EMPIRICAL INVESTIGATION OF ETHICAL ISSUES RAISED BY TWO RESEARCH ETHICS COMMITTEES REVIEWING BIOMEDICAL RESEARCH IN SOUTH AFRICA

By

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Thesis submitted in partial fulfilment of the requirements for the degree Doctor of Philosophy (PhD) in the School of Applied Human Sciences, College of Humanities, University of KwaZulu-Natal

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March 2017

DECLARATION

I, Blessing Silaigwana, declare that:

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2. This thesis has not been submitted for any degree or examination at any other university.

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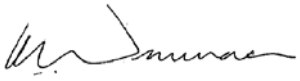

Signature

28th February 2017

DEDICATION

For my loving parents and siblings.

ACKNOWLEDGEMENTS

To God be the glory. I praise the Almighty God for blessing me with the strength to complete this long and tough journey towards a PhD degree.

I would like to thank my supervisor, Professor Wassenaar, for introducing me to the field of biomedical research ethics and the opportunity to pursue a PhD under his invaluable academic and scientific guidance. It was a challenging yet exciting journey in my career. I have benefited tremendously from his intellectual advice and personal support, especially during times of difficulty. I am also very grateful to him for reading through all the drafts of my thesis with great care and providing critical feedback and comments. This publication was partially supported by grant number: 5R24TW008863 from the President's Emergency Plan for AIDS Relief (PEPFAR), and the National Institutes of Health, U. S. Department of Health and Human Services through the UKZN MEPI award. Its contents are solely the responsibility of the author and do not necessarily represent the official views of the US government. Furthermore, I would like to thank Dr Nicole Mamotte for second coding my data. Finally, my research would not have been possible without the cooperation of REC members and administrators who agreed to be participate in this study despite their busy schedules and multiple pressure from other commitments. On a more personal note, I thank my parents and siblings for their enduring support, encouragement and prayers.

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COMMONLY USED ABBREVIATIONS

AIDS	Acquired Immuno-Deficiency Syndrome
CAPRISA	Centre for the Aids Programme of Research in South Africa
CAB	Community Advisory Board
CIOMS	Council for International Organizations of Medical Sciences
CSIR	Council for Scientific and Industrial Research
DSMB	Data Safety Monitoring Board
DHHS	Department of Health and Human Services (US)
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
HSRC	Human Sciences Research Council
IRB	Institutional Review Board
LMCIs	Low and Middle Income Countries
MRC	Medical Research Council
NIH	National Institutes of Health (US)
TB	Tuberculosis
R&D	Research and Development
REC	Research Ethics Committee
REB	Review Ethics Board
WHO	World Health Organization
WMA	World Medical Association

ABSTRACT

Research ethics committees (RECs) are required by national and international ethical frameworks to provide independent ethics review and approval of biomedical research. South Africa has approximately 44 RECs registered with the National Health Research Ethics Council. However, despite more than a decade of existence, little is known about the review activities of such committees. The purpose of this study was to investigate the ethical issues typically raised by two purposively selected biomedical RECs in South Africa. A systematic random sample of REC minutes and decision letters from 2009 to 2014 were retrospectively analysed using the ethical framework developed by Emanuel, Wendler, Killen and Grady (2004). Furthermore, semi-structured interviews were conducted with nine REC members to explore their views of the ethical issues identified. Overall, the most frequent ethical issues identified were informed consent (top ranked), followed by respect for participants (ranked 2nd) and scientific validity (ranked 3rd). Interestingly, administrative issues such as researchers' CVs and budgets were also frequently identified (ranked 4th) compared to other ethical issues such as collaborative partnership (ranked 5th), favourable risk/benefit ratio (ranked 7th) and fair participant selection (ranked 8th). The least frequent ethical issue was social value (ranked 10th). Data from semi-structured interviews suggested that all nine REC members were not surprised by the frequency or ranking of ethical issues identified in this study. They felt that such ranking reflected what their RECs should be querying during ethics review. However, disparate views emerged regarding the frequency of scientific validity issues. Some REC members believed there was an over-emphasis on scientific validity, and that it was not within the remit of RECs to query the scientific validity of research proposals. Nevertheless, it was reassuring that almost all the issues identified in this study were in accordance with existing national and international guidance. This

study provides important insights regarding the kinds of ethical issues raised by two SA RECs. The findings, however, may not be generalizable to the entire REC system, especially non-biomedical RECs, but is likely to be relevant to other biomedical RECs operating in South Africa with similar review loads.

CHAPTER ONE

BACKGROUND OF STUDY

1.0 Introduction

The present study is an investigation of ethical issues raised by two South African biomedical research ethics committees (RECs) during ethics review of biomedical research involving human participants. This chapter provides the background and rationale for the study. First, a general background on the importance of health-related or biomedical research is provided. Thereafter, the relationship between research and ethics is described. This is then followed by a brief introduction on the researcher's personal interest in the field of biomedical research ethics. This is followed by the problem statement and the research questions and objectives. Finally, the last section describes the motivation for the project and argues for its importance.

1.1 The importance of biomedical research

Biomedical research plays a critical role in advancing scientific knowledge for addressing public health challenges, informing evidence-based health policies, and enhancing the performance of public health systems (Department of Health, 2015; Senkubuge & Mayosi, 2013). If it were not for biomedical research, there would probably be no vaccines or chemotherapy drugs, or even organ transplants to save lives and reduce morbidity of many thousands of people daily in modern society. For example, it was through medical research that the world's first human-to-human heart transplantation was pioneered in 1967 by a South African surgeon named Christiaan Barnard. This medical procedure has since gone on to save millions of people's lives around the world (Cooper, 2001).

In 2009, South African researchers at the Centre for the Aids Programme of Research in South Africa (CAPRISA) discovered through research that initiating antiretroviral therapy at the same time as tuberculosis (TB) treatment when the immune system is still relatively intact reduces the risk of the human immunodeficiency virus (HIV) /TB related deaths by 56% (Abdool Karim, Morris & Moore, 2012). Implementing this life-saving policy, which is now endorsed by the World Health Organization (WHO), has resulted in about a hundred thousand more TB patients being initiated on antiretroviral therapy annually and is estimated to prevent 10 000 deaths a year in South Africa. Similarly in 2010, researchers at CAPRISA discovered through research that tenofovir gel, used as a vaginal microbicide, can prevent HIV infection in women. The findings influenced a change in the HIV/TB treatment policy in South Africa and worldwide as it was adopted by the WHO (Abdool Karim et al., 2012). These few examples highlight the importance of health-related research in improving lives and influencing policy.

Furthermore, excellent scientific research and development (R&D) and innovation contribute to a country's socio-economic growth through increased productivity and competitiveness in a knowledge-based global economy (Gumus & Celikay, 2015). Reports suggest that countries that have invested more in R&D yield higher added value and economic performance. A study involving 52 countries conducted between 1996 and 2010 found that R&D expenditure impacted positively and significantly on economic growth for the countries studied (Gumus & Celikay, 2015).

The burden of mortality and morbidity associated with devastating infectious diseases (e.g. HIV/AIDS and TB) and non-communicable diseases (e.g. Diabetes) continues to increase considerably, particularly in less developed countries (Bygbjerg, 2012). According to the UNAIDS (2015), an estimated 36.9 million people globally were living with HIV at the end of 2014. Sub-Saharan Africa accounted for more than half of the global prevalence of HIV with more than 25.8 million people living with HIV. Furthermore, women accounted for more than half the total number of people living with HIV in sub-Saharan Africa. Additionally, more than 1.4 million new HIV infections occurred in Sub-Saharan Africa, accounting for 66% of new infections worldwide. In the same year, there were more than 790,000 AIDS related deaths and 190,000 new HIV infections among Sub-Saharan African children (UNAIDS, 2015).

