An evaluation of ethical concerns raised by a South African research ethics committee using the principles and benchmarks proposed by Emanuel et al. (2004, 2008)

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by

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28 November 2022

DECLARATION

I, Melda Magolela, declare that:

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DEDICATION

The thesis is dedicated to my mother and aunt: Motsakwe Agnes Magolela and Lydia Makatikele Mahlo for nurturing my love for education, their unwavering support and cheering me on every time it got difficult and celebrating every small win with me. Thank you.

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ABSTRACT

"Mission creep", "closed doors", "bureaucracy", "time delays", "incompetence" are terms used in some of the arguments advanced by researchers who are not in favour of or are critical of the system of independent ethics review of research by Research Ethics Committees (RECs). "Human subjects' projection", "public accountability", "good research governance" are some of the terms used by researchers who embrace the system of independent ethics review of research. Also known and referred to as institutional review boards (IRBs), ethics review boards (ERBs), ethical review committees (ERCs), human research ethics committees (HRECs) evaluate all human research to ensure that proposed studies comply with international and national ethics principles and guidelines for conducting human research. These committees may either approve, reject, or require modifications to submitted protocols and their decision is binding. A key feature of such committees and their members is their independence.

Despite being for or against ethics review, there is a growing body of work attempting to describe and understand the functioning and outcomes of RECs in protecting research participants and promoting ethical research. In this area, there is relatively little work describing the actual issues that RECs look for and subsequently raise when reviewing research protocols. The current study therefore assessed minutes of a South African biomedical REC and identified ethical concerns raised during review of protocols submitted between 2015 - 2016. Ten sets of minutes were retrospectively analysed using Emanuel et al.'s (2004, 2008) framework to code, rank and classify the issues raised by the REC. There were 813 queries raised in the two-year period; 86% (697) of the queries were consistent with the framework. Top four most frequently queries were identified with scientific validity (38%) being the most frequently raised concern, followed by informed consent (33%), ongoing respect for participants (11%) and independent ethics review (9%).

Of the 813 queries raised, 14% (116) of queries could not be accommodated by the framework and these pertained to administrative issues. The results of this study support the findings of the primary study by Tsoka-Gwegweni and Wassenaar who were the first to propose and establish that the Emanuel et al. framework is a useful tool to categorize concerns raised by one South African REC. In this study, it was found that 99,7% of 1,043 queries raised for the years 2008 to 2012 were compatible with the Emanuel et al. framework with informed consent emerging as the most frequently raised concern. Equally comparable are the results of a subsequent study by Silaigwana and Wassenaar who also reported that 97,7% of the 1,272 queries raised for the years 2009 to 2014 could be categorised using the Emanuel et al. framework. The Emanuel et al. framework of eight principles and benchmarks proves to be a useful and important tool in evaluating ethical queries raised during EC protocol review meetings. Both the current study and these previous studies support use of this framework.

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CHAPTER ONE: INTRODUCTION

1.1 Introduction and background

That all research involving human participants is to be reviewed by an independent Research Ethics Committee (REC) is widely accepted in the global scientific community. However, describing RECs' functioning, review outcomes and effectiveness is very difficult because there is relatively little empirical research on African RECs (Tsoka-Gwegweni & Wassenaar, 2014). This is despite reports that show that the system of ethics review is now routine in Africa and overall, and that most research-active African countries have RECs (Ndebele et al, 2014). What has been lacking is data on the types of ethical issues that RECs raise when reviewing protocols.

Emanuel et al. (2004, 2008) delineated an eight-principle framework which can be used to clarify and or categorise type of queries raised during a protocol review at REC meetings. Having been developed with low income settings in mind, there was no empirical data that could ascertain whether this framework is compatible with work of African RECs. To date, there are only two studies published in peer reviewed journals which reported on the applicability of the Emanuel et al. framework (2004, 2008) with the primary study first conducted by Tsoka-Gwegweni and Wassenaar (2014) and later replicated by Silaigwana and Wassenaar (2019).

This lack of data meant that more studies which also seek to establish the type of ethical issues raised during REC meetings by different African RECs may help shed light on the work of African RECs. The current research forms part of an international collaboration involving the 2013 and 2015 South African Research Ethics Initiative (SARETI) Master's degree students from the University of KwaZulu-Natal, South Africa which sought to replicate this methodology in several African countries, including South Africa, Ghana, Malawi, Nigeria, Zimbabwe, Uganda and Cameroon.

More data is critical as RECs not only serve an important public protection function in providing oversight of human research, but their continued existence serves as an independent forum for the accountability of researchers conducting research with human participants (Ashcroft & Pfeffer, 2001).

1.2 Problem statement

In the twentieth-century, the scientific world was exposed to cases of abuse and exploitation of research participants, subsequently putting measures in place to initiate and strengthen human research protections to help govern the relationship between the pursuit of science, researchers, and research participants (National Institutes of Health, 2008; Training and Resources in Research Ethics Evaluation, 2009). This has been achieved through various efforts including development of ethical guidelines such as the Nuremberg Code (1947), and amendments of ethical guidelines such as Declaration of Helsinki (1964, last updated in 2013). Additionally, there has been effort geared towards establishment and capacity building of RECs throughout the world including Africa (Ndebele et al., 2014). Evidence of human subjects harms, questionable research practices as well as scientific misconduct continues to surface while on the other hand, heated debates continue about whether science should be regulated through independent review by RECs that are expected to play a critical role in protecting interests of research participants, promoting, and "enforcing" ethical research (Kim, 2012; Schrag, 2011). The debates go as far as questioning the effectiveness and necessity of RECs as primary custodians of human research especially as it pertains to review of social science research (Fost & Levine, 2007; Schrag, 2011).

Research activities also continue to increase worldwide, including in Africa, where many large-scale studies are funded by sponsors from high income countries (HICs) as attempts are made to address and respond to the continent's high disease burden (IJsselmuiden, Marais, Wassenaar & Mokgatla-Moipolai, 2012). While there are now many RECs in Africa (IJsselmuiden et al., 2012), there is a dearth of literature on the actual issues that RECs raise when reviewing protocols (Silaigwana & Wassenaar, 2019; Tsoka-Gwegweni & Wassenaar, 2014). This exacerbates existing concerns about the continent's vulnerability and its ability to prohibit exploitative research especially when dealing with funders from developed countries (Ndebele et al., 2014). RECs are ethically obligated to approve and support implementation only of research protocols and or proposals that comply with acceptable international and national ethical research guidelines. An insight into the issues that RECs raise during the review process may shed light on whether RECs in South Africa endorse research that reduce/minimize potential harms and maximize benefits to research participants and their communities which is what independent ethics review intends to achieve.

Central to the review process and decision-making is interpretation of international and national ethical guidelines by RECs (White, 1999). Concerns have been raised about the multiplicity of such guidelines including their application and relevance to African context as they are founded upon western principles and or culture (White, 1999). Emanuel, Wendler, Killen and Grady (2004) developed a framework of eight principles which mirrors the research process, encompassing existing guidelines whilst at the same time providing a more unified and practical guide that RECs in developing countries can follow during the review process.

As is it considered universal and a first attempt at developing a framework with developing countries in mind, it is also crucial to establish whether this framework is compatible with the work of RECs in Africa. The current study hopes to shed light on the applicability of the framework in an African context as well as provide comparative data on ethical issues raised by colleagues who evaluated the work of African RECs in South Africa, Ghana, Zimbabwe, Malawi and Uganda (Bengu, 2018; Frimpong, 2016; Kirimuhuzya, 2020; Madanhire, 2018; Mtande, 2018; Selormey, 2015; Silaigwana & Wassenaar, 2019; Tsoka-Gwegweni & Wassenaar, 2014).

1.3 Aim and objectives

Aim:

- The primary aim of the current study is to replicate a primary study conducted by Tsoka-Gwegweni and Wassenaar (2014) and later replicated by Silaigwana and Wassenaar (2019). The study aimed to identify the main ethical issues raised during ethics review of research proposals in 2015-2016 by a selected biomedical REC in South Africa while assessing their relative weight using Emanuel et al.'s (2004, 2008) recommended principles of ethical review of clinical research.
- The secondary aim of the study is to compare the findings of this study with data from eight other collaborating African countries that used a similar theoretical framework and methodology to facilitate comparisons.

Objectives:

- To study the minutes of systematically selected REC 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 the Emanuel et al. (2004, 2008) framework, ranking them quantitatively and identifying how they do or do not fit the framework.

Research questions:

- What ethical concerns does the REC under study raise when reviewing protocols?
- Does the REC under study systematically prioritise 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, 2008)?
- Does any feature of the Emanuel et al. (2004, 2008) framework dominate the concerns? If so, which one?
- Are there other concerns raised by the REC which are not consistent with the framework discussed by Emanuel et al. (2004, 2008)?

CHAPTER TWO: LITERATURE REVIEW

2.1 Introduction

RECs do not exist in isolation. They have resulted from and are further impacted by various historical and modern events that have taken place thereby paving a way to the current system of research governance that we have today. Below follows a brief discussion of these events to place the modern REC in context.

2.2 Human Experimentation: History and transformation of human research

In 1980, the World Health Assembly (as cited in Riedel, 2005, p. 25) announced that "the world and all its people have won freedom from smallpox, which was the most devastating disease sweeping in epidemic form through many countries since earliest times, leaving death, blindness and disfigurement in its wake". Regarded as the ‘‘scourge of mankind" then, smallpox plagued mankind for centuries and led to many deaths as well as contributing significantly to the fall of great empires such as Rome (Riedel, 2005). Whilst today smallpox is a thing of the past following the WHO's global campaign which saw smallpox being finally eradicated in 1977, it is Edward Jenner who is credited with being the first to introduce the idea of treating this infectious disease with a vaccine which he administered to his children and his neighbours' children who became immune to smallpox (Dhai, 2014; Kim, 2012; Riedel, 2005).

Coined by *The Times* as the "ascent of Everest" and possibly the most widely reported medical achievement in history, South African surgeon, Dr Christian Barnard led a team of specialists in successfully operating and performing the world's first human to human heart transplant in December 1976 at Groote Schuur Hospital in Cape Town, South Africa (Dhai, 2017a; Sliwa & Zilla, 2017).The patient was said to have been in end-stage heart failure and was 25 years old (Sliwa & Zilla, 2017) . While one cannot say for certain that this historic event was an experiment, this procedure was most likely done in a research setting (Dhai, 2017a).

The above examples of success stories suggest that it cannot be denied nor argued that human studies are an essential and a critical aspect of achieving medical and scientific progress (Dhai, 2017b; Kim, 2012; NIH, 2008). With human participants as object of enquiry, scientists and or researchers have been able to generate knowledge leading to better understanding and treatment of various diseases since the past century to current (Kim, 2012). Equally, there have been cases of abuse and exploitation of research participants in the name of research. For the purposes of this discussion, the researcher's interest in this chapter lies in some of the cases which led to the establishment of ethical codes and or guidelines which currently govern the relationship between researchers and research participants (NIH, 2008; TRREE, 2009). Amongst the well-known cases that triggered and led to the transformation of human research are the Nazi (medical) war crimes which took place between 1939 to 1945 (Kim, 2012; NIH, 2008).

Under the Nazi regime during World War II, Nazi physicians subjected thousands of unwilling concentration camps prisoners to various brutal, horrifying, and inhuman medical experiments in the name of research (Kim, 2012; NIH, 2008). Among others, the research/medical procedures involved placing the prisoners in ‘‘ high altitude low pressure tanks", forcefully submerging prisoners in "ice freezing water", injecting prisoners with "gasoline and live viruses" and forcing prisoners to "ingest poisons" (Kim, 2012; NIH, 2008). Because of the horrific nature and scope of this crimes, 16 physicians were imprisoned while seven were sentenced to death (NIH, 2008). To this day, it could be said that the medical and scientific research profession is still haunted by these events and the ethics of this profession is still recovering.

The outcome of the Nazi war crimes led to the establishment of the first ethical code known as the Nuremberg Code in 1947 (Kim, 2012; NIH, 2008). With the primary aim of preventing recurrence and replication of human experimentation abuses in biomedical research as evidenced in Nazi war crimes, the code provided ten directives necessary for human experimentation research which covered issues pertaining to informed consent, nonmaleficence and favourable risk-benefit ratio (NIH, 2008). Of significance is the code's attempt at preserving the autonomy of prospective individual participants as seen in its emphasis on the importance of voluntary informed consent (Emanuel, Wendler, & Grady, 2000). The code declares that potential research participants should be informed about the ‘‘nature, duration, purpose of the experiment including the method and means by which it is to be conducted together with all the inconveniences and hazards to be expected" (Nuremberg Code,1947, p. 181). The code further states that the potential participant ‘‘should be so situated as to be able to exercise free power of choice without intervention of any element of force, fraud, deceit and duress in addition to having sufficient knowledge and comprehension of the elements of the subject matter involved so as to enable him to make an understanding and enlightened decision" (Nuremberg Code,1947, p. 181). The limitation of this code is that it restricted or made no provision for persons incapable of making an informed consent decision to participate in research (Wassenaar, 2006). It could be argued that this limitation in part resulted from the fact that the code sought to address what was mainly seen as morally problematic in the Nazi experiments and therefore biased towards addressing the issue of concern, in this case being lack of informed consent, potentially overlooking other ethical concerns. However, this is not to suggest that had the prisoners been informed and agreed, the experiments would have been ethical. Lack of other ethical considerations such as unfavourable risk benefit ratio of the experiments would still have rendered these experiments unethical.

The Declaration of Helsinki by the World Medical Association followed in 1964 and it has since been revised seven times with the most recent version published in 2013 (NIH, 2008; WMA, 2013). Whilst it also made informed consent a fundamental ethical obligation, it filled the gap that resulted from the Nuremberg Code by taking a step further and making provision for proxy consent where potential research participants are incapable of giving consent due to various reasons such as legal/factual incompetence or compromised mental capacity (NIH, 2008). Whereas the Nuremberg

Code prohibited research with such persons, the declaration further differentiated between therapeutic and non-therapeutic research thereby making provision for research relevant to these previously excluded and vulnerable groups to be conducted (NIH, 2008). The South African, Department of Health (2015) research ethics guidelines define therapeutic research as "research that includes interventions that may hold out the prospect of direct health-related benefit for the participant". Non-therapeutic research is defined as "research that includes interventions that will not hold out the prospect of direct health-related benefit for the participant but may produce results that contribute to generalisable knowledge" (DoH, 2015, p. 29).

