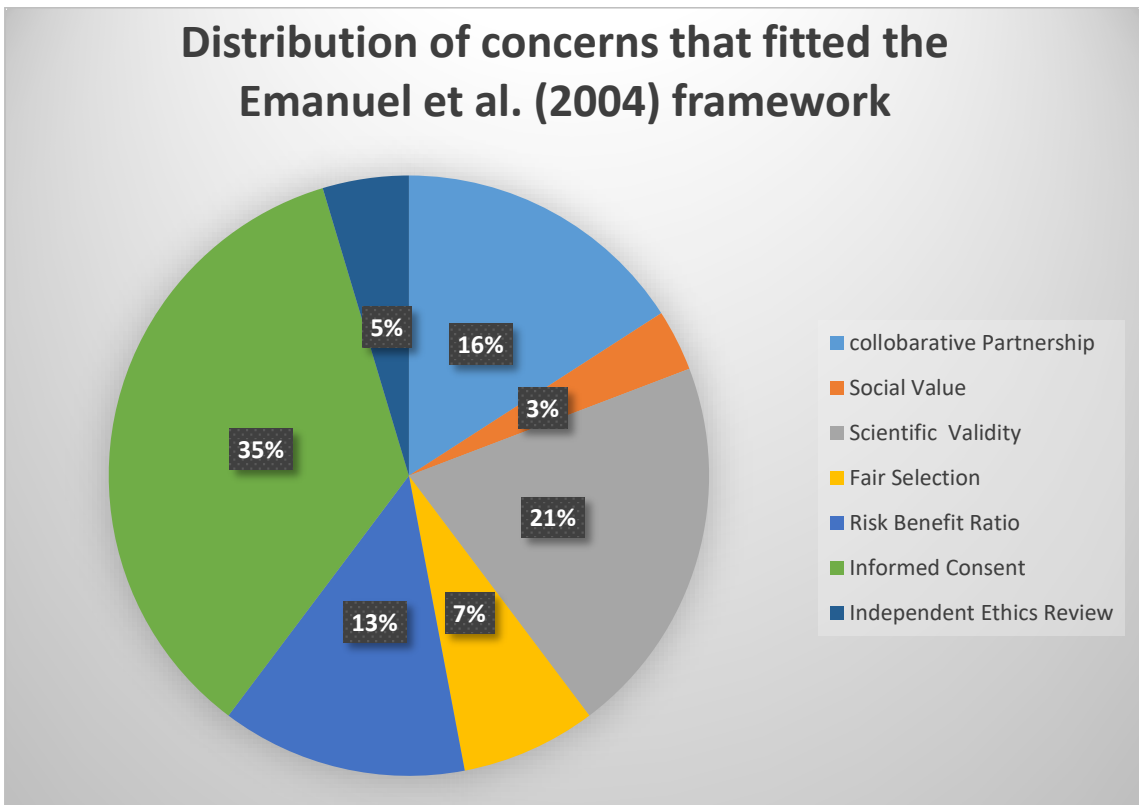


Figure 4: Distribution of concerns that fitted the Emanuel et al. (2004) framework only

Figure 3 and 4 provide an illustration of the distribution of only those concerns that fitted into the Emanuel et al. (2004) framework. It shows how informed consent dominated all of the

principles and also presents a clear picture of how some of the principles were almost invisible in the concerns. For example, social value had just one concern over the period of two years.

5.2.9 Other concerns

The analysis of data for this study revealed an array of other inter-related contextual factors and administrative requirements constituting concerns raised by the REC. These included (1) researchers not using the correct version of the application form; (2) conformity or resistance to the ethical review application administrative procedures; (3) the missing support documents; and (4) resource capacity and budgetary concerns. These four concerns were located in almost all the minutes that were reviewed. The other significant proportion of concerns was to do with typographical errors, that is spelling and grammar mistakes. These were raised in many instances. While the rest of the concerns were able to fit into the Emanuel et al. (2004) framework, it would be interesting to illustrate some of the common concerns that could not be fitted into the framework. Table 2 gives examples of some of these concerns.