In South Africa alone, a country at the epicentre of the global HIV/AIDS epidemic, there were more than 6.4 million people living with HIV in 2012, a 1.6% increase from 5.2 million in 2008, as well as 469,000 new infections and more than 450,000 AIDS-related deaths (Shisana et al., 2014). The high burden of disease, including diseases associated with poverty and underdevelopment, along with non-communicable diseases, has created the need for a broad spectrum of biomedical research in South Africa and other low and middle income countries (LMICs) (Department of Health, 2015). Consequently, there has been massive growth of health-related research in recent years sponsored wealthy countries and conducted in LMICs (Glickman et al., 2009). According to the online website of the South African National Clinical Trials Registry, (SANCTR) in May 2016, approximately 2,221 clinical trials had been registered in South Africa.

Beyond this devastating impact on human lives, the high HIV/AIDS burden has undermined the achievement of key Millennium Development Goals (MDGs) in Sub Saharan Africa (Alban & Andersen, 2007; Fourie & Schoeman, 2010). There is thus a pressing need to find evidence-based solutions through research in order to achieve the three health-related MDGs adopted in 2000, i.e. reduction in child mortality (Goal 4); reduction in maternal mortality and access to reproductive health care (Goal 5); and combating HIV/AIDS, TB, Malaria and other diseases (Goal 6) (United Nations, 2014), and the health-related Sustainable Development Goals (SDGs) adopted in 2015, i.e., ensure healthy lives and promote well-being for all at all ages (Goal 3) (United Nations, 2015). One of the specific targets of the SGD goal 3 is to "Support the research and development of vaccines and medicines for the communicable and non-communicable diseases that primarily affect developing countries…." (United Nations, 2015, p.3).

More concerning is the 10/90 gap, which implies that although 90% of the global disease burden is borne by developed countries, only 10% of all health research funding is used to address these diseases (Kilama, 2009). There is need therefore to develop and strengthen sustainable research capacity in developing countries through international and national collaboration. Significant strides have been made thus far in addressing the global health research inequity through partnerships with organizations such as World Health Organization (WHO) and Commission on Health Research for Development. The high burden of disease in South Africa and other Sub-Saharan African countries has necessitated an increase in health-related research over the past few decades in order to accelerate progress against the HIV and TB co-pandemic and other non-communicable diseases (Department of Health, 2015) and narrow the 10/90 global health disparities between developing and developed countries (Global Forum for Health Research,

2000). The recent Ebola outbreak in Western Africa has further highlighted the need for strong research capacity in Africa to adequately provide solutions to emerging infectious diseases (Pandor, 2014; Tomori, 2015).

The importance of health-related research has been well articulated by several policy-makers internationally (Commission on Health Research for Development, 1990; Global Ministerial Forum on Research for Health, 2008; Ministerial Summit on Health Research, 2004). For example, the Ministerial Summit on Health Research (2004) and Global Ministerial Forum on Research for Health (2008) recommended that governments in LMICs should spend at least 2% of their national health budget on health research, although data suggests that government expenditure on health research, at least in South Africa, is still far below the 2% recommended (Paruk, Blackburn, Friedman & Mayosi, 2014). In 2013, the Abuja Special Summit on HIV/AIDS, Tuberculosis and Malaria, accentuated the need to enhance Africa's research capacity, and develop novel and effective health solutions to address African health challenges (African Union Special Summit on HIV/AIDS, Tuberculosis and Malaria, 2013). More recently, the African Union adopted the Science, Technology and Innovation Strategy for Africa 2024 (STISA-2024) as a blueprint to promote and enhance capacity for research on the African continent.

The South African health research policy (Department of Health, 2001) emphasizes the importance of efficient health-related research in the country. The policy explicitly requires the establishment of Provincial Health Research Committees to coordinate and establish priorities

for local health research (Lutge & Mbatha, 2007). The need for health-related research in South Africa is clear. Given its high prevalence of HIV/TB, a thriving research infrastructure and expertise, and an enabling health research policy framework, South Africa has gained wide recognition as an international hub for health-related research (Department of Health, 2015). There are approximately 15 statutory research councils commissioned by Acts of Government to conduct various research for scientific and technological development (Scholes et al., 2008). Examples include the Council for Scientific and Industrial Research (CSIR), Human Sciences Research Council (HSRC) and Medical Research Council (MRC), constituted by Acts of Parliament in 1945, 1968, and 1969, respectively. These statutory research councils have been established to deliver outstanding health research to improve the lives of people in South Africa. In line with the Department of Health National Service Delivery Agreement (NSDA) for 2010-2014, research councils such as the Medical Research Council have set priorities to undertake locally responsive and globally relevant world class biomedical research aligned to the NSDA four main goals: 1) increasing life expectancy, 2) decreasing maternal and child mortality 3) combating HIV/AIDS and decreasing the burden of disease from TB, and 4) strengthening health system effectiveness (MRC, 2012).

Over the past decade, the landscape for biomedical research has evolved significantly in both scope and complexity and this continues to have profound ethical, policy and social implications on contemporary society. Biomedical research has increasingly become more globalized, collaborative and multidisciplinary (da Silva, Amato, Guilhem & Novaes, 2016). Notably, the volume of clinical trials funded by more developed countries and conducted in low and middle income countries (LMICs) has increased (Glickman et al., 2009). According to a 2014 report by

the US Institute for Health Metrics and Evaluation, more than $31.3 billion was invested for funding health research in LMICs in 2013, five-times more than in 1990.

Furthermore, given recent developments in the landscape of biomedical research, for example, genomics and whole-genome sequencing (Pinxten & Howard, 2014), biobanking (Dhai, 2013), data sharing (Bull et al., 2015; Denny, Silaigwana, Wassenaar, Bull & Parker, 2015) and linking personal medical record data with genomic sequence (ter Meulen, Newson, Kennedy & Schofield, 2011), the need for more effective and efficient research ethics oversight has become of paramount importance. On the one hand, these biomedical developments are phenomenal and significantly revolutionizing personal medicine and public health, but on the other hand, they raise numerous serious ethical issues and continuously frame ethical debates on issues such as informed consent, privacy and confidentiality, access to personal genetic information, the problem of incidental findings and the protection of personal genetic information stored in biobanks and databases and ownership of data and human biological materials (Millum, Sina & Glass, 2015).

Well-capacitated RECs have a central role to play in ensuring that the research they review is relevant to local health needs, is ethically sound and protects the dignity and welfare of research populations while supporting evidence-based improvements in public health. There would thus appear to be a need to conduct more empirical research to determine the resources, capacity and functioning of African research ethics committees (RECs) in dealing with ethical issues raised by recent developments in biomedical research (Silaigwana & Wassenaar, 2015).

There have been concerns about inadequate ethics oversight and research ethics capacity in LMICs (Bhutta, 2002; Hyder, Dawson, Bachani & Lavery, 2009). A survey of ethics review practices in developing country (Africa, Asia and South America), found that about 44% of researchers indicated that their studies were not reviewed by an REC or health authority in the developing country and one third of those studies were funded by U.S. sponsors (Hyder et al., 2004). A more recent study by Zielinski et al. (2014) surveyed 847 health research institutions in 42 African countries and found that only 51% of respondent institutions reported that they had policies on research ethics and only 58% had written policies requiring that researchers obtain the informed consent of research participants.