The Tuskegee study which took place between 1932 - 1972 is another well-known case which transformed human research (Kim, 2012; NIH, 2008). Undertaken on behalf of the United States Public Health Service (USPHS) in Tuskegee, Alabama, 600 African American man of which 400 had syphilis (experimental group) and 200 with no syphilis (control group) were unknowingly enrolled in research with the primary aim of observing the natural progression of syphilis (Kim, 2012; NIH, 2008). Without informed consent and as such having limited knowledge of what the study entailed, they were deceived and made to think that they were receiving some sort of free special medical treatment or health care from the government in the form of spinal taps which were in fact part of the study procedures (Kim, 2012; NIH, 2008). Many of the men in the experimental group died of complications as their illness progressed (NIH, 2008). Although syphilis was untreatable at the start of the study, penicillin became available in the 1940's after World War II, yet the researchers deliberately withheld information about its availability and further denied the men the treatment itself (NIH, 2008). The study was stopped following public outrage with an apology issued by then president of the United State, President Bill Clinton (NIH, 2008).

The outcome of this study led to the passing of the National Research Act in the United States in 1974 and later another ethical code known as the Belmont Report published in 1979 (NIH, 2008). The Belmont Report outlined three major principles namely respect for autonomy, beneficence, and justice (Kruger & Horn, 2014). Respect for autonomy is built on the premise that human beings (i.e., research participants) are self-governing, usually referred to as autonomous agents capable of making decisions concerning their lives and should therefore be treated as such (Kruger & Horn, 2014). Translated in a research setting, this principle requires that they be given complete and necessary information about the study and be left alone to make an informed decision about whether participation is in their best interest without any influence (Kruger & Horn, 2014). Further that those individuals with diminished autonomy such as children and mentally incapacitated adults should be protected (Kruger & Horn, 2014). In a research setting, this includes use of proxy consent. Beneficence obligates researchers working with human participants to maximize research benefits while on the other hand making every effort to avoid and minimize research harms and wrongs (nonmaleficence) (Slack et al., 2000). Justice requires researchers to treat research participants and host communities with fairness and equity during all stages of research including sharing of research benefits (Slack et al., 2000).

The death of 18-year-old Jesse Gelsinger is another case that transformed human research oversight and brought significant attention to how scientific interest and or benefits that researchers may have can influence their judgment during the study conduct to a point of exposing research participants to research harms. Jesse's death was reported as having resulted from his participation in a gene transfer clinical trial in 1999 and the only death that was attributable to adenoviral vector (Kim, 2012; NIH, 2008). He reportedly died of ornithine transcarbamylase deficiency and/or liver disease four days after he received experimental study product despite having been relatively "healthy" prior (Kim, 2012, p.7). Amongst other things the outcome of the investigation revealed that i) there had been animal data which suggested that there is a reasonable chance that the procedure could cause adenovirus-induced liver failure ii) that the investigators had reported cases of mild liver toxicity as adverse events to the research ethics committee in previous studies iii) that informed consent used for trial participants was not approved by a research ethics committee iv) the principal investigator and institution where the trial was conducted had financial interest in the trial in that they owned shares in the technology used as part of the trial (Kim, 2012; NIH, 2008). Use of un-approved informed consent forms raised questions about how much information was disclosed and or withheld especially as it pertains to safety issues mentioned above (Kim, 2012). This case brought to the fore the issue of conflict of interest in research. Today, researchers are ethically obligated to disclose any interest or goals they have in the study other than answering the research question (Kim, 2012; NIH, 2008). This ensures that their peers can look for any signs of bias in the study conduct and reporting of research results (NIH, 2008). It is crucial to note that conflict of interest in themselves do not render a study unethical but rather the potential for this interest to influence a researcher's judgment is what ought to be managed through disclosure.

The above discussion outlined the value of scientific progress achieved through human research whilst also highlighting examples of research studies which violated various ethical norms and those studies which upheld ethical principles in this pursuit. The quandary that is posed then is "how such an important, shared purpose can be pursued with full protection of individuals and communities, and those with vulnerabilities in particular" (Dhai, 2014, p.178). Beyond development and implementation of guidelines and regulations, an important stakeholder who has been assigned the task of independently applying or foreseeing that all human research observes acceptable ethical codes and norms is the Research Ethics Committee (REC) or Institutional Review Boards (IRBs) as known in the United States (CIOMS, 2016). A discussion on the roles and functions of RECs follows below.

2.3 The modern REC: Protectors of human research participants

The moral dilemma that research with human participants raises was best put into words by Katz (1972, p.1) when he asked, "when may a society, actively or by acquiescence, expose some of its members to harm in order to seek benefits for them, for others, or for society as a whole?" This question is crucial because while scientific progress has proven to bring about public good, modern-day abuses and scientific misconduct remind us that there is a need for continued vigilance if individual participants and communities are to be protected and trust between the public and science sustained (TRREE, 2014). If we do not learn from history, as George Santayana once observed "we may be doomed to repeat it". It was thought that abuses resulted from "carelessness or thoughtlessness or ignorance rather than vicious disregard for subject's welfare" (Jones et al., 2016, p.2393). A proposed solution was to rely on the informed consent and conscience of the individual investigator who will receive advice from professional peers when needed (Beecher, 1966). It appears that Katz's (1972, p.1) observation that there is a need to push towards a "system that would provide independent regulation not controlled by the medical profession and open to ''public and scholarly scrutiny" indeed was what is needed.

Of the structures or bodies that mitigate the central tension embedded in human research which is "protecting the interest of human participants vs allowing scientific progress" are RECs (Katz,1972). These are a "formally constituted group of suitably qualified persons who have a mandated authority at either institutional or national level to review and approve research involving human participants" (Kruger & Horn, 2014, p. 1). The REC provides a third party review (Kass et al., 2007). In so doing, their primary objective is to provide an independent review of research protocols to ensure that there is no deliberate or unintentional harm to potential research participants, judge the ethical and scientific aspect of the proposed protocol, by so doing safeguarding participant's rights, welfare, and wellbeing (NIH, 2008; TRREE, 2009). Additionally, they minimize "conflict of interest and protect the welfare of research participants by paying attention to risks, benefits and informed consent to limit potential for exploitation of vulnerable individuals and populations" (Kass et al., 2007, p. 0026).

How RECs achieve this function is by evaluating the science, ethics, and financial aspects of proposed research before any recruitment of potential research participants can commence (Emanuel et al., 2004; Emanuel et al., 2008). This is what can be considered as the first level of protection which lies at the design of the proposed protocol (Benatar & Vaughan, 2008). It is argued that a "study is either ethical or not at its time of inception" (Beecher, 1966, p. 372). As such, RECs evaluate proposed protocols which include participant material, study budget and researchers' qualifications to determine competence to carry out specified methods, to determine how sound or unsound the science of the protocol is, information contained in the informed consent forms including proposed process, ways in which potential research participants are to be identified and recruited, competency of the researcher, feasibility as well as the availability of the researcher to carry out and or supervise the research (Emanuel et al., 2004; Emanuel et al., 2008).

The outcome of competent independent ethics review determines whether approval will be granted for the researcher to commence with recruitment or not. If a proposal receives an unfavourable opinion, the committee may require modifications before approval is granted or may outright reject the proposed research if it is judged to show blatant disregard for participant safety or does not follow universally acceptable scientific standards (Emanuel et al., 2004; Emanuel et al., 2008). Regarded by some as "passive" oversight, the limitation, or shortcomings of this level of protection is that perfectly designed research protocols do not necessarily translate into ethical conduct and so this level of protection relies heavily on trust that researcher will implement the approved protocol and comply with approval conditions (Benatar, 2002). This shortcoming is mitigated by second level of protection which is achieved through post-approval monitoring and ongoing review of approved studies (TRREE, 2009). The REC achieves this through conduct of *ad hoc* visits to the research site (TRREE, 2009).

2.4 Resistance to research ethics review

Although the concept of independent ethics review of research is generally accepted within the scientific fraternity, it is not without controversies and or resistance. There exist debates, criticism, and resistance to the review process. Amongst others, there is unhappiness regarding time delays and inconsistencies that often characterize the review process (Wassenaar, 2006). The competence of the REC members to review broad spectrum of research methodologies has also been questioned (Grady, 2010). There are also doubts about the independence of RECs especially those operating at institutions as they might want to build the institution's research portfolio, or they are thought to impose silly restrictions on researchers thereby curtailing academic freedom (TRREE, 2009). It is worth noting that despite the resistance, it has become mandatory in many countries that all research intending to involve human participants as the subject of investigation is approved by an independent REC or IRB. Even with the criticisms or shortfalls such as the above which mainly deal with pragmatic or practicalities of the process, researchers are still expected to feature this process in their "research timelines" (Wassenaar, 2006).

2.5 Research cthics committees in Africa and challenges

In South Africa, Dr Bezwoda of the University of Witwatersrand conducted a study to test the efficacy of breast cancer chemotherapy without having received both ethical approval and individual informed consent from participants (Ndebele et al., 2014). In Zimbabwe, British anaesthetist Dr McGown was charged by the Harare court for conducting various human experiments on black patients leading to six deaths (Ndebele et al., 2014). This is to say, that like the rest of the world, Africa has not been immune to abuse of research participants. It is therefore not surprising that as with the rest of the world, there has been a significant increase and growth of research oversight in Africa. A significant portion is funded by sponsors from developed countries (Ndebele et al., 2014). This in part results from several issues such as the continent's serious health issues, because "it is or it is assumed to be less expensive, because it has become increasingly difficult to find sufficient number of qualified participants in the sponsors' home countries, and also because funders are responding to the need for research into questions pertinent to the African context" (IJsselmuiden et al., 2012, p. 2). For example, literature shows that over 90% of all external funding in Africa is geared towards Human Immunodeficiency Virus (HIV), Tuberculosis (TB), and malaria, which are three of the most urgent health issues that Africa is facing (IJsselmuiden et al., 2012).

However, there are legitimate concerns that as the health research initiatives grow in both scope and complexity, they have "not necessarily been accompanied by improvements in health research oversight systems, including ethical review committees and therefore leaving the continent vulnerable to potential exploitative research funded by resource-rich countries as well as researchers from developed countries who may thus conduct research in Africa that cannot easily be done in their own countries due to a robust research regulatory framework there, which is often not found in most African countries" (Ndebele et al., 2014, p. 3). To deal with such concerns and as well as improve the capacity of ethics oversight within the continent, several initiatives have been implemented by funders such as WHO-UNAIDS African AIDS Vaccine Programme (AAVP); the African Malaria Network Trust (AMANET); the National Institutes of Health's (NIH) Fogarty International Center's South African Research Ethics Training Initiative (SARETI) and the International Research Ethics Network for Southern Africa (IRENSA) (IJsselmuiden et al., 2012). With relatively little empirical research on African RECs, it remains difficult to ascertain the effectiveness of these initiatives (Tsoka-Gwegweni & Wassenaar, 2014).

Below follows a few studies that were conducted which helped to shed light on the current state of RECs in Africa.

Kass et al. (2007) conducted a case study where they sought to describe the experiences of twelve African bioethicists and the functioning of the RECs they are involved in within their respective countries. The following nine African countries were included in the study: Democratic Republic of the Congo, Ghana, Kenya, Nigeria, South Africa, Sudan, Tanzania, Zambia, and Zimbabwe. The findings or the results of this study revealed that although at varying degrees, all RECs in

these countries were functional with some such as South Africa and Zimbabwe having been established close to thirty years ago and some such as Kenya and Congo being recent. For example, South Africa's first REC was established in 1967 at the university of Witwatersrand and Zimbabwe in 1974, Kenya and Congo having been established "by two trainees a year before data collection of this case study" (Kass et al., 2007, p. 0027). Furthermore, of the twelve RECs, six had "Federal Wide Assurances (FWAs) from the US government, an indication that the institution had received US research funds or collaborated with US institutions" (Kass et al., 2007, p. 0027). Some of the biggest concerns and challenges that this report yielded was that often, most of the RECs had inadequate funding as well as training, especially the newest ones. For example, out of twelve RECs, nine relied on foreign agencies and charging fees for review whilst three reported to have no source of funding for operations (Kass et al., 2007, p. 0027). This lack of funding further led to weak monitoring systems of approved protocols while others resorted to "rubber stamp" approvals to secure international funding (Kass et al., 2007, p. 0027). Regarding training, two committees had members who had never been trained in ethics which impacted on the review process and resulted in "disproportionate focus on science" while neglecting the ethical aspect of the protocol under review (Kass et al., 2007, p. 0028).

IJsselmuiden et al. (2012), through the Mapping African Research Ethics Capacity (MARC) project helped identify existing capacity of RECs in Africa. Although this project was geared towards providing a platform for RECs and health research stakeholders in Africa with respect to capacity constraints, and development needs, it also provided useful information on RECs in Africa. Based on this project, twenty-five African countries were listed on the MARC project, with ninety-eight RECs reported to have registered and in existence in Africa and a further seventy-three RECs identified which meant that there were possibly one hundred and seventy-one RECs in Africa around 2012. Furthermore, the project was able to identify the number of individual professionals trained in research ethics by both region and country which totalled 179. In terms of regions, the southern African countries had a total of fifty-three RECs and eighty-nine trainees, the eastern region had forty-one RECs and thirty-one trainees, the western region also had a total of forty-one RECs and twenty-three trainees, the northern region had twenty-six RECs and thirty-two trainees, and the central region had ten RECs and four trainees. In terms of number of RECs per country, the following top twelve countries were identified: South Africa had thirty-five, Nigeria had nineteen, Egypt fifteen, Tanzania and Uganda had thirteen each, Sudan seven, Ethiopia, and Ghana six each, Botswana, Kenya, Cameroon, and Zimbabwe also had five each. The following countries had the highest number of people trained in ethics. South Africa had sixty-one trainees, Egypt had twenty-seven, Nigeria seventeen, Kenya, Tanzania, and Zimbabwe had ten trainees each, Zambia had nine, Uganda six and Ethiopia had five. South Africa had the highest number of both RECs and trainees.

Silaigwana and Wassenaar (2015) conducted a review on twenty-three empirical studies conducted between the years 2005 and 2014, which examined and reported on the structure, functions, and outcomes of African RECs. These studies shed light on different aspects of African RECs including history and establishment, structures and status, membership

and composition, resources and infrastructure, standard operating procedures, independence, workload, and ethics review capacity and training, application of international and national guidelines as well as ethical issues and decision outcomes (Silaigwana & Wassenaar, 2015). Based on this review, the authors identified the following challenges as they relate to effective functioning of RECs in Africa. Silaigwana and Wassenaar (2015, p. 12) state "the reviewed data suggest that membership of RECs is uneven, with medical professionals being the largest group" while ethicists, community members and females are often absent or typically underrepresented. For example, Milford et al., (as cited in Silaigwana & Wassenaar, 2015) report on a survey done with thirty-five RECs in which 40% of the members were medical doctors and 1% ethicists.

The data further showed that some RECs are faced with scarce resources. For example, six RECs in Tanzania reportedly had no office space (Silaigwana & Wassenaar, 2015). Other RECs identified a need for research ethics training and raised concerns regarding insufficient training of its members, such as one in Egypt (Silaigwana & Wassenaar, 2015). The authors also identified challenges which related to inadequate capacity to review and monitor studies, lack of national research ethics guidelines and accreditation of some but not all African RECs (Silaigwana & Wassenaar, 2015).