Table 2: ‘Other’ concerns not fitting the Emanuel et al. (2004) framework

Category	Examples of concerns
Budgetary concerns	<p><i>“Status of funding unclear.”</i></p> <p><i>“Research has no funding.”</i></p>
Administrative procedures	<p><i>“Researcher used outdated IRB application forms.”</i></p> <p><i>“Study needs to clarify researcher X’s role in the study.”</i></p> <p>International researchers needing to be approved by another board</p>
Typos	<p><i>“Font size on protocol needs to be changed.”</i></p> <p><i>“Typo errors on local language consent forms.”</i></p> <p><i>“Too many spelling mistakes.”</i></p>

5.4 General summary of the findings

The analysis of data for this study revealed a varied range of issues in the queries and concerns raised by RECs. These issues included (1) transportation and storage of research specimen samples; (2) conformity to the REC’s procedures; (3) budgetary concerns; and (4) other administrative issues (see Table 2). Some of the perceived concerns and queries had little or nothing to do with the ethical standing of the protocol, especially for example, concerns about font size.

The aim of this study was neither to formally assess the quality of the studies of the review process nor conduct a formal systematic review. That would have proven difficult because this is a 'mere' qualitative study. Its intent was rather to give a clear description of the concerns that the REC raised and demonstrate how many of these concerns did conform to Emanuel et al.'s (2004) eight principles and benchmarks. It was also the intent of this study to assess how applicable the framework is, in the process of ethical approval of research studies in the African context in general, and the Zimbabwean context in particular.

Three fundamental points can be raised related to the pattern shown by these concerns: Firstly, it is clear from the findings of this study that the REC did not necessarily confine their review process to the seven principles and their benchmarks as developed by Emanuel et al. (2004). Secondly, of the seven principles, informed consent seemed to attract more of the REC's attention as shown by the frequency of queries that were classified under this principle. Thirdly, "other" concerns appeared more than some of the Emanuel et al. (2004) principles.

These other factors constituted some 35% of the concerns. This might mean these other issues could be considered much more pertinent and important than some of the principles in the Emanuel et al. (2004) framework.

The researcher also did an analysis of the nature of concerns raised under each principle and found that the theoretical presumptions of the Emanuel et al. (2004) framework are very applicable in the Zimbabwean setting. Indeed, if adjusted to include some of the issues that were classified under the 'other' category, it could then be adequately comprehensive. In its current state, the framework is adequate as a basic guide to reviewers, especially if they use the benchmarks as a practical guideline on what they should be looking at under each principle.

The main findings show that concerns that were coded into the "other" category constituted 35% of all the concerns identified. Informed consent related concerns came second accounting for 23% of all concerns identified. Ranked third was scientific validity with 13% of all concerns, while concerns relating to collaborative partnership were ranked fourth and amounted to 10% of all concerns raised. Concerns relating to risk/benefit ratio and fair selection of participants were ranked fifth and sixth and accounted for 9% and 5% of all concerns raised respectively. Independent ethics review was the seventh in the rank order, amounting to 3% of the total number of concerns raised. Social value had the least number of

concerns, constituting a mere 2% of all concerns raised. The next section will discuss the results in greater detail.

Chapter 6

Discussion

6.1 Introduction

A very small number of studies have emerged to detail and document the nature and form of concerns raised during the review of research protocols by RECs in the context of Africa and the third world. The current study has shown how these concerns fare when analysed using internationally acclaimed principles and benchmarks. In this study, for example, it has been shown that over and above the Emanuel et al. (2004) principles, the REC considered several other issues that may be important in the conduct of research.

6.2 Findings of the present study

This present study found that informed consent was the most frequently raised concern. This finding seems to support findings from other previous studies from different settings. Available literature highlights informed consent as the most invoked ethical issue with regard to the ethics of research (Benatar, 2002; Emanuel et al., 2000; Essack et al., 2010). Historically, informed consent was mistakenly considered as the only determinant of ethical research (D'Agostino, 1995). Findings from this study show that concerns related to informed consent constituted 23% of all concerns that were extracted from the minutes. In South Africa, Tsoka-Gwegweni and Wassenaar (2014) found that informed consent was the most frequent ethical issue raised by the REC they studied, accounting for 27.4% of all the concerns they assessed. This percentage compares very well with the present study which found the same principle at the top with 35% of all concerns that fitted into the Emanuel et al, (2004) framework. However, whether this should be viewed as demonstrating the importance of informed consent ahead of other principles is a matter needing discussion and further inquiry.

A growing number of other studies have also demonstrated the dominance of informed consent-related issues in the work of RECs across the globe. For instance, Lidz et al. (2012) found 98% of reviews in their study raised concerns about informed consent. Similarly, Taylor and Bramley (2012) and Wel et al. (2010) found that informed consent was the most queried issue. In addition, Abbott and Grady (2011), in their systematic review of 43 studies, also found that informed consent issues were the main reason for protocol rejections. This is also consistent with other studies by Angell et al. (2007) and Sansone et al. (2004) that found that IRBs expend more effort on informed consent than any other area. Angell et al. (2007) suggest

that this may be explained by the fact that informed consent is auditable or is perhaps due to the general view that informed consent is the most thoroughly institutionalised bio-ethical concept (Clapp et al., 2017).