As the need for more health-related research in LMICs increases, so should research ethics capacity strengthening to ensure the protection of the rights and wellbeing of participants, while simultaneously contributing to the advancement of scientific knowledge (IJsselmuiden, Marais, Wassenaar & Mokgatla-Moipolai, 2012). It remains to be seen whether current research ethics systems in LMICs have kept pace with the increasingly challenging research milieu. However, several initiatives have made significant headway towards capacity building and enhancing research ethics systems in Sub-Saharan Africa (Ndebele et al., 2014a; Wassenaar, 2011) and other developing countries (IJsselmuiden et al., 2012; Oukem-Boyer, Munung, Ntoumi, Nyika & Tangwa, 2013). For instance, the Fogarty International Center, National Institutes of Health in the US invested approximately US$33 million between 2000 and 2012 to support and build research ethics capacity globally, with almost 40% (US$13 million) invested for research ethics capacity building in Sub-Saharan Africa alone (Ndebele et al., 2014a). Similarly, since 2007, the UK's Wellcome Trust has spent approximately £2million (with most of the support directed

towards research ethics projects in Sub-Saharan Africa) in supporting and enhancing bioethics research, research ethics training, and workshops in developing countries. Likewise, the European Developing Countries Clinical Trials Partnership (EDCTP) has spent over €3.2 million to support more than 54 research ethics projects in Africa between 2005 and 2011 (Ndebele, Mwaluko, Kruger, Oukem-Boyer & Zimba 2014b).

While such initiatives are laudable, it remains unclear what the optimal funding ratio should be for biomedical research versus research ethics. The aforementioned figures on research ethics spending by international organizations could probably still be far much lower than funding for clinical research. Considering that there is an increase in the amount and complexity of biomedical research conducted in Sub-Saharan Africa, more financial support towards research ethics capacity in Sub-Saharan Africa is still needed (Ndebele et al., 2014a). However, given that the REC capacity varies between countries, the optimal funding for research ethics capacity will inevitably vary between countries depending on their needs. Initiatives to build research ethics capacity in developing countries should also focus on REC administrators (Kasule, Wassenaar, IJsselmuiden & Mokgatla, 2016) in addition to scientists and REC members.

1.2 Research and Ethics

Research ethics is a field concerning the principles, norms, standards and guidelines regulating the conduct of research (Ajuwon & Kass, 2008; Resnik, 2015). Research ethics aim to protect participants by ensuring that the goals of research do not supersede the rights, dignity, safety and welfare of research participants (Ajuwon & Kass, 2008). While biomedical research is unquestionably essential, it concomitantly presents potential risks (e.g. physical, psychological, and social) to the participant and society. There are many documented cases of unethical research where participants have been harmed by research, sometimes even dying as a result (Emanuel, Crouch, Arras, Moreno & Grady, 2003; Nuffield Council on Bioethics, 2002).

This therefore necessitates ethical oversight mechanisms and processes for ensuring that such potential risks are carefully evaluated using established international and national ethical standards by an independent committee with no conflict of interests in relation to the proposed research (Council for International Organizations of Medical Sciences [CIOMS], 2002; WHO, 2011; World Medical Association [WMA], 2013). The goals of research should not supersede the rights, dignity, safety and welfare of research participants. Research ethics is therefore aimed at protecting the rights, dignity and safety of human participants and ensuring that research is carried out in the least harmful way in accordance with fundamental ethical principles (Belmont Report, 1979).

The ethics of biomedical research in developing countries has generated considerable debate about the appropriate ethics standards (Angell, 1997; Benatar, 2002; Benatar & Fleischer, 2007; Bhutta, 2002; Fitzgerald, Wasunna & Paper, 2003; Levine, 2002; Macklin, 2004; Nuffield Council on Bioethics, 2002; Perrey, Wassenaar, Gilchrist & Ivanoff, 2009; Shapiro & Meslin, 2001; Weijer, 1999). Some of the ethical issues may be exacerbated particularly in situations where individual research participants or communities may be vulnerable to risks of exploitation and harm if enrolled in certain research studies (Nuffield Council on Bioethics, 2002; Gbadegesin & Wendler, 2006; Horn, Sleem, & Ndebele, 2014). The main concern here is that research populations in developing countries may be predisposed to exploitation due to contextual factors such as low socio-economic background, power imbalances between researchers and participants, illiteracy and unfamiliarity with research (Dal-Ré, Ndebele, Higgs, Sewankambo & Wendler, 2014). Furthermore, participants and communities in less developed countries may be unfairly exposed to risks and burdens of research and yet may not have fair access to benefits derived such studies (Dal-Ré et al., 2014; Shapiro & Meslin, 2001; Weijer & Emanuel, 2000).

Furthermore, ethical challenges may arise when investigators have to obtain valid informed consent from participants with high levels of cultural and language differences (Hanrahan et al., 2015), and little or no understanding of clinical trial procedures such as randomization, double-blinding and placebo (Ndebele, Wassenaar, Masiye & Nkandu, 2014c). Moreover, investigators could be faced with ethical complexities of designing or implementing appropriate levels of medical care and treatment for participants – the so-called standards of care, where local available standard of care is close to nothing, or endeavouring to integrate research results into

the healthcare system where the healthcare infrastructure is archaic and fragmented (Angell, 1997; Emanuel et al., 2004; Fitzgerald et al., 2003; Levine 1998; Lindsey, Shah, Sibbery, Jean-Philippe & Levin, 2013; Lurie & Wolfe, 1997; Macklin, 2004; Millum et al., 2015; Varmus & Satcher, 1997).

The scope of research ethics has generally shifted beyond focusing only on the individual research participant, to more subtle concerns about social, cultural, political, and economic implications of proposed research on the entire community in which research is conducted (Emanuel et al., 2004). Of particular importance is the recognition for prior community consultation and engagement with local stakeholders in the design, conduct and implementation of the research and ensuring research has social value (Emanuel et al., 2004; Millum et al., 2015; Rivera & Borasky, 2010). A number of ethical guidelines have been produced specifically to address ethical issues in conducting biomedical research in developing countries (Nuffield Council on Bioethics, 2002). Although multiple international and national ethical guidelines exist, they do not always provide clear or unambiguous solutions to all the ethical complexities arising in the design and conduct of research in developing countries. The guidelines are sometimes contradictory and inconsistent and can be interpreted in varied ways (Emanuel et al., 2004; Wassenaar, 2006).

Research ethics committees (RECs), also known as institutional review boards (IRBs) in the US, can be described as multidisciplinary, independent groups of individuals appointed to conduct ethics reviews of research involving human participants (WHO, 2009). The primary

responsibility of RECs or IRBs is to protect the rights and welfare of human research participants (Amdur & Bankert, 2006). The authors argue that while IRBs or RECs are there to protect the rights and welfare of human research participants, they cannot afford to spend time on activities not required for protection of human research subjects in compliance with federal research regulations. Specifically, they mention that "1) The IRB is not an editorial service, 2) the IRB is not the office of the medical director, 3) the IRB is not the medical records department or confidentiality committee, 4) the IRB is not the risk-management committee, 5) the IRB is not the office of patient financial services, and 6) the IRB is not a data safety monitoring board" (p. 28).

The requirement for independent ethics review of research came about following several cases of unethical human research practices as those witnessed in the Nuremberg trials of doctors tried for crimes against humanity during World War II (Emanuel et al., 2003), other major concerns exposed by Beecher (1966), and as further publicized in the infamous Tuskegee syphilis studies (Brandt, 1978). The oversight of research involving human participants is an ethical and legal requirement in several countries worldwide (Department of Health and Human Services [DHHS], 2016; WHO, 2011). Since the Declaration of Helsinki guidelines were developed in 1964, RECs have increasingly become common in the ethical oversight of biomedical research. Their primary task is to ensure the protection of participants by conducting ethical reviews of research in accordance with national (Department of Health, 2015) and international ethical standards (c.f., CIOMS, 2002, WHO, 2011; WMA, 2013). Several countries in Sub-Saharan Africa and internationally have implemented or are enhancing regulatory frameworks for research involving human participants to ensure adequate ethics oversight (DHHS, 2016).