The above studies suggest that ethics review systems are growing and possibly becoming routine in Africa (IJsselmuiden et al., 2012; Ndebele et al., 2014; Silaigwana & Wassenaar, 2015). Some committees operate at institutions, some at national level while others operate privately (Ndebele et al., 2014). Furthermore, some RECs, especially those which have been in existence for a long time and have had their capacity developed such as those in South Africa are more stable, better equipped and often have well trained members (Ndebele et al., 2014). While others are still lagging, some African countries further have national laws and regulations which mandate review of research such as South Africa's National Health Act which further requires all RECs to be registered with the National Health Research Council of South Africa (NHREC) and Kenya's National Council for Science and Technology (Silaigwana & Wassenaar, 2015). Another example is Nigeria which has a National Health Research Ethics Committee (NHREC) as the national regulatory body, with adoption of the National Code of Health Research Ethics established in 2005 and 2007 respectively (Yakuba & Adebamowo, 2012). Finally, when a review of ethics regulation was done in Nigeria, Malawi, Cameroon, Rwanda, and Zambia for HIV vaccine research, it was established that "although not perfect, most countries had some form of legislative mechanisms to regulate research either at national or institutional level" (Silaigwana & Wassenaar, 2015).

Another challenge faced by RECs central to the review process and decision-making is interpretation of international and national ethical guidelines. Concerns have been raised about the multiplicity of such guidelines including their application and relevance to African context (White,1999). This is because in most cases, ethical principles are characteristically western and therefore "conflict is likely to emerge especially in situations where there is direct contact between potentially different ethical systems as in the conduct of transcultural research" (Christakis, 1992, p. 1079). For

example, the first three ethical codes, viz., the Nuremberg code, Declaration of Helsinki, and Belmont Report are founded on the "western concepts of human rights with particular focus on autonomy, beneficence and justice" (White, 1999, p. 87). The increase in scope and complexity of international collaborative medical research also raises "the problem of whether and how to maintain international ethical standards when research is conducted in countries with very different social and ethical values" (White, 1999, p. 87). This issues further raises considerable debate and the question of whether ethics are universal, absolute, or relative (Christakis, 1992; White, 1999).

The World Health Organization (WHO) and Council for International Organisations of Medical Sciences (CIOMS) guidelines were thus drafted to address cross-cultural research protocols, as well as providing recommendations for review to be utilized by research ethics committees (White, 1999). However, according to White (1999), REC members and administrators remain puzzled and uncertain about how to apply ethical guidelines during their ethical analysis mainly because while these key documents provide ethical principles and applications, they are not specific enough. It is therefore left to RECs to interpret and apply these guidelines in their review which may cause inconsistency in levels of research protection required by RECs. Molyneux and Geissler (as cited in Wassenaar & Mamotte, 2012, p. 274) argue, "there is a growing realization that it is difficult to apply abstract universal ethical principles in practice because of context, history, culture and politics as well as the social, gender and economic status of participants which can have implications for how ethical principles are applied in different settings".

Literature also reveals that, in the past, several international and local ethics guidelines have been developed, resulting in some confusion over which to use (Tsoka-Gwegweni & Wassenaar, 2014; Wassenaar & Mamotte, 2012). The most helpful has been the Emanuel et al. (2004) framework (Wassenaar & Mamotte, 2012). Unlike many international research ethics guidelines which were constructed in developed countries driven by scandals and based primarily on western ethical standards, the Emanuel et al. (2004) framework was purposefully created to suit research in developing countries (Emanuel et al., 2004; Wassenaar & Mamotte, 2012). Furthermore, they are unified, consistent, specific, and practical (Emanuel et al., 2004). The principles are further well-thought-out, still embedded in international research ethics principles and organized in such a way that they match the research design and process thereby enabling research ethics committees to assess how well the "enumerated ethical principles have been fulfilled in particular cases" (Emanuel et al., 2004, p. 930).
A discussion of this framework follows below.

2.6 Emanuel et al.'s (2004;2008) framework: Principles of ethical research

2.6.1 Principle of collaborative partnership:

Historically, researchers were accustomed to visiting communities, studying them with or without their knowledge and leaving without sharing the results and benefits of their research, commonly referred to as "helicopter" or "safari" research" (Emanuel et al., 2004). This lack of consultation and community engagement undermines the autonomy and interests of participants and host communities whilst at the same time denying them opportunities to collaborate and partner with researchers in the various stages of research including sharing responsibilities and research rewards and or benefits (Tsoka-Gwegweni & Wassenaar, 2014). This principle admonishes such practices and obligates researchers to recognize that often, communities are one of the many key stakeholders involved in scientific enquiry. Thus, researchers are ethically obligated to engage and collaborate with key stakeholders including, but not limited to, research participants, policy makers and host communities (Emanuel et al., 2004). This ensures that local traditions are respected and where possible incorporated in the research thereby exploring opportunities for capacity development allowing for a meaningful partnership which changes the narrative from doing research "on" or "about" to conducting research "with" communities (Emanuel et al., 2004). This is crucial in mitigating potential for exploitation.

Six benchmarks are necessary for a proposed protocol to be judged to have fulfilled this principle and these are delineated by Emanuel et al. (2004, p. 931) as:

- "Develop partnerships with researchers, makers of health policies, and the community".
- "Involve partners in sharing responsibilities for determining the importance of health problem, assessing the value of research, planning, conducting, and overseeing research, and integrating research into the health-care system".
- "Respect the community's values, culture, traditions, and social practices".
- "Develop the capacity for researchers, makers of health policies, and the community to become full and equal partners in the research enterprise".
- "Ensure that recruited participants and communities receive benefits from the conduct and results of research. Share fairly financial and other rewards of the research".

The first benchmark of developing partnerships with researchers, makers of health policies and the community has been expanded upon in the United Nations Programme on HIV/AIDS (UNAIDS) Good Participatory Practice (GPP) guidelines for biomedical HIV prevention trials (UNAIDS, 2011). These were developed jointly by the UNAIDS and AIDS Vaccine Advocacy Coalition (AVAC) to provide a framework for developing effective stakeholder engagement programmes and have proved a useful resource in the research landscape (UNAIDS, 2011).

2.6.2 Principle of social value:

The debate on whether research should be "spearheaded by scientific curiosity, or be mission orientated to solve specific problems" is ongoing (Benatar, 2008, p. 43). Despite the global and or local forces that may drive or influence the research agenda, it is widely accepted that human studies and or science is a public good with its value being deeply rooted in the estimated contribution that the data produced during the research will benefit either individual research participants, host communities, society, or the world at large (Emanuel et al., 2008). This value may be in a social, clinical, or scientific form (Emanuel et al., 2008). In addition to being costly, human studies and or scientific research carries with it a certain level of risk to its participants. By risk referring to the "probability that a certain harm will occur" because of research participation (NIH, 2008, p. 63). The degree and the duration of risk will vary depending on the research design or type but among others, risk or harm can be in a physical, psychological, emotional, or economic form (NIH, 2008). The question that follows then is, how do we justify to knowingly exposing our fellow human beings to risk or harm in the name of research? The answer lies in the anticipated social value of the proposed research. Today we speak of various effective vaccines, chemotherapies including other benefits that society enjoys which bear testament to how research is a fundamental and indispensable component of improving health (TRREE, 2014). Without human studies and the generosity of our fellow human beings in volunteering their time and willingness to take on the risk associated with research, none of this would have been possible.

It is against this background that the principle of social value justifies investment of scarce resources such as time, money, and human beings in research, all of which are indispensable to translating or to operationalize research questions (Emanuel et al., 2008). It, however, admonishes that our fellow human beings should not be exposed to risks and/or harms for no reason. If they are to be exposed, then there must be anticipated or immediate, direct, or indirect contribution and or benefits that the data or knowledge generated in this process and or research outcomes will bring direct or indirect benefits to individual participants, host communities, society, or world at large (Emanuel et al., 2008; Wassenaar, 2006). With no expected contribution or benefit to society, research as a social good becomes a tool for exploitation.

To minimize opportunities for exploitation, assist researchers in their research design and RECs in their review process, Emanuel et al. (2004, p. 931) delineated four benchmarks to help determine if the proposed protocol has principle of social value and these are that a proposed protocol must:

- "Specify the beneficiaries of the research".
- "Assess the importance of the health problems being investigated and the prospective value of the research for each of the beneficiaries".

- "Enhance the value of the research for each of the beneficiaries through dissemination of knowledge, product development, long-term research collaboration, and/or health system improvements".
- "Prevent supplanting the extant health system infrastructure and services".

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- "Prevent supplanting the extant health system infrastructure and services".

2.6.3 Principle of scientific validity:

While it is acknowledged that no research or experiment can be 100% accurate, researchers are ethically obligated to ensure that they avoid conscious or unconscious bias in their research design, conduct of the study and reporting of their research outcomes (Emanuel et al., 2008). Any form of bias, be it conscious or unconscious, purposeful, or accidental diminish the scientific validity of a study and is therefore unethical (Emanuel et al., 2008). This is because flawed research design or well-designed research that is poorly executed cannot generate valuable data or useful results thereby exposing potential research participate to risks and inconveniences when neither they, their communities, society nor scientific enterprise can benefit (Emanuel et al., 2008). Further, such research cannot lead to increase in knowledge which is problematic because no research project exists in isolation but ought to build on prior work (National Academies of Sciences & Medicine, 2019). Thus, there will be no value in other researchers examining or reviewing such work and the scare resources such as time and money could have been better diverted elsewhere (NASEM, 2019).

Below follow three benchmarks to help evaluate the scientific validity of proposed research as delineated by Emanuel et al. (2004, p. 931):

- "Ensure that the scientific design of the research realizes social value for the primary beneficiaries of the research".
- "Ensure that the scientific design realizes the scientific objectives while guaranteeing research participants the health-care interventions to which they are entitled".
- "Ensure that the research study is feasible within the social, political, and cultural context or with sustainable improvements in the local health-care and physical infrastructure".

This principle thus requires that the proposed research is based on reliable and valid research designs and methods of obtaining data, and is relevant to the objectives; the findings obtained must be relevant to the health problem being studied; and study design should not affect provision of current health care services and should be feasible within the local context of the research setting (Tsoka-Gwegweni & Wassenaar, 2014). This is because the value of scientific research is contingent on "effective design and execution" (NASEM, 2019).

2.6.4 Principle of fair participant selection:

Every research proposal must demonstrate fairness in the way potential research participants, communities and or study population are recruited and selected whilst ensuring that vulnerable groups are identified and protected from exploitation (Emanuel et al., 2008). Their suitability and or selection ought to be based on study goals as well as ensuring valid science. No research participants or community should be targeted because of their being vulnerable or easily accessible/approachable, out of convenience or their unfavourable socio-economic-political standing (Emanuel et al., 2008, Wassenaar, 2006). In short, the "population selected for the study should be those to whom the research question applies" to (Wassenaar, 2006, p. 71). Consequently, to include or exclude study population based on any reason other than the scientific objectives is unethical (Emanuel et al., 2008). Whereas it is documented that historically, vulnerable groups were often recruited for risky research, researchers and RECs are ethically obligated to ensure that such occurrences do not find expression today (Kim, 2012).

In instances where those who can best help answer a particular research question fall within vulnerable groups such as children, additional safeguards such as ensuring that in addition to parental consent, that the child is given the choice and freedom to choose and or decline participation (assent) are to be carefully implemented (Emanuel et al., 2008). Furthermore, whereas it allows for vulnerable groups to be excluded based on minimizing risk and these are widely documented including protections or various safeguards, it is crucial to also take note of situational factors such as poverty. As general rule, the largest burden of the research should be carried by those who are most likely to enjoy the rewards of the research outcomes (Wassenaar, 2006).

Emanuel et al. (2004, p. 931) delineated three benchmarks against which researchers and RECs can evaluate if proposed research fulfils this principle and these are:

- "Select the study population to ensure scientific validity of the research".
- "Select the study population to minimize the risks of the research and enhance other principles, especially collaborative partnership and social value".
- "Identify and protect vulnerable populations".

2.6.5 Principle of favourable risk-benefit ratio:

That any type of research involves an element of risk to potential research participants and that disclosing this information to allow a potential participant to knowingly accept this risk by granting consent to research participation is widely accepted (Capron, 2016). Depending on the type of research which will determine the degree and severity of risks, research participants may experience job loss (economic risk), depression and anxiety (psychological risk), death, disability (physical risk), stigmatization, discrimination (social risk) because of study participation (TRREE, 2009). The risk or burden may also be as simple as the time spent or inconvenience caused. Research participants can also enjoy certain benefits because of study participation such as access to successful interventions, treatment of disease and pure altruistic satisfaction of having given their time and themselves for the benefit of society (TRREE, 2009).

This principle calls for a balancing act, the research risk or burdens must be balanced out and or justified by the benefits that the research will bring first to individual participants, and then to host communities or society at large (TRREE, 2009). For a study to be considered to have favourable risk/benefit ratio, the potential benefits of study must outweigh the risks or harms associated with participation (TRREE, 2009). Key factors in this identification is that potential benefits or interventions must be related to both the participants' health as well as the research study and or study's objectives (Emanuel et al., 2008). Arguably, benefits unrelated to the research, generally called extraneous (secondary to research objectives) such as reimbursement and ancillary care are not to be considered in this ratio, albeit desirable (Emanuel et al., 2008). Therefore, a researcher cannot simply add more ancillary benefits, to offset the risky aspect of the research.

Emanuel et al. (2004, p. 931) delineated two benchmarks against which researchers and RECs can evaluate if proposed research fulfils this principle and these are:

- "Assess the potential risks and benefits of the research to the study population in the context of its health risks".
- "Assess the risk-benefit ratio by comparing the net risks of the research project with the potential benefits derived from collaborative partnership, social value, and respect for study populations".

2.6.6 Principle of independent ethics review:

While researchers generally have genuine altruistic objectives/interest for conducting research, like any other human beings, they may also have other multiple legitimate interests ranging from personal, financial, intellectual as well as professional interest, commonly referred to as ‘‘conflict of interest” (Emanuel et al., 2008). Whilst there is nothing inherently wrong with their having such benefits or interest in themselves, it is the potential for such interests or benefits to clash with or their ability to influence their research decision-making regarding study design, study conduct and or reporting of results (Emanuel et al., 2008). It is critical that these interests are recognized, disclosed, and managed.

One way of managing them is through the process of independent review by competent independent RECs which entails reviewing ethical, scientific, and financial aspect of the proposed research to ensure that it meets scientific and ethical standards (Emanuel et al., 2008; TRREE, 2009). Because they are not affiliated or connected to the protocol or research under review, RECs are able to objectively consider ways in which the research can better enhance benefits, lessen risk to participants and even spot ways in which researchers may have overlooked certain scientific elements and ethical principles which can help improve and make their research more scientifically and ethically adequate research (Emanuel et al., 2008). Through the review processes, RECs may make recommendations that better maximize protection of potential participants such as recommending alternative less riskier methods or recommend inclusion of services that enhance benefits to participants, by so doing enhancing the quality of the research (Emanuel et al., 2008; Wassenaar, 2006).