According to Tsoka-Gwegweni and Wassenaar (2014), the eight principles are not weighted, and it is not known how they are distributed in a typical REC approval process. If the frequency of concerns related to a particular principle is anything to go by, then the data from the present study seem to suggest that informed consent is the principle that seems to catch the attention of reviewers the most. As argued above, the dominance of informed consent-related concerns were not unexpected and is not peculiar to this study. It does resonate with observations and findings from other related studies. Whether the high percentage of the concerns that were classified under informed consent does point to it being given more attention than other principles is a matter that cannot be addressed by this study. Many reasons could explain the relatively low frequencies of concerns related to other principles. It might well be the fact that the protocols submitted were sound in all the other principles. One of the reasons which might provide an explanation for the pattern that was found is the fact that due to the burdensome workload of the REC, the review time may be insufficient for a thorough protocol review. In such circumstances, RECs might just consider their two principal tasks: firstly, they must review a research protocol to ensure that the potential risks of the study are commensurate with the anticipated benefits, and secondly, they must ensure that research participants are adequately protected prior to reaching their decision (Emanuel, Crouch et al., 2003). It may then fairly be said that RECs may be tempted to focus on these two areas. This view may then raise concerns about the adequacy of IRB/REC review processes.

Informed consent and favourable risk-benefit ratio were the most invoked ethical principles in this study. Thus, risk-benefit ratio analysis was the second-most frequent concern raised in this present study. However, other studies of a relatively similar nature found a higher percentage of queries related to informed consent. Thus, it is still clear that informed consent might be the one attracting the most attention globally. This, however, does not mean that the other principles should be completely neglected, or are of less importance, because the frequencies of the concerns related to each principle does not necessarily indicate the usefulness of each principle. Thus, further studies might be needed as more and more RECs become increasingly skilled and able to utilise internationally recommended ethical guidelines.

The present analysis also revealed an ecology of factors and context-based concerns and issues that constitute what the REC viewed as queries to be addressed before they could approve a research protocol as ethically sound. Over and above the eight principles, the data has shown a range other of concerns that revealed that the REC's ethical approval process in line with both international guidelines and the local contextual and regulatory factors. The other concerns that were extracted and classified under 'other' issues are not completely new and are in fact consistent with available literature. For instance, Dixon-Woods et al. (2014) found that 87% of applications not approved at first review had issues that included procedural violations, missing information, errors in grammar and spelling, and discrepancies between different parts of the application. Consistent with this finding, some concerns classified in the "other" category in this study were entirely administrative and could be viewed as trivial in nature, for example, concerns around 'font size' used by researchers in the protocol and accompanying information forms. Concerns such as these may result in the researcher assuming that the reviewers sometimes focus on issues that are not relevant to the issues of ethics and/or scientific merits of the protocol

While 65% of all the concerns identified in this present study were consistent with the Emanuel et al. (2004) principles and benchmarks, this is significantly less than 99.7% reported by a similar study in South Africa (Tsoka-Gwegweni & Wassenaar, 2014). It is still reasonable considering the differences in local contextual factors. This seems to point to the universally applicable nature of the framework. However, slightly above a quarter of the concerns raised by this REC (35%) did not fit into the framework. While this may be reflective of undue attention being given to issues of no ethical or scientific importance, it may also imply that some important concerns related to the overall quality of the proposals fall out of the purview of this framework. Local administrative issues and requirements might also be of critical importance.

The capacity of RECs to review scientific studies is rarely called into question (Mutenherwa & Wassenaar, 2014). While this principle is generally directed to the RECs themselves, it is clear that they rarely question their own conduct. The concerns that were put in this category were generally concerning research studies that had already started without ethics approval from. Concerns about fair subject selection revolved around the need for justification for including and excluding certain population groups.

A close look at the other concerns supports the perception that the REC seemed keen to point out administrative errors made by the applicants, even though some of the errors are of no ethical concern. This finding supports the findings of Clapp et al. (2017), which points to the

fact that RECs have a tendency to concentrate on issues with no ethical ramifications. Authors like Schneider (2015) and Nelson (2004) might be perceived as having justifiable doubts about whether RECs have enough detailed understanding to avoid unduly censoring attempts to move away from established disciplinary conventions (Clapp et al., 2017).