In South Africa, the National Health Act No. 61 (2003) necessitates ethics reviews of all health-related research by RECs registered with the National Health Research Ethics Council (NHREC), a national body which regulates the structure and functioning of local RECs (Department of Health, 2015). Currently, there are approximately 44 registered RECs in South Africa. While all ethics review activities of RECs in South Africa are, in principle, guided by the Department of Health (2015) guidelines, very little is known about the ethical issues raised by these committees in practice. This thesis provides a pilot study of the ethical issues typically identified during ethics review by two biomedical RECs in South Africa.

1.3 Personal interest in biomedical research ethics

The researcher's interest in biomedical research ethics and the regulation of human research developed after receiving a Medical Education Partnership Initiative (MEPI) Research Ethics fellowship at the University of KwaZulu-Natal (UKZN), South Africa. This fellowship was aimed at PhD students to develop understanding and capacity in research ethics. During the fellowship, the researcher was involved in reviewing biomedical research proposals, observing meetings or deliberations of a biomedical REC and reading selected literature on research ethics. During literature search, the researcher noted that there was a dearth of information on the ethical issues that are raised by RECs reviewing biomedical research both locally and internationally. Therefore, this motivated the researcher and the supervisor to embark on a project which would utilize and study minutes and decision letters of a sample of biomedical RECs in order to provide empirical evidence on the ethical issues raised by a sample of South African RECs. Some of the burning questions that the researcher wanted to investigate included the following:

- What are the ethical issues typically raised by RECs during ethics review?
- What are the views of REC members/ ethics experts regarding the ethical issues raised by RECs during ethics review of biomedical research?
- Do the review activities of local RECs adhere to national ethics regulations and international guidance?

Hence, these questions led to the conceptualisation of the present study which aims to provide empirical evidence on the issues raised by RECs during ethics review.

1.4 Problem statement

Despite their important work in ensuring the ethical acceptability of proposed research and protection of research participants, there is very limited empirical research on the ethical review activities of RECs (Silaigwana & Wassenaar, 2015). Although there is plentiful literature in developed countries such as the UK (Angell, Biggs, Gahleitner & Dixon-Woods, 2010; Angell, Bryman, Ashcroft & Dixon-Woods, 2008; Angell, Tarrant & Dixon-Woods, 2009; Dixon-Woods, Angell, Tarrant & Thomas, 2008), Spain (Martin-Arribas, Rodriguez-Lozano & Arias-Diaz, 2012) and US (Abbott & Grady, 2011; Lidz et al., 2012), not much has been published about the ethical issues raised by RECs in South Africa. The few available studies have generally focused more on the structure, functioning, resources and workload of RECs in Africa, including South Africa (Cleaton-Jones, 2012; Cleaton-Jones & Grossman, 2015; Cleaton-Jones & Vorster, 2008; Kass et al., 2007; Moodley & Myer, 2007; Silaigwana & Wassenaar, 2015).

Less attention, however, has focused specifically on the kinds of ethical issues identified during ethics reviews (Clarke, 2014; Cleaton-Jones, 2010; Tsoka-Gwegweni & Wassenaar, 2014). In principle, RECs are expected to apply national ethical guidelines and regulations (Department of Health, 2015) and other international standards as a foundation for their decisions when reviewing applications for ethics approval. However, very little is known about what RECs actually do in practice. Up to now, despite more than a decade of functioning since formal ethics review was legislated in South Africa (National Health Act, 2003), there are still gaps in what is known regarding the ethical issues raised by RECs. Furthermore, there have been very few, if any, studies exploring the views of South African REC members on the ethical issues arising in their typical review work. This is perhaps one critical gap necessitating further exploration in order to understand what local RECs are actually doing in practice. In view of their important work in protecting research participants, and the costs associated with operating RECs (Sugarman et al., 2005; Wagner, Cruz, & Chadwick, 2004), it is crucial to understand specifically the kinds of ethical issues that RECs raise when reviewing research protocols. As such, the overarching objective in this present study was to investigate the specific ethical issues raised by two South African biomedical RECs at two leading health research universities.

1.5 Aims and objectives

Given the few existing studies on the review activities of RECs in South Africa, this project aimed to describe the ethical issues raised by RECs. Specifically, the objectives of this study were:

1. To identify the ethical issues typically raised.
2. To apply the Emanuel et al. (2004) framework to evaluate the ethical issues raised.
3. To qualitatively explore the views of REC members regarding the issues identified in (1) above.
4. To determine whether findings in (1) align with national research ethics guidance.

1.6 Research questions

The specific research questions of this study were:

1. What specific ethical issues are raised by two large biomedical RECs?
2. Is the theoretical framework by Emanuel et al. (2004) compatible with the ethical issues and concerns raised by two large biomedical RECs in South Africa?
3. What are the views of REC members regarding the ethical issues raised in (1) above?
4. Do ethical issues raised by RECs align with established national ethics guidance?

1.7 Scope of thesis

This study investigated the ethical issues raised by two purposively sampled biomedical RECs in South Africa. It drew on three different data collection and analytic sections: 1) retrospective review of minutes and decision letters for the period 2009-2013; 2) semi-structured interviews with a random sample of RECs members from the two committees included in this study; and 3) comparative analysis of findings in objective (1) with existing national guidelines (Department of Health, 2015). While this thesis provides some crucial insights into the ethical issues raised by RECs during ethics review, it is beyond the scope of this thesis to provide definitive analyses of the entire ethics review system in South Africa. Furthermore, the present study did not aim to conduct an ethnographic study and discourse analysis of what transpires during REC meetings (de Jong, van Zwieten & Willems, 2012; Klitzman, 2015; Stark, 2012; Tolich, 2014). Similarly, it is also beyond the scope of this study to audit the biomedical RECs, or to make detailed recommendations relating to the weaknesses or potential problems or inadequacies of the South African ethics review system. What this thesis fundamentally aimed to achieve was to highlight the ethical issues typically raised by RECs and develop some perspective in understanding what REC members think about these kinds of issues and whether they fairly reflect their understanding of the core business of an REC. Ultimately, it is hoped that this thesis will provide preliminary insights into the kinds of ethical issues raised by two purposively sampled biomedical RECs in South Africa.

1.8 Contribution of this study to general knowledge

The research question addressed by this thesis is largely descriptive and unsophisticated, and may simply be put as "What are the ethical issues raised by research ethics committees reviewing biomedical research in South Africa". The answer to this question was simply not known at the time that this study was initiated. Answering this seemingly unsophisticated question will hopefully potentially facilitate better understanding of exactly what ethical issues are raised by RECs in their important work, contributing to growing scholarship on the activities and outcomes of RECs that typically occur 'behind closed doors' to quote Laura Stark's (2012) ethnographic study of IRB decision making. This thesis reports on the ethical issues typically identified by a sample of two RECs in South Africa. Furthermore, it reports on the perspective of REC members regarding these ethical issues.