While it may not be possible to eliminate a researcher’s conflict of interest entirely, they are at least minimized by this system of independent review (Emanuel et al., 2008). This further ensures that RECs fulfil their secondary role of preserving the trust that public and or society has in science or research. Why public trust and or accountability is important, is because science is not an isolated discipline, it is not self-serving but rather, science should serve society and it is dependent on society to materialize and prosper (ION, 2009). Therefore ‘‘to keep its position in society, it requires legitimacy”, consequently the relationship between science and society which is built on trust, honesty and transparency must be maintained (ION, 2009, p1). Historically and recent times, this relationship has been strained.

Emanuel et al. (2004, p. 931) delineated three benchmarks against which research and RECs can evaluate if proposed research fulfils this principle and these are:

- “Ensure public accountability through reviews mandated by laws and regulations”.
- “Ensure public accountability through transparency and reviews by other international and nongovernmental bodies, as appropriate”.
- “Ensure independence and competence of the reviews”

2.6.7 Principle of informed consent:

That researchers have an ethical obligation to obtain informed consent from potential research participants before commencement of any study procedures is widely recognized and documented in various international and national ethical guidelines as well as legislation (Andanda, 2005). It is therefore not surprising that it has become a central and much debated ethical principle articulated in most guidelines and literature (Eriksson et al., 2008). Founded upon the principle of respect for persons, it requires that researchers provide potential research participants with "clear, detailed and factual information about the study, its methods, its risks and benefits, along with assurances of the voluntary nature of participation, and the freedom to refuse or withdraw without penalties" (Wassenaar, 2006, p. 72). This information allows an autonomous person to deliberate and make an informed choice on whether study participation aligns with their interest and or values (Emanuel et al., 2000).

There are four widely accepted basic elements of informed consent which date to the Nuremberg Code. These are competence, disclosure, understanding and or comprehension as well as voluntariness (Andanda, 2005; TRREE, 2014). As a result, researchers are ethically obligated to ensure that a potential research participant is legally and factually competent to decide, that he or she is mentality capable to engage with the provided information which is to be presented in a language that the potential participant can understand (Andanda, 2005; TRREE, 2014). Any form of deliberate manipulation, undue inducement and or coercion which impairs, threatens, or limits a participant's freedom by any of the research team including a participant's family, community nullifies any given informed consent (TRREE, 2014). In short, any consent that is not freely given is not consent. Those potential participants with compromised autonomy and or lacking capacity and competence ought to be identified and protected by putting measures in place to ensure their autotomy is not trampled upon such as using proxy consent with due care (TRREE, 2014).

Emanuel et al. (2004, P. 931) delineated five benchmarks against which researchers and RECs can evaluate if proposed research fulfils this principle and these are:

- "Involve the community in establishing recruitment procedures and incentives".
- "Disclose information in culturally and linguistically appropriate formats".
- "Implement supplementary community and familial consent procedures where culturally appropriate".
- "Obtain consent in culturally and linguistically appropriate formats".
- "Ensure the freedom to refuse or withdraw".

Although essential, informed consent is not the only determinant of ethical research and therefore, that a potential participant provided voluntary consent does not mean that the proposed research is ethical in the absence of other ethical considerations (DOH, 2015). Only in the presence of other ethical considerations (as outlined in sections 2.6.1

to 2.6.8), can consent be given. It has become increasingly common that this decision is recorded or documented in some form to allow for verification.

2.6.8 Principle of respect for recruited participants and study communities:

Beneficence, nonmaleficence and respect for autonomy includes some principles which underpin the principle of respect for persons (Emanuel et al., 2004). This principle is concerned with obligations that researchers have towards potential, actual and former research participants including host communities which ought to happen prior, throughout and after the research project (Emanuel et al., 2004). These obligations extend beyond given consent and call for an ethical commitment to keep confidential the research data during collection and storage to show respect to the dignity of participants as human beings (Emanuel et al., 2004). This means identifying any threats and limitations to upholding privacy and confidentiality which are to be disclosed as part of the consent process and informing participants of any confidentiality breaches should they happen after consent was given (Emanuel et al., 2004). A commitment to participant's health by providing necessary care, sharing research results whether negative or positive, and not shying away from post-research responsibilities such as availing successful interventions to research participants and host communities where possible (Emanuel et al., 2004).

Emanuel et al. (2004, p. 931) delineated five benchmarks which researchers and RECs can use to ascertain whether there is adherence to this principle, and this are:

- "Develop and implement procedures to protect the confidentiality of recruited and enrolled participants".
- "Ensure that participants know they can withdraw without penalty".
- "Provide enrolled participants with information that arises in the course of the research study".
- "Monitor and develop interventions for medical conditions, including research-related injuries, for enrolled participants at least as good as existing local norms".
- "Inform participants and the study community of the results of the research".

2.7 Limitations of the Emanuel et al. framework

While the Emanuel et al. (2004, 2008) framework is lauded for its usefulness in describing and categorizing core activities of an REC (Tsoka-Gwegweni & Wassenaar, 2014), some limitations have also been identified. It is reported that Médecins Sans Frontiéres found the framework to be restrictive and or rule-like, thereby not allowing opportunity for discussion which often characterise typical REC meetings (Tsoka-Gwegweni & Wassenaar, 2014). Additionally, the eight principles of the framework and the benchmarks are intended to be considered equally (Emanuel et al., 2008) and this lack of weighting may give rise to conflict as it may appear to prevent foregrounding some principles over others (Silaigwana & Wassenaar, 2019; Tsoka-Gwegweni & Wassenaar, 2014). As such, in an event where reviewers are faced with a conflict, it is silent on what considerations should be prioritised to arrive at a decision (Silaigwana, 2017; Silaigwana & Wassenaar, 2019; Tsoka-Gwegweni & Wassenaar, 2014).

2.8 Applicability of the Emanuel et al. (2004, 2008) framework to African RECs

The Emanuel et al. framework is widely referenced in literature (Tsoka-Gwegweni & Wassenaar, 2014). Amongst other uses, Médecins Sans Frontiéres' own REC used it to develop their standard operating procedures while Wassenaar and Mamotte (2012) recommend it for ethics review of social science research (Tsoka-Gwegweni & Wassenaar, 2014). Rid and Emanuel (2014) used it to outline ethical considerations of experimental interventions in the Ebola outbreak. Mutenherwa and Wassenaar (2018) employed this framework to conduct a review of literature on ethical issues associated with HIV phylogenetics in HIV transmission dynamics research. As stated earlier, while the framework was developed to help guide review of research in low income countries (LICs), until recently, it could not be said whether this framework is applicable to issues raised by African RECs.

A brief history of the framework may be useful to note here. Emanuel, Wendler and Grady (2000) first published this framework with seven principles in 2000 and these were i) social value; (ii) scientific validity; (iii) fair participant selection; (iv) favourable risk–benefit ratio; (v) independent ethics review; (vi) informed consent; and (vii) ongoing respect for participants. Emanuel, Wendler, Killen and Grady (2004) authored the first revision in 2004 which resulted in the inclusion of collaborative partnership as the eighth principle. Emanuel, Wendler and Grady (2008) later published this revised version of eight principles again in 2008. The current study as well as below studies employed either one and or combination of the 2004 and 2008 version as their conceptual framework. It should be noted that there was no content change with respect to the principles and benchmarks in both the 2004 and 2008 versions, hence the use of either-or combination of both years by the authors.

To date, there are eight known studies which have used the above-mentioned eight principle framework as a tool to describe and categorise core activities of one or various African RECs. The primary study by Tsoka-Gwegweni and Wassenaar (2014) represented the first known attempt to use this framework to analyse REC minutes and shed light on

its applicability to the work of African RECs. The authors assessed 98 protocols of a South African REC and found that the framework was able to categorize 99,7% of 1,043 queries raised. Selormey (2015) analysed twenty-two protocols of a Ghanaian REC which yielded 232 queries, 80% of which were accommodated by the framework. Similarly, Frimpong (2016) reported that 97.7% of 1,205 queries raised by another Ghanaian REC were accommodated by the framework. Madanhire (2018) reported that the framework accommodated 65% of 232 concerns raised by a Zimbabwean REC.

Mtande (2018) was able to code 88,8% of 1,274 concerns raised by a Malawian REC and Bengu (2018) reported that 98% of 998 concerns raised by a South African REC were accommodated by the framework. Silaigwana and Wassenaar (2019) report that the framework accommodated 83% of 1,272 queries raised by two RECs. Kirimuhuzya (2020) reported that 90.5% of 2008 queries raised by a Ugandan REC could be accommodated by the Emanuel et al. (2008) framework.

Overall, when retrospective review of 8264 minutes of the 8 African RECs over a 7 (2008-2014) year period were analysed using this framework, it was found to be compatible with their work thereby proving its usefulness in low income countries as originally intended by the authors. Beyond ascertaining the compatibility and/or incompatibility of the framework to African RECs, as with the current study, the authors further sought to ascertain any pattern to the ethics concerns raised, while also ranking the order and or frequency of principles in light of queries raised. Section 2.8 below follows, presenting the most frequent ethical issues raised by African RECs for the years 2008-2014. Additionally, an overview of the actual results of the above-mentioned studies is provided for context.

2.9 Ethical Issues Considered by African RECs as Identified by the Emanuel et al. (2004, 2008) framework

Social value, scientific validity, fair participant selection, favourable risk–benefit ratio, independent ethics review, informed consent and ongoing respect for participants are the eight principles identified by Emanuel et al. (2004,2008) as determinants of ethical research. Ideally, all eight principles should be considered and weighted equally. Table 1 below provides an overview of the actual results of the respective eight African studies discussed in the previous section and the weighting of the principles by the respective RECs. Overall, the eight principles of ethical research were reflected in the minutes of the eight African RECs, although the weighting and or prioritisation of the issues differed across RECs.

Table 1: Ethical issues raised by African RECs using Emanuel et al's. (2004, 2008) framework

	South Africa			Ghana		Zimbabwe	Malawi	Uganda
	Tsoka-Gwegweni & Wassenaar (2014)	Bengu (2018)	Silaigwana & Wassenaar (2019)	Selormey (2015)	Frimpong (2016)	Madanhire (2018)	Mtande (2018)	Kirimuhuzya (2020)
The Emanuel et al. (2004, 2008) principles	**Rank Order n=1040**	**Rank Order n=900**	**Rank Order n=1469**	**Rank Order n=232**	**Rank Order n=1177**	**Rank Order n=151**	**Rank Order n=1125**	**Rank Order n=1818**
Collaborative partnership	8th (n= 31)	8th (n= 10)	4th (n= 116)	8th (n= 0)	6th (n= 48)	3rd (n= 24)	4th (n= 59)	3rd (n= 118)
Social value	7th (n= 43)	7th (n= 72)	8th (n= 22)	6th (n= 2)	8th (n= 7)	7th (n= 5)	6th (n= 47)	8th (n= 19)
Scientific validity	2nd (n= 222)	2nd (n= 210)	3rd (n= 298)	3rd (n= 57)	1st (n= 618)	2nd (n= 31)	1st (n= 488)	1st (n= 1208)
Fair participant selection	3rd (n= 145)	4th (n= 141)	6th (n= 77)	4th (= 9)	7th (n= 33)	5th (n= 11)	8th (n= 37)	4rd (n= 87)
Favourable risk-benefit ratio	5th (n= 94)	5th (n= 37)	5th (n= 90)	5th (n= 6)	5th (n= 53)	4th (n= 20)	7th (n= 45)	7th (n= 25)
Independent ethics review	6th (n= 76)	6th (n= 11)	7th (n= 62)	2nd (n= 70)	4th (n= 71)	6th (n= 7)	3rd (n= 118)	5th (n= 83)
Informed consent	1st (n= 285)	1st (n= 305)	1st (n= 463)	1st (n= 79)	2nd (n= 248)	1st (n= 53)	2nd (n= 282)	2nd (n= 228)
Respect for participants	4th (n= 144)	3rd (n= 110)	2nd (n= 341)	4th (n= 9)	3rd (n= 99)	8th (n= 0)	5th (n= 49)	6th (n= 50)

Collaborative partnership: This principle was ranked as the third most frequently raised ethical query by a Zimbabwean and a Ugandan REC (Kirimuhuzya,2020; Madanhire, 2018), fourth ranked by a Malawian and South African REC (Mtande, 2018; Silaigwana & Wassenaar, 2019), sixth raised by a Ghanaian REC (Frimpong, 2016) and least raised at eighth position by two South African RECs (Bengu, 2018; Tsoka-Gwegweni & Wassenaar, 2014). One of the eight African RECs, only one REC in Uganda did not raise this principle at any point during their protocol review (Selormey, 2015).

Social value: This principle was raised as the sixth raised ethical query by two RECs (Mtande, 2018; Selormey, 2015), seventh raised ethical query by three RECs (Bengu, 2018; Madanhire, 2018; Tsoka-Gwegweni & Wassenaar ,2014) and the eighth and or least ethical quey by another three RECs (Frimpong, 2016; Kirimuhuzya ,2020; Silaigwana & Wassenaar, 2019).

Scientific validity: This principle was raised as the most frequently raised query by three RECs (Frimpong, 2016; Kirimuhuzya, 2020; Mtande, 2018), the second most frequently raised query by another 3 RECs (Bengu, 2018; Madanhire, 2018; Tsoka-Gwegweni & Wassenaar, 2014) and the third most frequently raised query by two RECs (Selormey, 2015; Silaigwana & Wassenaar, 2019).

Fair participant selection: This principle was raised as the third frequently raised query by one REC (Tsoka-Gwegweni & Wassenaar, 2014), fourth raised ethical query by three RECs (Bengu, 2018; Kirimuhuzya, 2020; Selormey, 2015), fifth raised by one REC (Madanhire, 2018), sixth raised (Silaigwana & Wassenaar, 2019) , seventh raised (Frimpong, 2016) and eighth raised (Mtande, 2018) ethical query by individual RECs, respectively.

Favourable risk-benefit ratio: This principle was raised as the fourth frequently raised query by one REC (Madanhire, 2018), fifth raised by five RECs (Bengu, 2018; Frimpong,2016; Selormey, 2015; Silaigwana & Wassenaar, 2019; Tsoka-Gwegweni & Wassenaar,2014) while emerging as the seventh raised query by the remaining two RECs (Kirimuhuzya, 2020; Mtande, 2018).

Independent ethics review: This principle was raised as the second most frequently raised query by one REC (Selormey,2015), while the additional RECs raised it as the third raised (Mtande,2018), fourth raised (Frimpong,2016), fifth raised (Kirimuhuzya, 2020), sixth raised by three RECs (Bengu,2018; Madanhire, 2018; Tsoka-Gwegweni & Wassenaar,2014) and seventh raised by remaining one REC (Silaigwana & Wassenaar, 2019).