6.3 Limitations of the current study

Beyond description, it was not really known how to further interpret the data because, the study only looked at new submissions excluding the expedited reviews since these were not captured in the minutes. Apart from that, this research work was done on the assumption that the minutes are a true reflection of the meetings, yet issues debated easily and normally may not be included in the minutes. There was also a chance of errors in coding some of these issues.

6.4 Weaknesses of the Emanuel et al. framework

That the framework does not attempt to rank or weight the eight principles according to priority and or importance might well be its weakness, in the sense that the current study and other previous studies have constantly shown informed consent to be the most prominent one among the eight principles.

This study has also shown that the eight principles and their benchmarks are not exhaustive since a substantial proportion (35%) of concerns could not be fitted into the framework. There are very important issues, especially budgetary issues, which also do not seem to be covered in the seven principles. The next section will present the conclusions of the study and provide some recommendations

Chapter 7

Conclusion, summary and recommendations

7.1 Introduction

This chapter reports the conclusions and recommendations that resulted from this study.

7.2 Summary

The overriding purpose of this study was to analyse the ethical issues and concerns using the Emanuel et al. (2004) framework, ranking them and identifying how they do or do not fit the framework. The study also set out to describe the concerns that African RECs raise in the process of ethical review of research protocols. To accomplish these goals, it became necessary to access some archived records of a Zimbabwean REC's protocol review meeting minutes. All the concerns from the minutes were extracted in order to determine which principle each concern was connected to.

The study's results show that about 35% of the concerns raised in the REC's review did not fit into the framework. These findings possibly point to the need to critically look at the adequacy of the principles with a view to including some pertinent issues that are often contentious in the review of protocols in African contexts. It might probably reflect on the level of skill of the REC, or the applicants, or this could simply be a result of coding errors.

7.3 Conclusions

Although exploratory, the findings of this study add to the relatively limited body of literature that examines the concerns raised by RECs in Africa in general and in Zimbabwe, in particular. When considered in view of all concerns identified in the context of the frequency with which they occurred, informed consent was ranked first. Although the study sites were different, an interesting comparison of these findings with the work done by Tsoka-Gwegweni and Wassenaar (2014) can be made. Tsoka-Gwegweni and Wassenaar (2014) conducted a study in South Africa and found that informed consent had the highest number concerns linked to it. Their study also found that there was a small number of administrative issues that did not fit into the Emanuel et al. (2004) framework.

7.4 Recommendations

It is our hope that researchers, research ethics committees (RECs) and other key stakeholders in health research may find the recommendations made in this study useful. This study has demonstrated that the Emanuel et al. (2004) framework is applicable in the Zimbabwean context but it needs to be expanded to include more issues. The findings of this study, together with a modest body of literature, have shown that this framework is not exhaustive. Given the diversity of other concerns and issues raised by the REC, it would arguably be more effective if the framework also included budgetary concerns. The concerns around budgetary issues were also significant; hence, it would be important to factor in such issues. The pattern observed in this study and other related studies seems to suggest that informed consent is at the core of ethics review; hence, one would suggest putting informed consent as the first priority if there is any ranking of some sort for these principles.

The following recommendations are offered for related research in the field of health research ethics education.

1. Given the dynamic nature of health research and the ethics review process in general, it would be important to consider longitudinal studies, which would help to document trends. This research would thereby be relatively current and less exposed to personal bias. Knowledge of such trends can help to shape ethics training and also help to formulate ethics review policies and strategies. Health research ethics review is not static; hence, it needs to adjust and readjust over time as contexts change, feedback is provided, and histories develop.
2. This study showed that there were some concerns outside the framework; in some cases, these did not necessarily have anything to do with ethics. For example, there was a preoccupation with spelling mistakes and other minor typographical errors. One would recommend that REC members should be exposed to training and workshops on where they can best be directing their energy.
3. Further research related to other concerns raised by the RECs might be needed to provide a means of defining their contribution to the ethics review process of research protocols. A systematic approach for organising these concerns is also recommended.
4. Based on the results of this research, it is recommended that the work of RECs in Zimbabwe might need to develop internal monitoring strategies to ascertain that they

remain focused on ethical issues. This might not only apply to Zimbabwe but all other RECs in African countries.