As mentioned above, there has been relatively little research on the kinds of ethical issues raised by RECs in general and African RECs specifically, when reviewing biomedical research proposals. In a review of African RECs (Silaigwana & Wassenaar, 2015), only three studies (Clarke, 2014; Cleaton-Jones, 2010; Tsoka-Gwegweni & Wassenaar, 2014) out of 23 included studies, had addressed the actual ethical issues raised by RECs. This research therefore aims to assist in broadening knowledge of what ethical issues are typically raised by RECs, tests a conceptual framework for doing so (Emanuel et al., 2004), and hopefully contributes to better evidence-based understanding of what RECs do, what issues they typically raise, and how this might inform training or REC improvement programmes. Hence the study hopefully makes a useful empirical contribution to the scholarly literature on RECs, specifically revealing and discussing the ethical issues identified by such committees. The study hopes to generate data

which may hopefully be of interest to other researchers, scholars and even RECs themselves. As far as can be ascertained from available databases, the present study is the first doctoral project investigating RECs in South Africa. Therefore, by its very discussion of RECs and the ethical issues they raise, together with an analysis of the views of a sample of their members on these ethical issues, the present study is hopefully novel. Considering that RECs are notoriously known to be difficult to access for research purposes (de Jong et al., 2012; Klitzman, 2015; Stark 2012), the present study hopefully provides a rare but important, glimpse into the kinds of ethical queries contained in the minutes and decision letters of two active biomedical RECs.

Therefore, it is hoped that this study has potential significance because:

1. The study will provide empirical evidence of the ethical issues raised by local RECs during review of health research.

2. The study will contribute knowledge regarding the adequacy of the Emanuel et al. (2004) framework in addressing ethical issues identified by two SA RECs.

3. Furthermore, the study has potential to provide a standardised methodology/approach for similar studies nationally and internationally.

Understanding ethical issues raised by RECs is essential for several reasons. Firstly, it serves as an important process for accountability (O'Reilly, Dixon-Woods, Angell, Ashcroft & Bryman, 2009), i.e., helping to provide evidence of what RECs (the guardians of research participants' rights, safety and wellbeing) are actually doing. Second, it provides evidence of perhaps the ethically challenging issues where researchers and RECs may need further education and guidance.

1.9 Summary and overview of thesis

In this chapter, an introduction on the biomedical research landscape and its importance in addressing public health challenges was briefly described. This was followed by a brief introduction to research ethics, some key historical drivers of the development of research ethics and its importance in protecting research participants. Furthermore, a problem statement and objectives of the study, research questions and the contribution of this study to general knowledge were articulated. The subsequent chapters of the thesis provide more detailed information as outlined below.

Chapter 2 reviews the literature on research ethics from a global context, followed by a focus on the South African context. Thereafter, literature critiquing mandatory ethics review is reviewed. The chapter then reviews empirical studies on ethical issues raised by RECs conducted internationally and concludes by reviewing empirical studies that have been conducted to investigate the ethical issues raised by African RECs.

Chapter 3 gives a brief overview of the theoretical framework on which the present study was premised.

Chapter 4 highlights the main aim of the study, the specific objectives and research questions.

Chapter 5 describes the methodology used in this study - the study design, sampling and data analysis techniques used for the three work packages in this study. Furthermore, ethical considerations of the study are highlighted.

Chapter 6 describes the results from the three work packages included in this study. Direct

quotes from the data, which have been anonymized, are used to illustrate the findings.

Chapter 7 provides a discussion of the findings and interprets the results with reference to the theoretical framework and the published literature.

Chapter 8 provides limitations, conclusions and recommendations, in light of the study findings.

CHAPTER TWO

LITERATURE REVIEW

2.0 Introduction

The main objective of this chapter is to present a review of literature on the ethical issues raised by RECs reviewing biomedical research. The chapter is divided into various sections as follows:

- The first section of the literature review begins with the history and development of research ethics from an international context. It specifically reviews some of the scandals and tragedies of research with human participants that were foundational to the development of modern day research ethics.
- The second section discusses some of the key international ethical guidelines including the Belmont Report's fundamental ethical principles and their application.
- The third section describes the South African research ethics review landscape. It commences with the history of the South African research ethics system. Thereafter, the South African legislative framework and national ethical guidelines for research are described.
- The fourth section reviews literature critiquing mandatory REC ethics review.
- The fifth section reviews literature on some of the ethical issues arising in biomedical research. The list of issues described in this chapter is by no means exhaustive. These issues have been purposively selected to facilitate discussion and interpretation of the findings of the present study.
- The sixth section reviews and discusses previous empirical studies that have been conducted to investigate ethical issues raised by RECs internationally.

- The seventh section reviews and discusses previous empirical studies aimed at investigating ethical issues raised by African RECs.
- The chapter concludes with a summary of the literature reviewed and some of the key findings from the previous studies.

2.1 History and development of research ethics

The field of research ethics has evolved over the past decades since the Nuremberg Code in 1947, resulting in a plethora of ethical guidelines, codes, and regulations for research involving human participants. Historical events involving some unethical experiments involving human participants, for example, without their informed consent, withholding information and coercive influence over vulnerable populations, were largely responsible for the promulgation of some research ethics guidance (Beecher, 1966; Brandt, 1978; Emanuel et al., 2003; Katz, Capron & Glass, 1972). On the other hand, the globalization of research and dilemmas encountered in the dynamic health research milieu also led to the development of some research ethics guidelines, codes and regulations (Nuffield Council on Bioethics, 2002; Rivera & Borasky, 2010). While there are several cases of scandals and unethical research in the history of human research misconduct, the section below will outline some examples of studies that were ethically controversial and which led to the development of some key international ethical codes, declarations, guidelines and regulations.

2.1.1 Tuskegee Syphilis study (1932-72)

The Tuskegee syphilis study began in 1932 and continued until 1972 and was commissioned by the United States Public Health Service (USPHS). The study apparently sought to investigate the natural course of latent, untreated syphilis in black males at a time when no treatment existed (Brandt, 1978). Approximately 400 African-American men with syphilis were recruited and assigned into the experimental group and another 200 uninfected men were assigned to the control group. It is reported that these men were enrolled into the study after misleading promises that they would receive new treatment (Brandt, 1978). Yet, even when safe and effective penicillin antibiotics were discovered and became widely available in the early 1950s, treatment for men infected with syphilis was still withheld from the patients, apparently because this would disrupt the natural history findings. Shockingly, the USPHS actually sought to prevent treatment on several occasions and a committee at the Center for Disease Control decided in 1969 that the study should be continued (Brandt, 1978). Sadly, the majority of the men in the experimental group suffered from severe morbidity and many died as a result of advanced syphilis. The study was eventually halted by the US Department of Health Education and Welfare in 1972 after the atrocious details of the study were publicized nationwide. Consequently in 1997, Bill Clinton, then president of U.S, issued a public apology to a few men and the families of the deceased who had survived this atrocious (Clinton, 1997) and awarded compensation to affected families.

Ethical violations of the Tuskegee study include enrolling participants without informed consent as the men were misinformed to believe that they would be receiving special treatment for syphilis (Heintzelman, 2003). Also, the researchers never gave the patients information on penicillin when it became available or a choice to voluntarily continue or withdraw from the study despite the availability of penicillin, an effective anti-syphilis drug. Furthermore, there was exploitation as the researchers recruited vulnerable African-American men of poor socioeconomic status with inadequate medical treatment and care (Heintzelman, 2003). Another ethical issue, perhaps more troubling, was the withholding of treatment to patients in dire need of treatment, for the purpose of research (Brandt, 1978). The investigators should have obtained voluntary informed consent from the men before enrolling them into the study. Furthermore, when it became available in the early 1950s, penicillin should have been provided to the infected men. The direct result of the publicity of the Tuskegee Syphilis study was the establishment of the National Research Act (1974) which created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research and in turn published the Belmont Report in 1978 (described in detail in subsequent sections).