Informed consent: This principle was raised as the most frequently raised query by five RECs (Bengu, 2018; Madanhire, 2018; Selormey, 2015; Tsoka-Gwegweni & Wassenaar,2014) and further raised as the second most frequently raised query by the remaining three RECs (Frimpong, 2016; Kirimuhuzya, 2020; Mtande, 2018). In all the studies, this principle emerged as either the most frequently raised query or the second most frequently raised queries across board.

Respect for participants*:* This principle came second in one REC (Silaigwana & Wassenaar, 2019), third in two RECs (Bengu,2018; Frimpong,2016), fourth in additional two RECs (Selormey, 2015; Tsoka-Gwegweni & Wassenaar,2014) as well as fifth raised (Mtande, 2018), sixth raised (Kirimuhuzya, 2020) and eighth raised (Madanhire, 2018) query.

When data from the eight studies were combined and analysed, scientific validity, informed consent and respect for persons were found to be the three most frequently raised principles by the African RECs in the eight studies. These results are shown on Table 2 below in a descending order. Overall, scientific validity (39%) was found to be the highest most frequently raised query accounting for 3132 of the 8264 combined queries raised. Informed consent (25%) followed as the second most frequently raised query accounting for 1947 of the 8264 queries raised. Respect for persons (10%) was found to be a distant third most frequently raised query accounting for 802 of the 8264 combined queries raised.

Table 2: Frequency of ethical concerns raised by African RECs 2008-2014 *(N=7912)* (Descending)

Emanuel et al. (2004,2008) principles	Number of queries(N)	Percentage of queries(%)	Rank of frequency
Scientific validity	3132	39%	Highest
Informed consent	1947	25%	
Respect for participants	802	10%	
Fair participant selection	540	7%	
Independent ethics review	498	6%	
Collaborative partnership	406	5%	
Favourable risk-benefit ratio	370	5%	
Social value	217	3%	Lowest

Fair participant selection, independent ethics review, collaborative partnership and favourable risk-benefit ratio ranked as the fourth, fifth, sixth and seventh least raised ethical queries at 7%, 6%, 5% and 5% respectively. The least most frequently raised query by the eight African RECs was social value (3%) accounting for only 217 of the combined 8264 queries. This ranking was also consistent across the respective individual RECs, wherein, social value consistently emerged as the least most frequently raised query.

2.10 Summary

This chapter provided an overview of developments that led to establishment and adoption of ethical guidelines and RECs to regulate human research thereby promoting research that is both ethically and scientifically sound. This is crucial as while society continues to harness the benefits of research, it unacceptable to do so at the expense of exploiting research participants and their communities. Emanuel et al. (2004, 2008) developed a framework of eight principles that can be used by RECs during protocol review and until recently, it could not be said whether this framework is compatible with the work of African RECs. A first known attempt to ascertain its relevance to African REC was conducted by Tsoka-Gwegweni & Wassenaar in 2014, later replicated by Silaigwana & Wassenaar (2019). The current study forms part of a collaborative effort by 2015 SARETI students who aimed to provide comparative data on ethical issues raised by African RECs in South Africa, Ghana, Zimbabwe, Malawi and Uganda using the Emanuel et al. (2004,2008) framework.

CHAPTER THREE: METHODOLOGY

3.1 Research design

Multiple types and definitions of research design exist. The definition adopted for the current study is from Durrheim (2006, p. 34) who defines research design as a "strategic framework for action that serves as a bridge between research questions and the execution or implementation of the research". The overall aim is to ensure that research activities are planned and guided to enable the researcher to draw sound conclusions (Durrheim, 2006). This planning, also referred to as systematic observation is what distinguishes research from everyday observation thereby making research results plausible and acceptable by the scientific community and society as opposed to when one merely observed the world and attempted to draw conclusions from their observation (Durrheim, 2006).

Creswell (2009) identifies three types of designs that researchers can use, namely quantitative, qualitative and mixed method research design. The current study employed a mixed method research design which involves an integration of both qualitative and quantitative designs (Creswell, 2009). Burke-Johnson, Onwuegbuzie and Turner (2007, p.123) define mixed methods research as a type of research in which a "researcher or team of researchers combines elements of qualitative and quantitative research approaches (e.g., use of qualitative and quantitative viewpoints, data collection, analysis, inference techniques) for the broad purposes of breadth and depth of understanding and corroboration". The mixing stage can occur at data collection stage, data analysis stage and or at all stages of the research (Burke-Johnson et al., 2007). Yin (2009, p. 204) argues that at a minimum, all mixed methods involve "integrating conclusions that are drawn from various strands in the research".

The present study set out to retrospectively analyse the content of 2015 2016 minutes of a selected REC in South Africa to identify main ethical concerns raised and assess their relative weight using Emanuel et al.'s (2004, 2008) framework. The process involved assigning codes derived from the Emanuel et al. (2004, 2008) framework to the REC minutes under study as well as recording the frequency of occurrence for each principle and or category. Morse and Niehaus (2009) note two points of integration which can occur, namely, the results point of integration and the analytical point of integration. On the analytical point of integration, researchers can use a theoretical framework to bind together the data sets (Creswell and Plano Clark, 2011). Schoonenboom and Burke-Johnson (2017) argue that it is this mixing and or integration that is a distinguishing feature of mixed methods research design. Schoonenboom and Burke-Johnson (2017, p. 116) define this point of integration as "any point in a study where two or more research components are mixed or connected in some way".

In keeping with a mixed method approach, qualitative and quantitative content analysis was used in this study to make provision for the qualitative aspect of assigning categories to text which is the REC minutes and the quantitative aspect

of analysing the frequencies of categories derived from the data. Smith (as cited in Zhang & Wildemuth, 2009, p. 2) argues "qualitative analysis deals with the forms and antecedent-consequent patterns of form, while quantitative analysis deals with duration and frequency of form".

Weber (as cited in Zhang & Wildemuth, 2009, p. 2) argues that "the best content-analytic studies use both qualitative and quantitative operations". Krippendorff (as cited in Elo & Kyngäs, 2008) lauded content analysis for being content-sensitive. Duncan (1989, p. 27) noted it as a "technique which lies at the cross-roads of qualitative and quantitative methods thereby allowing for one to quantify the frequency with which certain qualities appears in a sample of documents". Harwood and Garry (as cited in Elo & Kyngäs, 2008) lauded it for its flexibility and Prasad (2008) for how it offers researchers an unobtrusive way of researching sensitive and or confidential topics, which is why the researcher employed this method in this study.

Content analysis is defined by Holsti (as cited in Duncan,1989, p. 27) as the "application of scientific methods to documentary evidence". Cole (as cited in Elo & Kyngäs, 2008, p. 107) defined it as a "method of analysing written, verbal or visual communication messages". Krippendorff (2004 , p. 18) defined it as a research technique for making replicable and valid inferences from texts (or other meaningful matter) to the contexts of their use". A content analysis researcher thus studies the content of communication to decipher the meanings, context and or intentions contained in the said communication (Elo et al., 2014; Prasad, 2008).

3.2 Sampling and data collection

Representativeness with respect to the universe where the researcher will draw their sample and size with respect to the sample being large enough to allow the researcher to conduct reliable analysis are the two broad considerations for sampling in content analysis (Duncan, 1990). To achieve the first consideration i.e., representativeness, Beardsworth (as cited in Duncan,1990) argues that the researcher must define the said universe explicitly and choose their sample randomly. The researcher can employ an intellectual strategy through use of practical knowledge in the research area and or topic to define and or identifying the universe, thereby actively selecting the most appropriate sample that will be most productive considering the research questions (Duncan,1990).

On sample size, qualitative research often means dealing with large volume of documents which can prove difficult to analyse in their entirety. Elo and Kyngäs (2008, p. 113) argue, "regardless of the 'quality' of qualitative data, its sheer quantity can be daunting, if not overwhelming". To help work out sample size from the excessive body of content, judgment sampling can be used as well as determining a period to cover (Elo & Kyngäs, 2008; Prasad, 2008).

Purposive sampling, also referred to as judgment or relevance sampling was used in this study (Elo & Kyngäs, 2008; Marshall, 1996). Elo et al. (2014, p. 4) argues "purposive sampling is suitable for qualitative studies where the researcher is interested in informants who have the best knowledge concerning the research topic". Purposive sampling was thus employed to select the REC under study.

The section below outlines the process followed:

- A South African REC was identified, UKZN postgraduate approval and relevant gatekeeper permissions were sought, and permissions received (letters withheld to uphold confidentiality).
- UKZN Biomedical Research Ethics Committee approval (BCA 342/16) was obtained in 2017 (See appendix A).
- Confidentiality agreement was signed, and minutes of the REC were made accessible by the REC administrator electronically.
- The inclusion criteria specify only minutes recorded for all newly submitted protocols.
- The sample size for the research was unlimited and depended on the workload of the REC under study within the stipulated time frame (2015 - 2016).
- The REC met 11 times a year from February to December of each year. As a result, a total of 22 sets of minutes with 11 from each year were made available for review which came to a total of 55 newly submitted protocols, 24 reviewed in 2015 and 31 reviewed in 2016.
- To ensure that all the REC minutes had an equal chance of being included for the analysis, systematic sampling was used to select every second set of minutes in each year which yielded 5 sets of minutes per year. Therefore, a sample of 10 sets of minutes were evaluated and coded using the eight principles and benchmarks of the Emanuel et al. (2004, 2008) framework.

The researcher adopted the working definition of sampling by Durrheim (2006, p. 49) for this study which is the "selection of research participants from an entire population, and involving decisions about which people, settings, events, behaviours, and or social processes to observe".

3.3 Data analysis

A “directed”, “deductive” qualitative content analysis was used to analyse the data and or the review meeting minutes gathered from the REC under study. This method is useful in cases where previous research findings, theories, or conceptual frameworks regarding the phenomenon of interest already exist, as well as instances where the researcher seeks to test previous theory and or compare categories in a different situation or different period (Elo & Kyngäs, 2008; Hsieh & Shannon, 2005). Hsieh and Shannon (2005, p. 1278) define qualitative content analysis as ‘‘a research method for the subjective interpretation of the content of text data through the systematic classification process of coding and identifying themes or patterns”. To classify the body of text, categories are developed. Berelson (as cited in Prasad 2008, p. 12) argues that this is because “content analysis stands or falls by its categories”. Zhang and Wildemuth (2009) identified three sources from which coding categories can derive and or be developed from and these are research data, previous related studies, or theories. If the source was existing data, they are said to have been developed inductively and if the source was previous studies or theories, they are said to be developed deductively (Zhang & Wildemuth, 2009).

The choice of this method is because the current study intends to build or provide comparative data to the primary study conducted by Tsoka-Gwegweni and Wassenaar (2014) which was a first attempt at evaluating ethical queries raised by a REC using principles and benchmarks proposed by Emanuel et al. (2008). The current study adopted the simplified categories from Tsoka-Gwegweni and Wassenaar (2014) study which were developed using the Emanuel et al. (2008) framework, (See table 1 below). This research further forms part of an international collaboration involving the 2013 and 2015 South African Research Ethics Initiative (SARETI) Master’s degree students from the University of KwaZulu-Natal, South Africa. The partner countries include South Africa, Ghana, Malawi, Nigeria, Zimbabwe, Uganda, and Cameroon. The series of the studies including the current study, investigate whether demographic location and culture affect decision-making process of RECs. The categories applied are presented in Table 3 below.

Table 3: Coding framework

	Principles	Categories utilised
1.	Collaborative partnership	Community representation
		Responsibility sharing
		Respect for local context
		Fair research benefits for community
		Sharing of products
2.	Social value	Research beneficiaries
		Research benefits
		Enhancing research benefits
		Impact on health system
3.	Scientific validity	Appropriate design and methods
		Applicability of results
		Impact on provision of healthcare services
		Study design feasibility
4.	Fair participant selection	Suitable study population
		Risk minimisation
		Benefits to study participants
		Vulnerability
5.	Favourable risk-benefit ratio	Risk identification and minimisation
		Type, probability and magnitude of benefits
		Comparison of risks and benefits
6.	Independent review	Regulatory compliance
		REC members' conflict of interest
		Transparent review
		Minimisation and reconciliation of multiple reviews
7.	Informed consent	Recruitment and incentive applicability to local context
		Appropriate disclosure documents and processes
		Presentation and accuracy of information
		Legally authorised representative
		Gatekeeper's permission
		Context of consent processes
		Respect for autonomy
8.	Respect for participants	Monitoring health and well-being
		Confidentiality and privacy
		Voluntariness
		Research results dissemination
		Post-research obligations

For internal validity, Weber (as cited in Elo & Kyngäs, 2008) notes that one can use agreement coefficients between co-researchers to help settle disagreements resulting from alternative and or different interpretations. Graneheim and Lundman (as cited in Elo & Kyngäs, 2008) argues for the value of dialogue. To this end, the researcher shared a sample of coded REC minutes with a fellow researcher from South Africa to check for consistency in application of the categories and to ensure reliability. Deferring in opinions were settled through discussion and or dialogue.

3.4 Validity, reliability and rigour

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

For both practical and logistical reasons, it will not be possible for the researcher to incorporate all 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' – the inclination of some researchers to convince both themselves and their readers that the findings of their study are genuine results, based on a critical unbiased analysis of the data collected and not based on a few 'well-chosen examples' – as a potential threat to the overall validity of the study.

Other threats to both the internal and external validity of this present study were identified by the researcher during the design process. The researcher acknowledges Cook and Campbell's (1979) taxonomy of threats to validity and recognises that a) because the research was a desk review, carried out on specific documents kept for specific purposes with 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) and b), that because the sample population was primarily selected using purposive methods, the element of randomness is not present in the selection process. This may, therefore, impact upon the internal validity of the study's results.

3.5 Ethical considerations in conducting this research using Emanuel et al. (2004, 2008) framework

Collaborative partnership: The current study is part of a collaborative project involving other African countries whose results will be pooled to identify the type of ethical issues that African RECs raise when reviewing research protocols.

Social Value: While this project was conducted in partial fulfilment of the requirements for obtaining a degree, it provided experience and training in scientific methods for a young researcher which is part of the social value of this research. Further, the study may provide comparative data to previous research in view of the compatibility of Emanuel et al. (2004, 2008) framework in African settings.

Scientific validity: The current study sought to replicate a primary study conducted by Tsoka-Gwegweni and Wassenaar (2014) and later replicated by Silaigwana and Wassenaar (2019). As such, the research design for the study is scientifically sound and has already undergone peer review and has been published. Further, as part of a collaborative project involving other African collaborators, standard methodology was used across all studies to replicate the primary studies.

Fair subject selection: No human participants were involved in the study as it pertained to review of minutes of REC meetings. Systematic sampling was used to select every second set of minutes in each year.