5. Finally, RECs in Zimbabwe might want to consider research ethics training not only for their members but also for health researchers. Ndebele et al. (2014) reported that by 2012 there were at least 13 Zimbabweans who had received advanced research ethics training, suggesting that there is local capacity to run an annual research ethics training programme for researchers and REC members to ensure ongoing, competent protection of human research participants.

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Appendix 1: University of KwaZulu-Natal ethical approval



04 September 2017

Mr Claudius Madanhire (student no.:213569750)
c/o Prof D Wassenaar
Discipline of Psychology
School of Applied Human Sciences
wassenaar@ukzn.ac.za

CLASS APPROVAL

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

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

The conditions have been met and the study is given full ethics approval with effect from the date of the original full approval by UKZN HSSREC (HSS/1450/014CA). Your response dated 11 August 2017 submitting site permission from Medical Research Ethics Council of Zimbabwe in response to BREC letter dated 21 June 2016 has been noted by BREC.

This approval is valid for one year from 04 September 2017. To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

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

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

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

The sub-committee's decision will be RATIFIED by a full Committee at its meeting taking place on 10 October 2017.

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

Yours sincerely

Professor J Tsoka-Gwegweni
Chair: Biomedical Research Ethics Committee

cc: Mr C Madanhire
Postgraduate officer: sherrylei@ukzn.ac.za


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Appendix 2: Host country ethical approval

Telephone: 791792/791193
Telefax: (263) - 4 - 790715
E-mail: mrcz@mrcz.org.zw
Website: <http://www.mrcz.org.zw>



Medical Research Council of Zimbabwe
Josiah Tongogara / Mazoe Street
P. O. Box CY 573
Causeway
Harare

APPROVAL

REF: MRCZ/B/1299 11 August 2017

Claudius Madanhire
University of KwaZulu-Natal
Department of Human Sciences
Durban
South Africa

RE:- An Evaluation Of The Ethical Concerns of Zimbabwean Research Ethics Committee (RECs), Using the Emanuel et al (2004) Principles and Benchmarks.

Thank you for the application for review of Research Activity that you submitted to the Medical Research Council of Zimbabwe (MRCZ). Please be advised that the Medical Research Council of Zimbabwe has **reviewed and approved** your application to conduct the above titled study.

This approval is based on the review and approval of the following documents that were submitted to MRCZ for review:-

- Protocol
- Data collection tool

• **APPROVAL NUMBER** : MRCZ/B/1299
This number should be used on all correspondence, consent forms and documents as appropriate.

- **TYPE OF MEETING** : Full Board
- **EFFECTIVE APPROVAL DATE** : 11 August 2017
- **EXPIRATION DATE** : 10 August 2018

After this date, this project may only continue upon renewal. For purposes of renewal, a progress report on a standard form obtainable from the MRCZ Offices should be submitted three months before the expiration date for continuing review.

• **SERIOUS ADVERSE EVENT REPORTING:** All serious problems having to do with subject safety must be reported to the Institutional Ethical Review Committee (IERC) as well as the MRCZ within 3 working days using standard forms obtainable from the MRCZ Offices or website.


• **MODIFICATIONS:** Prior MRCZ and IERC approval using standard forms obtainable from the MRCZ Offices is required before implementing any changes in the Protocol (including changes in the consent documents).

• **TERMINATION OF STUDY:** On termination of a study, a report has to be submitted to the MRCZ using standard forms obtainable from the MRCZ Offices or website.

• **QUESTIONS:** Please contact the MRCZ on Telephone No. (04) 791792, 791193 or by e-mail on mrcz@mrcz.org.zw.

Other

- Please be reminded to send in copies of your research results for our records as well as for Health Research Database.
- You're also encouraged to submit electronic copies of your publications in peer-reviewed journals that may emanate from this study.

Yours Faithfully

MRCZ SECRETARIAT
FOR CHAIRPERSON
MEDICAL RESEARCH COUNCIL OF ZIMBABWE

MEDICAL RESEARCH COUNCIL OF ZIMBABWE
2017 -08- 11
APPROVED
P.O. BOX CY 573 CAUSEWAY HARARE

PROMOTING THE ETHICAL CONDUCT OF HEALTH RESEARCH

Appendix 3: Data collection pro forma (data collection sheet)

REC Code name: ZVM

For Minutes of each protocol reviewed, code the frequency with which the following issues were raised (Some issues can occur several times in the review of a single protocol)

Protocol no:	Collaborative Partnership	Social Value	Scientific Validity	Fair Selection	Risk Benefit Ratio	Informed Consent	Independent Ethics Review	Other 1	Other 2	Other 3