2.1.2 Nazi medical war crimes (1939-45)

One of the most infamous examples in the history of research ethics is the experiments on Jews during the Nazi regime during World War II. In these experiments, thousands of concentration camp prisoners were subjected to numerous brutal experiments (Emanuel, et al., 2003). One example of these experiments was the high altitude (low pressure) experiments in which prisoners were put into low pressure tanks to determine how long they could survive with little

oxygen. Several people who did not die immediately were then put under water until they succumbed to death. Another example is the Malaria experiment whereby prisoners were deliberately infected with Malaria and then provided with different drugs purported to be antimalarial drugs (Emanuel, et al., 2003; Korda, 2006). Other examples of experiments included, but are not limited to, freezing experiments, mustard gas experiments, sulphanilamide experiments, typhus experiments, poison experiments, incendiary bomb experiments and sterilization experiments (Emanuel et al., 2003; Korda, 2006). Many of the prisoners subjected to these experiments succumbed and unfortunately died, often after prolonged suffering (Emanuel et al., 2003). After World War II, in response to these atrocities, 23 Nazi doctors and administrators were tried for the brutal atrocities they inflicted on thousands of concentration camp prisoners by the international military tribunals in Nuremberg 1947. Seven defendants were found guilty and sentenced to death, eight were sentenced to imprisonment from ten years to life, and the remaining seven were found not guilty (Emanuel et al., 2003). The Nuremberg Code (see section 2.2.1) was established in 1947 as a direct result of the trial.

2.1.3 Willowbrook State School Hepatitis Study (1956)

The Willowbrook state school hepatitis study, led by Dr Saul Krugman of New York University in 1956, involved more than 700 mentally ill children whom were deliberately infected with Hepatitis A virus ostensibly to investigate the children's level of immunity against hepatitis, and to discover a cure for the disease (Krugman & Ward, 1958). The children did not receive treatment despite the discovery of an effective vaccine for Hepatitis in 1969 (Rothman, 1982). The study needlessly exposed vulnerable children to serious risks and most of them subsequently

developed symptoms such as swollen liver and yellowing of the skin. The researchers argued that 90% of children would still have been exposed to Hepatitis A at some point in their everyday life, i.e., the study did not expose these children to greater risks than those they would otherwise ordinarily have been exposed to due to the high incidence of the disease during those days (Rothman, 1982).

Although informed consent was obtained from parents, and the study was approved and reportedly had a favourable risk/benefit ratio (Krugman & Ward, 1958), the study was ethically controversial (Robinson & Unruh, 2008). Firstly, the study did not adequately inform parents about the serious nature of risks posed by the experiments (Robinson & Unruh, 2008). Furthermore, mentally ill children who were institutionalized, constitute a vulnerable population whose autonomy is clearly diminished (or absent) with regard to giving valid and voluntary informed consent or assent (Robinson & Unruh, 2008). From an ethical perspective, the study might have been considered for competent adults first before deliberately injecting live Hepatitis virus into vulnerable mentally ill children. Moreover, it can be argued that there was undue inducement as parents of the children may have been unduly influenced by being offered admission for their children into a new unit of the Willowbrook school (after the school had closed its admission for new students due to overcrowding in 1964) only if they agreed to participate in the Hepatitis study (Robinson & Unruh, 2008; Won, 2012).

2.1.4 Jewish Chronic Disease Study (1963)

The legitimacy of research involving humans once again came under the spotlight after the Brooklyn Jewish chronic disease study in 1963. The Jewish chronic disease study was conducted by three doctors who deliberately injected live cancer cells into twenty-two chronically ill and debilitated elderly patients supposedly to investigate a patient's ability to reject foreign cells (Katz, Capron & Glass, 1972). Although the study had been approved by the board of the Jewish Chronic Disease Hospital, (Katz et al., 1972), it violated fundamental ethical principles for research with human beings. Firstly, the doctors/researchers did not inform the patients that they were being injected with live cancer cells, nor were the patients informed that this was an experimental procedure and not part of their routine therapy (Katz et al., 1972; Lerner, 2004). That is, despite the doctors having obtaining verbal consent from the patients, the consent process was not truly informed because there was apparently no discussion with the patients to inform them about the study procedures and that they would be injected with cancer cells. Moreover, because of their incapacitated physical and mental condition, some patients would probably not have been able to give valid informed consent. Therefore, these doctors should have sought valid informed consent from an authorized adult person with legal capacity to provide proxy consent after adequate disclosure of the nature of the study and the potential risks, including the procedure for injecting cancer cells.

Furthermore, it is stated that the informed consent from the patients was not documented and nor was the study approved by the hospital's research committee (Katz et al., 1972; Lerner, 2004). However, one of the doctors involved in the study – Chester Southam – argued that the study

presented no risk to the patients because there was scientific evidence suggesting that the injected cancer cells would cause an immune reaction that would lead to their expulsion from the patient's body (Emanuel et al., 2003). Furthermore, the investigator argued that fully informing the patients about the study details, particularly the term cancer, would have caused them unnecessary risk of psychological distress. In other words, he did not inform the patients because he was trying to minimize the risk of psychological distress to the patients (Emanuel et al., 2003). However, the New York Board of Regents in 1966 rejected both arguments and found the doctors guilty of fraud or deceit (Katz et al., 1972; Lerner, 2004). When Henry K. Beecher published his exposé of unethical research in the New England Journal of Medicine later in 1966, the Jewish chronic disease hospital scandal was among the twenty-two cases he cited (Beecher, 1966). This work is discussed in more detail below (2.1.5).

2.1.5 Henry Beecher's expose (1966)

In 1966, a US professor and anaesthetist Henry Beecher, published his article describing unethical medical research which had been conducted by medical doctors (Beecher, 1966). In summary, the article outlines 22 examples of studies in which patients were deceived or exposed to unnecessary risks without their consent. Of great concern was that several of these studies were conducted by esteemed researchers in well-known institutions, and were funded by reputable sponsors such as the US military, the National Institutes of Health and well-respected pharmaceutical companies. One such example was the study of cyclopropane anaesthesia and cardiac arrhythmias in which 31 patients were deliberately injected with toxic carbon dioxide into their closed respiratory systems and maintained for considerable periods ranging from two

to four and half hours until cardiac arrhythmias appeared (Beecher, 1966). Some of the ethical issues included, lack of informed consent, coercion or undue pressure on volunteers (or parents to volunteer their children), exploitation of vulnerable populations, withholding information about risks, withholding available treatment, exposing participants to undue risk that outweighed benefits, and the use of deception (Beecher, 1966).

While most of the cases of unethical research involving human participants that led to the development of research ethics were predominantly of biomedical nature, there were also several cases of unethical research in the behavioural and social sciences. Perhaps one of most outstanding was the Milgram's 1963 study of obedience to authority described below (2.1.6).

2.1.6 The Milgram Study (1963)

The Milgram study was a psychology experiment conducted by psychologist Stanley Milgram, that studied obedience to authority by instructing a group of approximately 40 male volunteers ("the teachers") to administer potentially lethal electrical shocks to others ("the learners") (Milgram, 1963,1965). Motivated by the defence testimony of the Nuremberg Trial accused, who stated that they were merely obeying orders, Milgram set out to determine under what conditions will people carry out the commands of an authority figure to inflict suffering on others, and whether and when will they refuse to obey such instructions (Milgram, 1963). The study involved the use of deception. The participants were misinformed about the true nature of the research study, by being deceived into thinking that they were involved in an experiment on the impact of punishment on memory (Milgram, 1963). The Milgram study is controversial because

of its lack of valid informed consent about the true nature and psychosocial risks of the experiment and its use of deception (although deception is now allowed by guidance and research ethics committees in certain justifiable instances). Furthermore, the study was unethical because of the potential risks of psychological distress on the participants after realizing they could have deliberately administered electrical shocks and caused suffering to another innocent human being (Won, 2012).