Independent review: The current study was independently reviewed and approved by the University of KwaZulu-Natal's Biomedical Research Committee (UKZN BREC, approval number BCA342/16).

Informed consent: Gatekeeper approvals from institution and the REC under investigation were sought and granted.

Favourable risk-benefit ratio: The study is minimal risk, with no human participants although it involved accessing confidential information. To this end, a confidentiality agreement was signed with the REC and the identity of the REC as well as identifiers in the data set have been anonymised.

Respect for participants and study communities: The reporting of the results is anonymous thereby ensuring the confidentiality of the REC under study. Additionally, the minutes were stored safely in a password protected computer at home and a password was utilised to access the computer used to analyse data. The research results will further be shared with the REC under study.

CHAPTER 4: RESULTS

4.1 Introduction

The current study set out to answer the following six questions:

(i) What ethical concerns does the REC under study raise when reviewing protocols?

(ii) Does the REC under study systematically prioritize some ethical issues over others?

(iii) Is there an observable pattern to the ethical concerns raised by committee members? If so, what is the pattern?

(iv) Are the concerns raised consistent with the framework developed by Emanuel et al. (2004, 2008)?

(v) Does any feature of the Emanuel et al. (2004, 2008) framework dominate the concerns? If so, which one?

(vi) Are there other concerns raised by the REC which are not consistent with the framework discussed by Emanuel et al. (2004, 2008)?

Below follows a presentation of the results addressing the above questions.

4.2 Concerns raised by REC in view of the Emanuel et al. (2004; 2008) framework

The REC under investigation held 11 meetings annually from February to December in each year of the two-year period (2015 - 2016) under study. A total of 22 sets of minutes derived from 55 protocols were made available for review. Twenty-four of which were reviewed in 2015 and thirty-one reviewed in 2016. Systematic sampling was used to select every second set of minutes in each year which yielded 5 sets of minutes per year. Therefore, a sample of 10 sets of minutes were sampled and analysed for the study. Only newly submitted protocols were examined in the study (i.e., no recertifications or amendments were included). The studies selected were those that were more than minimal risk and thus not eligible for expedited review according to the Department of Health, Republic of South Africa, *Ethics in Health Research* (2015).

Figure 1: Concerns raised by REC in 2015 - 2016 (*n*=813)

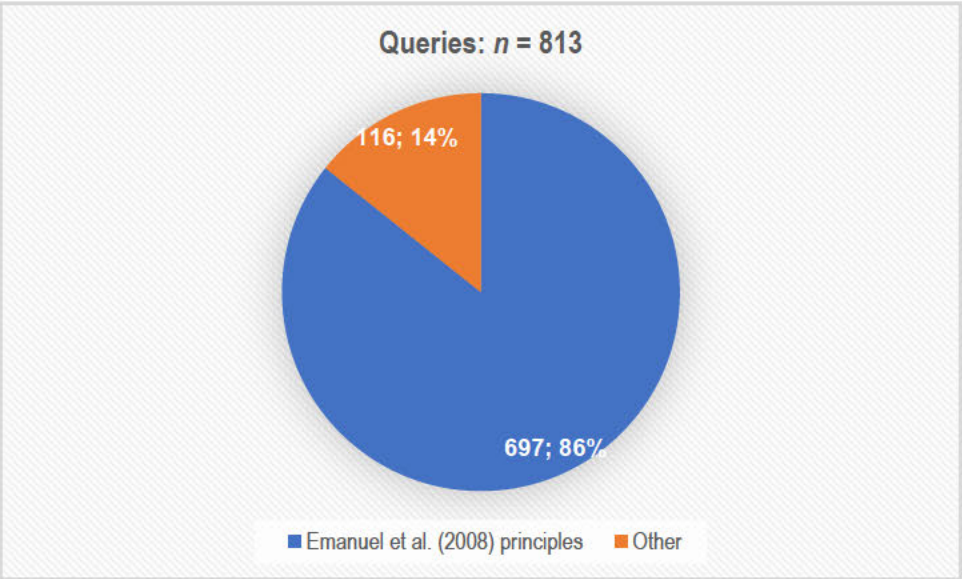


Figure 1 above shows that a total of 813 concerns were raised by the REC under study, with 86% (697) of the 813 concerns raised dealing with issues which were found to be accommodated by/compatible with the Emanuel et al. (2004, 2008) framework. The remaining 14% (116) of queries could not be accommodated by the framework and were coded under the category of "Other".

Table 4 below illustrates how each principle ranked in a descending order of frequency.

Table 4. Rank order of queries (Descending)

Principles	No of Queries	Percentage
Scientific Validity	262	32%
Informed Consent	233	29%
Other	116	14%
Respect for participants	77	10%
Independent Review	60	7%
Fair Participant Selection	31	4%
Favourable Risk-Benefit Ratio	16	2%
Collaborative Partnership	15	2%
Social Value	3	0%
Total	813	100%

Figures 2 and 3 below illustrate the distribution of the frequency of ethical concerns (number and percentages)

Figure 2. Distribution of all ethical concerns raised (number).

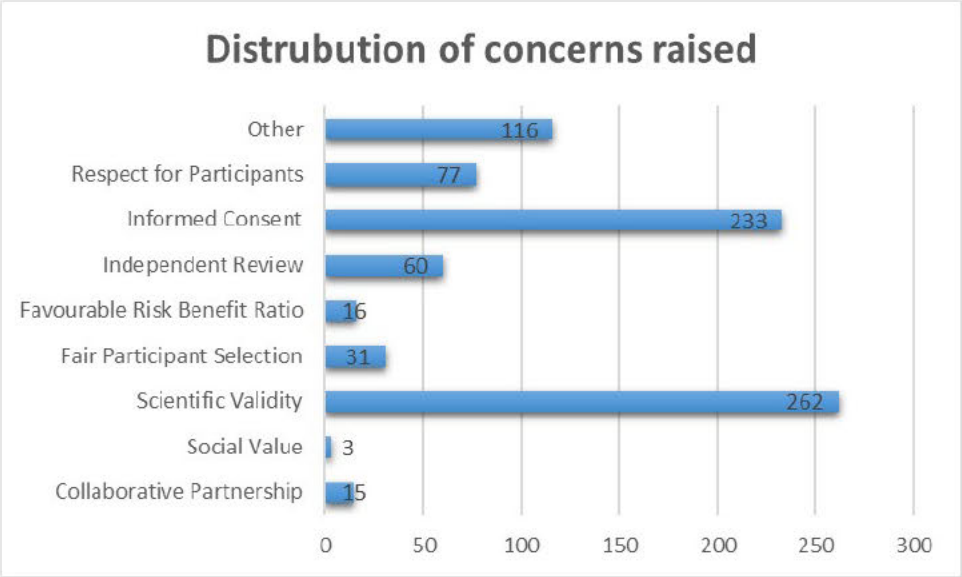
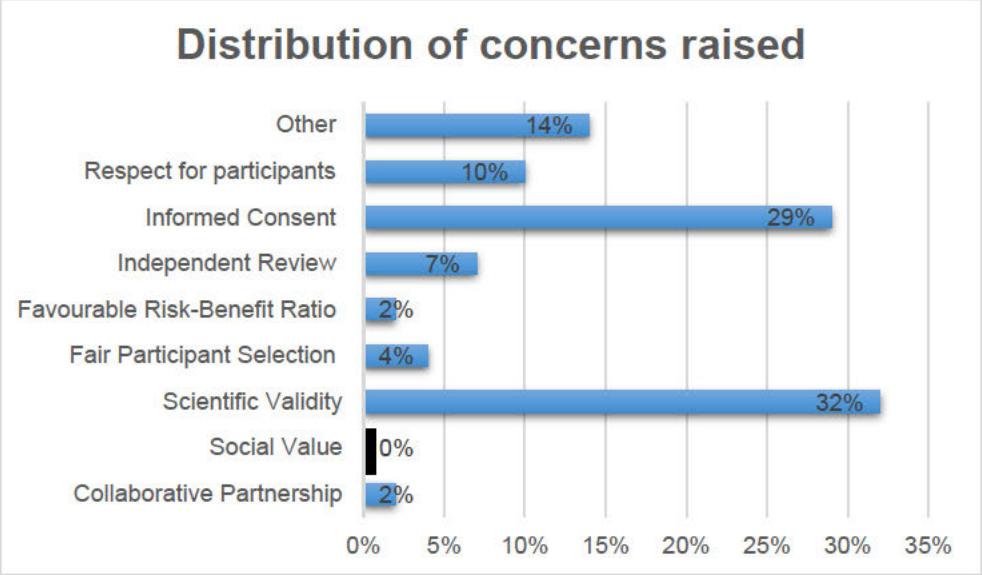


Figure 3. Distribution of all ethical concerns raised (percentages).



4.3 Systematic prioritisation of some ethical issues over others

Of the 55 protocols assessed, 262 of the 813 queries raised pertained to scientific validity (38%), 233 informed consent (33%), 77 respect for participant (11%), 60 Independent review (9%), 31 fair participant selection (5%), 16 favourable risk-benefit ratio (2%), 15 collaborative partnership (2%) and 3 social value (0%). As such, a closer analysis of the minute's shows prioritisation of four ethical issues over others as can be seen in below figures (Figure 4 and Figure 5), respectively. Further, a closer look shows prioritisation of certain benchmarks within each ethical principle.

Figure 4: Ethical queries raised by REC under study 2015 – 2016 (*n*=697)

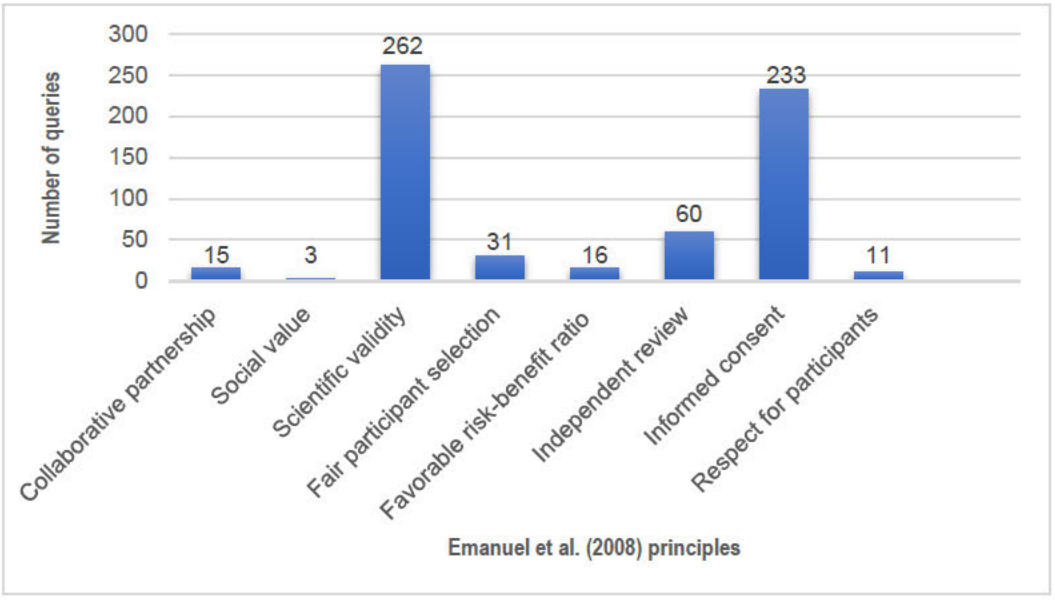
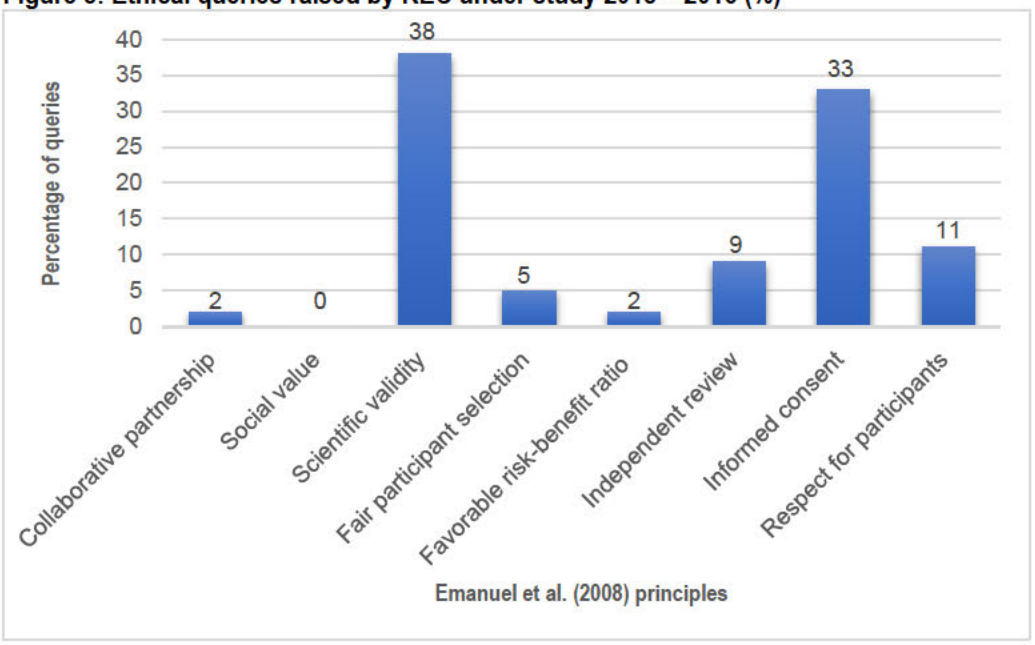


Figure 5: Ethical queries raised by REC under study 2015 – 2016 (%)



4.3.1 Principle 1: Collaborative partnership

There are five categories that underpin the principle of collaborative partnership. These are community representatives, responsibility sharing, respect for local context, fair research benefits for community, and sharing research products. Of the 813 queries raised within 55 protocols, 15 (2%) queries were identified as pertaining to collaborative partnership.

In terms of the frequency of concerns raised per coding category under this principle, responsibility sharing (53%) was identified as the most frequently raised query, followed by community representatives (40%) and fair sharing of responsibility (7%). There were no concerns raised relating to respect for local content and sharing of products. Overall, this principle emerged as the second least raised query by the REC in this study and ranked seventh out of the eight principles.

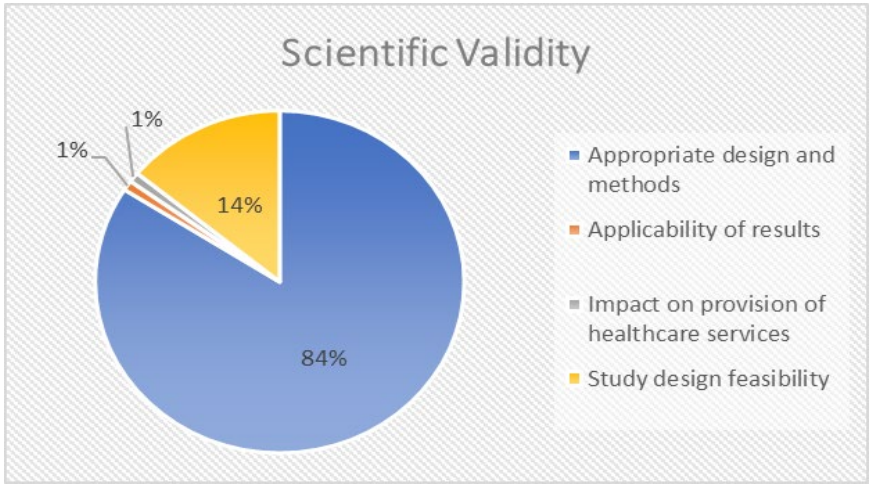
4.3.2 Principle 2: Social value

Four categories underpin the principle of social value namely research beneficiaries, research benefits, enhancing research benefits and impact on health systems. Of the 813 queries raised within 55 protocols, 3 (0.4%) queries raised pertained to social value. In terms of the frequency of concerns raised per coding category under this principle, research benefits (67%) was identified as the most frequently raised query followed by research beneficiaries (33%). No queries relating to enhancing research benefits and impact on health system were raised. Overall, this principle emerged as the least raised query by the REC in this study and ranked eighth out of the eight principles.

4.3.3 Principle 3: Scientific validity

Four categories underpin the principle of scientific validity namely appropriate design and methods, applicability of results, impact on provision of healthcare services and study design feasibility. Of the 813 queries raised within 55 protocols, 262 (38%) were identified as pertaining to scientific validity.

Figure 6: Frequency of scientific validity concerns raised by the REC under study



As illustrated in figure 6 above, appropriate design and methods (84%) emerged as the most frequently raised issue, while study design (14%) was second most frequently raised query. Applicability of results (1%) and impact on provision of healthcare services (1%) were the least raised queries.

Overall, this principle was the highest and most frequently raised query by the REC in this study and ranked first out of the eight principles of the Emanuel et al. framework (2004, 2008). Below follows an example of the qualitative description of the type of ethical issues raised under this principle as captured in the REC minutes to situate the findings and or support the results.

> *"The three column Likert scale is not good – there is no place for this scale in this study". (REC minutes)*
>
> *"Please provide information on statistical planning and data analysis". (REC minutes)*
>
> *"The Secondary aim "To determine HIV biochemical and clinical feature correlation to bronchoalveolar lavage (BAL) fluid findings in HIV-infected sub-groups" is not clear and needs to be explained. The last 2 aims are not in the study design and will need to be included if the investigators are testing for this". (REC minutes)*

4.3.4 Principle 4: Fair participant selection

Four categories underpin the principle of fair participant selection namely suitable study population, risk minimisation, benefits to study participants and vulnerability. Of the 813 queries raised within 55 protocols, 31 (4%) queries raised pertained to fair participant selection. Suitable study population (84%) was the most frequently raised issue of concern followed by risk minimisation (7%), benefits to participants (6%) and vulnerability (3%). Overall, this principle was the fourth least raised query by the REC in this study and ranked fifth out of the eight principles.

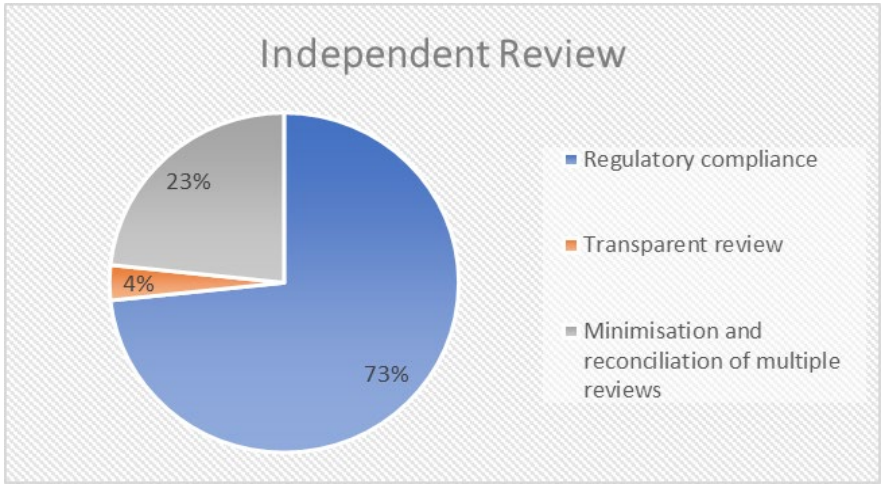
4.3.5 Principle 5: Favourable risk-benefit ratio

Three categories underpin the principle of favourable risk-benefit ratio namely risk identification and minimisation, type, probability and magnitude of harm and comparison of risks and benefits. Of the 813 queries raised within 55 protocols, 16(2%) queries raised pertained to favourable risk-benefit ratio. Risk identification and minimisation (87%) was the most frequently raised category followed by comparison of risks and benefits (13%). No queries relating to type, probability and magnitude of harm were raised. Overall, this principle was the third least raised query by the REC in this study and ranked sixth out of the eight principles.

4.3.6 Principle 6: Independent review

Four categories underpin the principle of independent review namely regulatory compliance, REC member's conflict of interest, transparent review and minimisation and reconciliation of multiple reviews. Of the 813 queries raised within 55 protocols, 60 (8%) queries were raised that pertained to independent review.

Figure 7: Frequency independent review concerns raised by the REC under study



As illustrated in figure 7 above, regulatory compliance (73%) was the most frequently raised whilst minimisation and reconciliation of multiple reviews (23%) was the second most frequently raised query with transparent review (4%) being the least raised query. No queries relating to REC member's conflict of interest were raised.

Overall, this principle was the fourth most frequently raised by REC in this study and ranked fourth out of the eight principles. Some examples are provided below of the qualitative description of the type of ethical issues raised under this principle (as captured in the REC minutes) to situate the findings and or support the results.

> *Pg. 45 of the Site Manual (Version 10.0) states that data will be stored for 10 years – please note SA regulations for Clinical Trials require 15 years data storage". (REC minutes)*

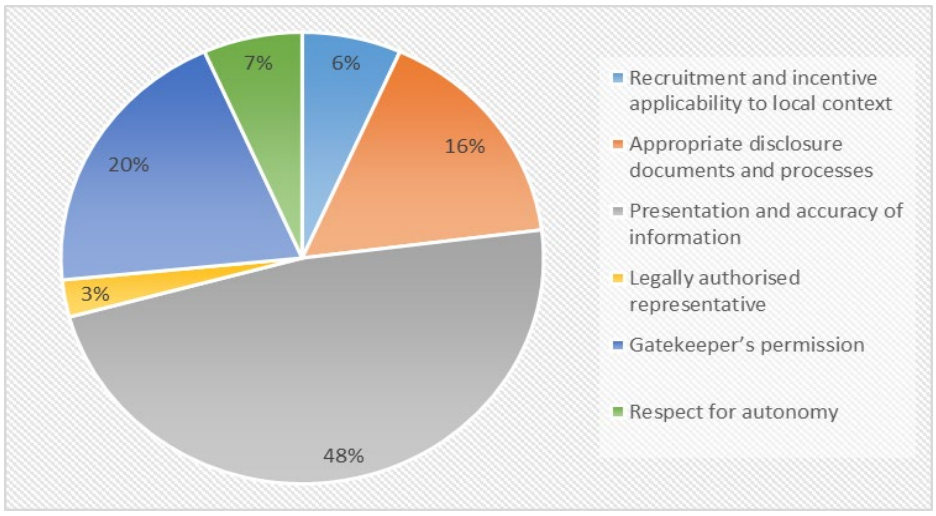
> *"Please provide MCC approval and SANTCR registration proof". (REC minutes)*

> *"An export permit and International Aviation Clearance Certificates and a Materials Transfer Agreement are required for the export of blood samples". (REC minutes)*

4.3.7 Principle 7: Informed consent

Seven categories underpin the principle of informed consent. These are recruitment and incentive applicability to local context, appropriate disclosure documents and processes, presentation and accuracy of information, legally authorised representative, gatekeeper's permission, context of consent processes and respect for autonomy. Of the 813 queries raised within 55 protocols, 233 (33%) queries raised pertained to informed consent.

Figure 8: Frequency of informed consent concerns raised by the REC under study



As illustrated in figure 8 above, presentation and accuracy of information (48%) was the most frequently raised query. The second most frequently raised query was gatekeeper's permission (20%), followed by appropriate disclosure documents and processes (16%), respect for autonomy (7%), recruitment and incentive applicability to local context (6%) and least query raised was relating to legally authorised representative (3%). No queries relating to context of consent process were raised.

Overall, this principle was the second most frequently raised query of the framework raised by REC in this study and ranked second out of the eight principles. Some examples follow below of the qualitative description of the type of ethical issues raised under this principle as captured in the REC minutes to situate the findings and or support the results.

> *"The Consent form does not mention that this is a control study and some people will be in the control arm". (REC minutes)*

> *"There is no clear indication in the informed consent form that children in group 1 must be HIV negative although language in the assent form is clear in this respect. It erroneously provides an impression that all children eligible for participation must be HIV negative and may cause unwarranted stress to parents of children in group 1 who may misinterpret this as meaning that their uninfected child is HIV positive". (REC minutes)*

> *"Informed Consent document is very long, although the reviewer agrees that much of the content is very relevant. A short format is recommended for participants". (REC minutes)*

4.3.8 Principle 8: Respect for recruited participants

Five categories underpin the principle of respect for recruited participants namely monitoring health and well-being, confidentiality and privacy, voluntariness, research results dissemination and post-research obligations. Of the 813 queries raised within 55 protocols, 77 (9%) queries that were raised pertained to respect for recruited participants.

Figure 9: Frequency of respect for recruited participants concerns raised by the REC under study

Monitoring health and well-being (61%) was the most frequently raised query followed by post-research obligations (16%) with confidentiality and privacy (15%) following closely behind. The least frequently raised query was research results dissemination (8%). No queries relating to voluntariness were raised.

Overall, this principle was the third most frequently raised by REC in this study and ranked third out of the eight principles. Below follow some examples of the qualitative description of the type of ethical issues raised under this principle as captured in the REC minutes to situate the findings and or support the results.

> *"What specific counselling will be given to women who seroconvert with regard to ARV or PMTCT prophylaxis?" (REC minutes)*

> *"How will the PI deal with a possible adverse event eg injury as a result of participation in the study?" (REC minutes)*

> *"How will the PI deal with any possible adverse event?" (REC minutes)*

4.4 Concerns raised not compatible with the Emanuel et al. (2004, 2008) framework

There were 14% (116) issues identified by REC during protocol review which could not be coded using the Emanuel et al. (2008) framework and as such, were coded under the category of "Other". These issues pertained to funding/budget, CV's, application slip-ups (missing/incomplete information), REC review fees and grammatical/typo errors.

CHAPTER FIVE: DISCUSSION

5.1 Systematic prioritisation and most frequent ethical issues considered by the REC as identified by the Emanuel et al. (2004, 2008) framework

To assist researchers, RECs and sponsors involved with conduct and or review of research in developing countries such as South Africa, Emanuel et al.'s (2004, 2008) delineated a framework of eight principles which characterise ethical research. This framework is geared towards mitigating various factors such as poverty, limited health-care services including weak infrastructure which enables and or heightens opportunities for exploitation of prospective individual participants and host communities (Emanuel et al., 2008). They assert that ethical research should have collaborative partnership, social value, scientific validity, fair selection of participants, favourable risk-benefit ratio, informed consent, independent review, and demonstrate on-going respect for participants and study communities. Using this framework to assess the minutes of a selected REC, the present study found that 86% of the queries and or concerns raised by the REC under study could be accommodated by the framework. Further, that four of the eight ethical principles dominated the review process of the REC meeting between 2015 – 2016.

The results of this study are comparable with the results of the previous studies which also found the Emanuel et al. framework to be applicable to the protocol review minutes of several African RECs.

While the current study found that 86% of the queries were compatible with the framework, four of the eight studies reported even more favourable results with Tsoka-Gwegweni and Wassenaar (2014) reporting the highest applicability of the framework in all the studies having found the framework accommodated 99,7% of the queries in their review. The second highest level of compatibility was reported by Bengu (2018) at 98% followed by Frimpong (2016) as the third highest at 97,7% and Kirimuhuzya (2020) as the fourth highest at 90,5%. Mtande (2018) report a compatibility of 88,8% thereby becoming the fifth highest followed by the current study which report compatibility of 86% in the sixth place. Silaigwana and Wassenaar (2019) reported compatibility of 83% occupying the seventh position. Selormey (2015) reported compatibility of 80% at eighth place. Only one study reported compatibility of less than 70% at 65% out of the nine studies including the current study (Madanhire, 2018).

The frequency of the categories raised by the current REC are also discussed in descending order below.

Principle 3 (scientific validity) accounted for 38% of these queries and ranked as the most frequently raised ethical query followed by Principle 7 (informed consent) which ranked second at 33%. The third ranked concern was Principle 8 (respect for participants) at a distant 11 % whilst Principle 6 (independent review) accounted for 9% of the queries and ranked as the fourth most frequently raised ethical query.

When the results of the current study are compared with the overall results of the combined eight studies, scientific validity was found to be the most frequently raised query, informed consent the second most frequently raised and respect for participants the third most frequently raised queries. The weighting of the fourth most frequently raised query differs as shown in Table 6 above with the current study having found independent review to be the fourth whilst the results of the eight studies identified fair participant selection as the fourth most frequently raised query.

The four least raised queries by the REC for the current study were found to be Principle 4 (fair participant selection), Principle 5 (risk-benefit ratio), Principle1 (collaborative partnership) and Principle 2 (social value) accounting for only 5%, 2%, 2% and 0% respectively. Similarly, when the combined results of the eight studies were examined, four principles emerged as the least raised queries namely, Independent review at 6%, collaborative partnership and favourable risk benefit ratio both at 5 % with social value being the least raised query at 3%. The consistently low ranking of the principle of social value reported across all the studies conducted can possibly be attributed to the fact that, the inherent value of human research lies in its anticipated social value without which, there could be no ethical justification for conducting scientific research. Therefore, on this basis, it can then be argued that all protocols assessed had satisfactorily addressed this principle as it seems unlikely, intuitively, that the REC would overlook this principle. This could be tested in future research.

Whereas the current study ranked fair participant selection as the fourth least raised ethical query, the combined results of the eight studies ranked independent review as the fourth least raised query and fair participant selection as the fourth most frequently raised query. Collaborative partnership and favourable risk-benefit ratio ranked as the third and second least raised query by the eight studies. Similarly, the current study ranked favourable risk-benefit ratio and collaborative partnership as the third least and second least raised query respectively. Both the results of the eight studies and the current study found social value to be the least raised ethical query by all the RECs.