2.1.7 Tearoom trade study (1970)

The so-called tearoom trade study was conducted in the 1970s by Laud Humphreys towards his PhD, wherein he studied men who have sex with men in public toilets of city parks (Humphreys, 1970). Such acts were illegal at that time and homosexuality was highly stigmatised. In the first component of the study, Humphreys apparently impersonated a "watch queen" who was on the lookout and would notify the men if somebody was approaching. Apparently, the aim of the study was to understand the relationship of these men's clandestine homosexual activities in relation to their daily public lives. Humphreys sought to counter prejudice against homosexuality. In the second component of the study, Humphreys noted down the men's vehicle licence plate numbers and tracked approximately fifty men to their home addresses through municipal records where he masqueraded as a social health researcher conducting interviews with the men in their homes to gather personal information on their marital status, sexuality and occupations (Humphreys, 1970). These men were not informed of the fact that Humphreys was a researcher and therefore they became unwitting research participants. After publishing his

findings, controversy arose. A major concern was the use of deception and invasion of privacy (Lenza, 2004).

The current section has described some examples of controversial and unethical research involving humans that led to the development of modern day research ethics. While most of these scandals were in biomedical research, the literature review has also shown that there were also examples of unethical social science and behavioural research involving humans that caused ethical controversy (see 2.1.6 and 2.1.7). The next section describes some of the key international codes, declarations and guidelines that were developed as a result of the unethical research scandals described above.

2.2 Key international research ethics codes and guidelines

2. 2. 1 Nuremberg Code (1947)

The Nuremberg Code (1947) was one of the first internationally recognized code of research ethics to be promulgated in response to unethical research conducted in humans. The Code outlined ten sets of principles for research involving humans including the need for voluntary consent, avoiding harm to research participants, and weighing up the risks against potential benefit. Specifically, the Nuremberg Code stated that:

1. “The voluntary consent of the human subject is absolutely essential.
2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.
3. The experiment should be so designed and based on the results of animal experimentation and knowledge of the natural history of the disease or other problem under study, that the anticipated results will justify the performance of the experiment.
4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.
5. No experiment should be conducted, where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.
6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.
7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death
8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.
9. During the course of the experiment, the human subject should be at liberty to bring the experiment to an end, if he has reached the physical or mental state, where continuation of the experiment seemed to him to be impossible.

10. During the course of the experiment, the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgement required of him, that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject" (Nuremberg Code, 1947, pp. 181-182).

Although the Nuremberg Code was published in 1947, there were other ongoing and later scandals and unethical medical research involving human beings carried out at leading research institutions and hospitals in the US (Beecher, 1966). The Nuremberg Code did not have a great impact on the way in which clinical research was being carried out in other countries as it was seen as only being of direct application to the physicians that were on trial. According to Faden, Lederer and Moreno (1996), some researchers were against the Nuremberg Code for three main reasons namely 1) discrepancies between what investigators had come to know in real practice in research with patient-subjects and what they read in the lofty, idealized language of the Nuremberg Code, 2) others simply were not in agreement with some elements of the Code and 3) others decried the notion of a "one-size-fits-all" standard to guide research in such a complex landscape of human experimentation.

Therefore, after it was established, the Nuremberg Code had little effect in curbing unethical research practices in other developed countries such as the US (Faden et al., 1996). This was evident from the fact that despite the publication of the Nuremberg Code in 1947, many instances of unethical research conducted on vulnerable persons in other countries continued or

were initiated, often without their knowledge and voluntary informed consent (Beecher, 1966), which subsequently led to the creation of a number of key international ethical guidelines which are discussed in the next section. The Nuremberg Code enshrined voluntary informed consent above anything else. This later proved to be an unworkable impediment to research on certain populations (e.g. unconscious patients, psychotic patients and children). Emanuel et al. (2003) importantly point out that most codes were drafted driven by a scandal, causing them to be flawed in some way to prevent that particular scandal from recurring.

2.2.2 Declaration of Helsinki (1964)

The World Medical Association (WMA) published the Declaration of Helsinki in 1964, outlining ethical principles for medical research involving human subjects, including research on identifiable human material and data. This declaration, with very similar guidance to the Nuremberg Code, mainly focused on medical research intended for therapeutic purposes. Although the Declaration of Helsinki (1964) had many similarities to the Nuremberg Code (1947), the feature that distinguished it from the previously promulgated Nuremberg code, was the need for independent ethical review by RECs. Key issues addressed in the Declaration of Helsinki included:

- Research with humans should be based on laboratory and animal experimentation
- Research protocols should be reviewed by an independent committee
- Informed consent is necessary
- Research should be conducted by medically/scientifically qualified individuals

- Risks should not exceed benefits

Since 1964, the Declaration of Helsinki has gone through several revisions (1975, 1983, 1989, 1996, 2000, 2008) and most recently in 2013 during the 64th WMA General Assembly in Brazil (WMA, 2013). Briefly, the Declaration of Helsinki (2013) provides guidance on the following ethical issues: risks, burdens and benefits; vulnerable groups and populations; scientific requirements, research ethics committees; privacy and confidentiality; informed consent; use of placebo, post-trial access; public and dissemination of results; and unproven interventions in clinical practice (WMA, 2013).

2.2.3 US National Research Act (1974)

When the Tuskegee Syphilis study, which began in 1932 (described in section 2.1.1) was publicised and there was public outcry in 1972, the US Congress passed the National Research Act in 1974 (Emanuel et al., 2003). Subsequently, the National Research Act established the National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research to identify the basic ethical principles that should underpin the conduct of biomedical and behavioural research involving human participants and to develop guidelines governing studies involving human participants to ensure the protection of human research participants. To that end, the US National Commission developed the Belmont Report (1979) (see next section), a foundational document guiding the ethics of human participants research in the United States. The National Research Act required prior IRB approval of biomedical and behavioural research (Williams, 2005).

2.2.4 The Belmont Report (1979)

The Belmont Report is a statement of basic ethical principles and guidelines that provide an analytical framework to guide the resolution of the ethical problems arising from research with human subjects (Belmont Report, 1979). It was developed in 1979 by the US government appointed National Commission for the Protection of Human Subjects in Biomedical and Behavioural Research. The three basic ethical principles (respect for persons, beneficence and justice) and their applications are summarized in Table 1 below:

Table 1: Belmont Report (1979) basic ethical principles and their application

Principle	Application

Respect for persons
• Persons should be treated as autonomous individuals
• There should be protection for persons with diminished autonomy.
	Informed consent
	• Participants must freely choose whether or not to participate in research
	• The essential elements of the consent process are:
	  • Information disclosure,
	  • Understanding, and
	  • Voluntariness.

Beneficence • There should be no harm to human participants • Proposed research should ensure that possible benefits are maximized possible harms minimized.	**Assessment of risks and benefits** • There should be systematic assessment of risks and benefits to ensure favourable risk/benefit ratio
Justice • There should be fair distribution of research benefits and risks.	**Selection of participants** • Selection of participants must be unbiased such that there is fair distribution of research benefits and risks

2.2.5 US Code of Federal Regulations "Common Rule"

In 1981, the Department of Health and Human Services (DHHS) and the Food and Drug Administration (FDA) issued their regulations based on the Belmont Report. DHHS issued Code of Federal Regulations (CFR) Title 45 (public welfare), Part 46 (protection of human subjects). The US Federal Policy for the Protection of Human Subjects, also known as the "Common Rule" was published in 1991 (DHHS,1991; Williams, 2005). The regulations, 45 CFR part 46, (45 CFR 46) consists of four subparts: subpart A, basic HHS policy for protection of human research subjects; subpart B, additional protections for pregnant women, human foetuses, and neonates; subpart C, additional protections for prisoners; subpart D, additional protections for children and subpart E, registration of IRBs (45 CFR 46). The Common Rule led to the proliferation of IRBs to provide independent review of research involving human participants and requirements for obtaining and documenting informed consent (Emanuel et al., 2003).