As can be seen above, although the order of priority and frequency differs in some respect, these findings are nevertheless largely comparable to these eight other studies which used the same analytical and or theoretical framework to assess and or evaluate ethical issues raised by several African RECs in South Africa (Bengu, 2018; Silaigwana & Wassenaar, 2019; Tsoka-Gwegweni & Wassenaar, 2014), Ghana (Frimpong, 2016; Selormey, 2015), Zimbabwe (Madanhire, 2018), Malawi (Mtande, 2018) and Uganda (Kirimuhuzya, 2020).

Overall, scientific validity was found to be the highest and most frequently raised query by the REC in this study and ranked first out of the eight principles. One of the benchmarks or standards used to judge the scientific validity of a proposed research is use of reliable, valid research designs and data collection methods which are to be considered in relation to research objectives (Emanuel et al., 2004; Tsoka-Gwegweni & Wassenaar, 2014).

This is because flawed research and or bad science is not only unethical as it exposes research participants to harm, leads to wastage of scare resources and can compromise public trust, it further undermines the very foundation or value that scientific research is contingent upon which is effective design and execution (NASEM, 2019).

This is in keeping with appropriate design and methods benchmark which accounted for 84% of issues raised under the scientific validity principle, thereby making this benchmark the most frequently raised issue under principle 3. Frimpong (2016) observed similar results in a Ghanaian REC whereby scientific validity was found to be the dominant and frequently raised principle occupying 51.3% of queries raised of which 92.4% were classified under appropriate design and methods in 153 protocols assessed between 2012 to 2013. Similarly, Mtande (2018) reported scientific validity as having occupied 38.3% of queries raised by a Malawian REC assessment in 136 protocols submitted between 2013 – 2014 of which, 64.3% issues pertained to appropriate methods and design. Kirimuhuzya (2020) reports scientific validity at 54.1% in 110 of protocols in a Ugandan REC meeting minutes between 2012-2013. This principle was further ranked second in two South African RECs as observed in the primary study by Tsoka-Gwegweni and Wassenaar (2014) as well as Bengu (2018) and one Ghanaian REC (Selormey, 2015) with appropriate design and methods benchmark also observed to be the most frequently raised issue under this principle. Overall, the results showed that scientific validity is a critical aspect of protocol review and pre-occupation with this ethical principle is supported by various ethical guidelines. To this end, researchers are to ensure that they employ scientific methods which follow generally acceptable standards (Emanuel et al., 2008).

The principle of informed consent was found overall to be the second most frequently raised query by REC in this study and ranked second out of the eight principles. Of the 33% of issues raised under the principle of Informed Consent, 48% of these issues pertained to presentation and accuracy of information intended for participants.

The results are comparable to three similar studies or to the work of three RECs where informed consent was identified as the second most dominant principle considered by the RECs as reported by Frimpong (2016) in Ghana, Mtande (2018) in Malawi and Kirimuhuyza (2020) in Uganda. In Frimpong's (2016) study, appropriate disclosure accounted for 53.6%; in Mtande's (2018) study, presentation and accuracy of information benchmark accounted for 41%, in Kirimuhuyza's (2020) study, the context of the consent process accounted for 26.32%. Additionally, this principle was identified as the most frequently raised ethical query in the primary study by Tsoka-Gwegweni and Wassenaar (2014), as well as other subsequent studies by Bengu (2018), Selormey (2015), Madanhire (2018) and Silaigwana and Wassenaar (2019). Although the order of priority and frequency of raised benchmarks differs, the results are nevertheless comparable.

Grady (2015, p. 855) notes that "informed consent, in principle, is authorization of an activity based on an understanding of what that activity entails and in the absence of control by others". Given that the intention is to provide assurance that

prospective participants were neither deceived nor coerced into study participation, it therefore requires that the study related information presented to participants be complete, accurate and clear (Emanuel et al., 2008).

As efforts are made to satisfy the legal, ethical, and regulatory requirements, it is argued that the informed consent document is reportedly increasing in length and in complexity, factors which make it less likely or difficult to be read and understood (Grady, 2015). O'Neill (2003, p. 5) argues, "the inclusion of excessive or technical detail will eventually overtax even the most energetic, and undermine the possibility of informed consent, on the other hand, consent that is too vague and general may also fail to legitimate action". In view of this, researchers are thus urged to avoid using jargon for example or unexplained technical and or acronyms and lengthy informed consent documents or information sheets (O'Neill, 2003).

This is crucial because ultimately, research participants make study related choices based on the information presented and or provided to them. If the information provided is too complex, it is less likely to be understood whilst on the other hand, if the informed consent document is too long, participants are more likely to be overwhelmed and lose focus (Lentz, Kennett, Perlmutter, & Forrest, 2016; O'Neill, 2003). Although it may be difficult to achieve the theoretical ideal, researchers ought to balance providing complete and relevant study related information to prospective participants whilst at the same time ensuring that the informed consent documents provided are not too long and complex (Lentz et al., 2016; O'Neill, 2003). Of the proposition provided to strike this balance, there is a consensus that, researchers can adopt a "tiered" approach when developing their informed consent documents (Lentz et al., 2016).

Respect for participants was the third most frequently raised query in this study, with the monitoring health and wellbeing of participants benchmark accounting for 61% of issues raised under this principle. The REC minutes showed that reviewers required and or looked for evidence on the measures that researchers had specified to provide care to participants.

This highlights researcher's obligations which extend beyond obtaining informed consent in that even though participants have consented to the risk in the form of possible adverse events, it does not absolve researchers from putting measures in place to ensure both the known and unknown harms that could results from participation are still minimized and or prevented.

Selormey (2015) observed similar results in her examination of a Ghanaian REC minutes, although research results dissemination benchmark occupied 44.44% of issues raised under this principle. In Silaigwana and Wassenaar (2019) study examining two South African RECs, this principle was observed as the second most frequently raised issue at 19% with majority of queries pertaining to post-research obligations, in particular post-trial access.

This principle was further ranked as the fourth raised concern in an examination of another South African REC by Bengu (2018), with confidentiality and privacy of research participants occupying 40.4% of the queries. These findings prove

that showing respect to participants' autonomy by obtaining an informed consent is not nearly enough. Since no researcher can recruit and or enrol participant's without REC approval and that stamp of approval assures both participants and the public that the wellbeing and rights of participants are safeguarded, it then stands to reason that RECs will show concern and will seek to see to it that participants are adequately protected during and after the trial. A commitment to protecting their rights and wellbeing does not end at enrolment and researchers ought to ensure feature plans for safety monitoring amongst others in the design of their protocols. Participants' safety and needs always come before the value of science.

Independent review was the fourth ranked ethical query raised by REC in this study with regulatory compliance benchmark being the most frequently raised concern at 73%. The results are comparable to a Ghanaian REC wherein it also emerged as the fourth raised principle and accounted for 5.9% queries that were raised by the REC with regulatory compliance benchmark occupying 57.7% of the queries (Frimpong, 2016). Similarly, Mtande (2018) recorded it as the third raised principle in an examination of a Malawian REC attracting 9.3% of the queries with compliance issues accounting for 93%. Although the order of priority differs from the findings of the primary study by Tsoka-Gwegweni and Wassenaar (2019) wherein it was recorded as the sixth raised query, it is interesting that regulatory compliance was also the highest raised benchmark accounting for 41.8% as in this study.

To this effect, Tsoka-Gwegweni and Wassenaar (2015, p. 39) reports that these issues were "in relation to the regulatory and related to the requirements of the Medicines Control Council (Regulator in South Africa), the South African Clinical Trials Registry, Data Safety Monitoring Boards, tissue export permits, and Materials Transfer Agreements (MTA)". As can also be seen with the below excerpts, REC required evidence of compliance with laws and regulations governing human research in South Africa. For example, the requirement for Data and Safety Monitoring Boards, registration with the Medicines Control Council now called South African Health Products Regulatory Authority as well as South African Clinical Trials Registry are stipulated in the South African Good Clinical Practice (2006) whilst the requirement for Material Transfer Agreements are prescribed by the National Department of Health guidelines on *Ethics in Health Research* (2015).

That the REC raised these queries is expected because beyond reviewing and or judging the ethical and scientific acceptability of proposed research, REC further evaluate proposed research to determine compliance with applicable national regulations and laws governing human research (Grady, 2015).

5.2 An observable pattern to the ethical concerns raised by the committee

In the two-year period (2015 - 2016), Principle 3 (scientific validity), Principle 7(informed consent), Principle 8 (respect for participants) and Principle 6 (independent review) were consistently the most frequently raised queries whilst Principle 4 (fair participant selection), Principle 5 (risk-benefit ratio), Principle1 (collaborative partnership) and Principle 2 (social value) were consistently the least raised principles by the REC accounting for only 5%, 2%, 2% and 0% respectively. While the results suggest a pattern to the types of queries that the REC raised, the difference in weight and or priorities when compared to the three South African studies by Tsoka-Gwegweni and Wassenaar (2014), Bengu (2018) and Silaigwana and Wassenaar (2019) suggest that it may not necessarily be the case. Lastly, it may be interesting to see the weighting of the principles of the same protocols where they to be reviewed by a different REC.

5.3 Concerns raised not compatible with the Emanuel et al. (2004; 2008) framework

There were 14% (116) issues identified by REC during protocol review which could not be coded using the Emanuel et al. (2008) framework and as such, were coded under the category of "Other". These issues pertained to funding/budget, CV's, application slip-ups (missing/incomplete information), REC review fees and grammatical/typo errors. The findings in this study support Wassenaar and Slack (2016) who noted the importance and value in reading small print as well as understanding the REC processes and forms to avoid frustrations and delays when submitting protocols. They encourage researchers to be proactive by for example, downloading research ethics policies and REC application forms of their respective RECs (Wassenaar & Slack, 2016). The results contradict assertions by Clapp, Gleason, and Joffe, 2017 in their argument that RECs focus on minor mistakes and or errors at the expense of substantive ethical issues. As previously noted, minor errors accounted for only 14% of quires raised in this study whilst the 86% of queries pertained to substantive ethical issues.

5.4 Limitations of the study

The study's limitations are like those already identified by the authors of the primary study (Tsoka-Gwegweni & Wassenaar, 2014). The sample of study is quite small which makes generalizing the results to RECs in South Africa difficult. Further, beyond providing a description of the concerns raised by this REC, any further interpretation of the results will be premature. Further, the REC minutes are a summary of the issues that needed further clarity from the researcher and do not necessarily convey the full discussions that take place during the meetings. As such, it is not assumed that the REC minutes are a true reflection of the review meetings nor that they reflect a full picture of the deliberations held during protocol review. Lastly, it is possible that there were errors in the coding process although the researcher was careful to ensure that she has familiarised herself with the framework and coding categories before she began with the coding process.

5.5 Conclusion

Of the eight principles of the Emanuel et al.'s (2004, 2008), scientific validity was found to be the most frequently raised query, informed consent the second most frequently raised query and respect for participants the third most frequently raised queries, with fair participant selection emerging as the fourth most frequently raised query by eight studies that examined minutes of African RECs. Similarly, the current study identified four frequently raised queries with scientific validity taking first place followed by informed consent in second place followed by respect for participants in the third place. Unlike the results of the other eight studies, the current study identified independent review as the fourth most frequently raised query versus fair participant selection which was identified as the fourth most frequently raised query in the eight studies. All the studies, including the current study identified social value as the least raised query by all the RECs under study and this was consistent across the various years and various RECs. This study has hopefully provided a description of the type of issues raised by a South African REC and the results largely support the findings of eight previous studies that employed the same research methodology in other settings. Together with the current study, the data suggest that the Emanuel et al. (2004; 2008) framework does appear to be compatible with the work of African RECs and appears to be a useful tool with which to categorise queries raised during protocol review in Africa and possibly other LMICs.

5.6 Recommendations for RECs and future research

The current study reported on findings derived from a retrospective analysis of one South African REC's minutes covering a two-year period. It formed part of an international collaborative study which is among the first attempts to describe the most frequent ethical issues raised by a wide spectrum of African RECs using the Emanuel et al. (2004, 2008) framework. It has, arguably, contributed to an evidence-based understanding of the ethical concerns raised by African RECs in the course of their work.

It is recommended that future research combine findings derived from this study as well as studies from the previously mentioned African countries and into a consolidated submission to a suitable peer-reviewed journal to allow access to wider audience and bring about academic debate which may generate further interest in this area of study. A combined analysis and a larger pool of comparative data may lead to two things:

- An African response on the Emanuel et al. (2004, 2008) framework's applicability to African RECs.
- A standardized approach to ethics review on the African continent informed by the results of the outcomes of larger pool of empirical data which may be published on REC review outcomes and review frameworks.

There are numerous stakeholders involved in research and a standardized approach to addressing ethical concerns in health research could be helpful in illuminating the types of ethical issues research stakeholders could proactively pay attention to from protocol development phase, thereby, potentially reducing the turn-around time for protocol review and approval.

It is not known whether the framework was used in reviewing applications by the committee under study and how this would have influenced the review process. A search on the REC's website and their standard operating procedures did not explicitly list nor make mention of the Emanuel et al. framework as reference material – although it is referenced in the National Department of Health guidelines on *Ethics in Health Research* (2015). This suggests that if it was used by the REC's reviewers, it was based on their particular training and familiarity with the framework and/or the current national research ethics guidance.

It is further recommended that the Emanuel et al. (2004, 2008) framework become a standard framework to be incorporated into research ethics training for both researchers and REC members as, despite not accommodating all the concerns raised by the REC under study, it still accommodated the vast majority of the REC's ethical queries. It thus appears to be a useful training and resource tool for conducting ethics review and possible further training of REC members.

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APPENDIX A : Copy of UKZN BREC ethics clearance letter

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Prof J Tsoka-Gwegweni
Chair
BREC
Research Office
UKZN

10th October 2017

BCA 342/16: Additional Masters student Ms Melda Magolela 2150820046

Dear Professor Tsoka-Gwegweni,

I trust this finds you well.

I am hereby applying to add a new student to my SARETI class-approval group project: *An evaluation of the ethical concerns of research ethics committees in selected African countries using the principles and benchmarks proposed by Emanuel et al. (2004, 2008).*

I am hoping that she can review a recent sample [redacted]

I would appreciate provisional approval of this student's application so that I can assist her further with site permission applications.

I will send postgraduate and site permissions letters once BREC provisional approval has been granted.

Your assistance is much appreciated.

Yours sincerely,

[redacted]

Prof D R Wassenaar
PI: SARETI

South African Research Ethics Training Initiative
SARETI
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NIH Fogarty International Center
Advancing Science for Global Health

Fogarty International Center, National Institutes of Health
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APPENDIX B: Data collection pro forma (data collection sheet)

REC Codename: _____

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

APPENDIX C : Copy of REC permission letter

(Withheld to preserve confidentiality; Copy available upon request for audit purposes)