The current section has highlighted the key international ethics codes and guidelines that were developed as a result of research scandals such as the Tuskegee Syphilis study (see 2.1.1) and Nazi medical war crimes (see 2.1.2). In conclusion, the Nuremberg Code (1947), Belmont Report (1979), Declaration of Helsinki (1964) and Common Rule (1981) formed the foundation for modern day research ethics guidelines. Today, several international and national ethical guidelines have been developed. Examples of other international ethical guidelines include the CIOMS (1993) guidelines and later revised in 2002 (and currently under revision), the International Conference on Harmonization-Good Clinical Practice (ICH-GCP) guidelines (1996), Nuffield Council on Bioethics (2002) guidelines on the ethics of research related to

healthcare in developing countries and WHO (2011) standards and operational guidance for ethics review of health-related research with human participants.

Having described the development of research ethics from an international perspective, the focus of the next section is to highlight the history and development of the South African research ethics system. This is important considering that the current thesis was aimed at analysing ethical issues raised by two South African biomedical RECs.

2.3 Research Ethics Review in South Africa

2.3.1 History of ethics review in South Africa

The history of ethics review in South Africa goes back to the mid-1960s. In 1966, John Hansen, professor of paediatrics at the University of the Witwatersrand, advocated for the establishment of the first-ever REC at his university. This REC has functioned continuously ever since (Cleaton-Jones & Wassenaar, 2010). From 1977, the number of RECs expanded with almost every South African university with a medical school having established its own REC. Similarly, the Department of Health, Medical Research Council, and South African Medical Association also established their own RECs. In 1995, a private REC named Pharma-Ethics REC was also established (Cleaton-Jones & Wassenaar, 2010). Currently, there are approximately 44 RECs operating in South Africa (NHREC, 2015). Some of the characteristics of the South African research ethics review system are that RECs are institutional and not regional as in some developed countries such as Sweden (Hedgecoe, Carvalho, Lobmayer & Raka, 2006); some are

private with no affiliation to any research institution (e.g. Pharma-ethics); some RECs were reported as dominated by doctors and health professionals (Moodley & Myer, 2007). Since 2006 there is a central national health research ethics council, the NHREC, which registers and audits all RECs in the country.

2.3.2 Legislative Context

Laws for the ethical conduct of research involving human participants exist in several countries. South Africa is no exception - all health-related research is regulated by legislation. Firstly, the South African Constitution Act (1996), states that "everyone has inherent dignity and the right to have their dignity respected and protected" (p. 6). Furthermore, in paragraph 12.2, the Constitution states that "everyone has the right to bodily and psychological integrity, which includes the right: (a) to make decisions concerning reproduction; (b) to security in and control over their body; and (c) not to be subjected to medical or scientific experiments without their informed consent" (p. 6). In other words, the Constitution's Bill of Rights requires informed consent to be obtained from the research participant before participating in any research. Furthermore, research on human participants in South Africa is guided by the National Health Act No. 61 of 2003.

The South African Research Ethics Committee (REC) system was legally established in 2005 in terms of the National Health Act 61 of 2003 (National Health Act, 2003). The legislation passed in 2005 in most respects merely legalized and formalized the features of an earlier South African ethics review system which had operated since the first REC in 1966 (Cleaton-Jones &

Wassenaar, 2010), and made it absolutely clear that it was obligatory for a health-related research proposal to obtain ethics review and approval from an REC before commencement (Department of Health, 2015). According to the National Health Act No. 61 of 2003, all health-related research projects must be submitted for approval by an REC registered with the NHREC. Section 73 of the National Health Act (2003) explicitly states that, "(1) Every institution, health agency and health establishment at which health research is conducted, must establish or have access to a health research ethics committee, which is registered with the National Health Research Ethics Council. (2) A health research ethics committee must (a) review research proposals and protocols in order to ensure that research conducted by the relevant institution, agency or establishment will promote health, contribute to the prevention of communicable or non-communicable diseases or disability or result in cures for communicable or non-communicable diseases; and (b) grant approval for research by the relevant institution, agency or establishment in instances where research proposals and protocol meet the ethical standards of that health research ethics committee" (National Health Act, 2003, p. 74). Furthermore, the National Health Act provides for the establishment of the NHREC appointed by the Minister of Health. The functions of the NHREC are to:

- "Determine guidelines for the functioning of health research ethics committees;
- Register and audit health research ethics committees;
- Set norms and standards for conducting research on humans and animals including norms and standards for conducting clinical trials;
- Adjudicate complaints about the functioning of health research ethics committees and hear any complaint by a researcher who believes that he or she has been discriminated

against by a health research ethics committee;

- Refer to the relevant statutory health professional council matters involving the violation or potential violation of an ethical or professional rule by a health care provider;
- Institute such disciplinary action as may be prescribed against any person found to be in violation of any norms and standards, or guidelines, set for the conducting of research in terms of this Act; and
- Advise the national department and provincial departments on any ethical issues concerning research" (National Health Act, 2003, p. 74).

2.3.3 Research ethics guidelines in South Africa

The first set of research ethics guidelines, entitled "Guidelines on Ethics for Medical Research" was produced by the South African Medical Research Council (SAMRC). These guidelines were not nationally binding on all researchers. In 2000, the national Department of Health produced Guidelines for Good Clinical Practice (GCP) which were updated in 2006 (Cleaton-Jones & Wassenaar, 2010; Department of Health, 2006). The section below briefly outlines the first South African national research ethics guidelines, i.e., the Department of Health (2004). (Note that the RECs studied in this study were at the time subject to the 2004 guidance, hence the 2004 guidance is described in detail below, despite a later version being published in 2015 (Department of Health, 2015). An online certificate-generating educational module based on the 2004 South African guidance was launched on the TRREE website (see http://elearning.trree.org/).

2.3.3.1 Department of Health guidelines (2004)

The Department of Health (2004) guidelines were based on some of the key international guidelines previously discussed. These guidelines are underpinned by three fundamental principles, including respect for persons, beneficence, and justice. The ethical principles contained in the Department of Health national guidelines (2004) are described below.

- Respect and dignity

The dignity, safety and well-being of participants should take precedence in all research involving human participants, i.e., the aim and goals of scientific research should not in any way override the an individual participant's dignity, safety and welfare. Furthermore, appropriate consideration should be given to the local language and cultural values of the communities in which research is conducted (Department of Health, 2004).

- Social value

The research to be conducted should have a social value to the participants and the community as well. In other words, it should be relevant to the local health needs (Department of Health, 2004). The research should be of benefit to participants and ultimately be a value to the research community by translating the research findings into mechanisms for improving the health status and healthcare system of South Africa (Benatar & Singer, 2010; Department of Health, 2004).

- Scientific Integrity

In order to ensure that health research is conducted in an ethically appropriate manner, investigators and ethical reviewers should ensure that proposed research has scientific validity.

This encompasses an extensive literature review of previous similar studies, results from preclinical studies, as well as a rigorous and appropriate methodology which can help to provide answers to the questions the research intends to investigate (Department of Health, 2004).

- Roles and responsibilities of the principal investigator

According to the Department of Health (2004) guidelines, principal Investigators (PIs) bear full responsibility for the scientific and ethical aspects of the planned research study. Furthermore, research should be conducted by a local investigator who is competent and qualified in terms of education, knowledge, certification and experience. When the study is in progress after ethical approval has been obtained from the relevant REC and/ or MCC, the PI should continue to be the means of communication between the trial sponsor and the local RECs. This involves reporting adverse events that may occur to the research participants (Department of Health, 2004).

- Informed consent

Research participants should give both verbal and written informed consent (Department of Health, 2004). However, there are exceptions to this requirement, for example in emergency situations or where the individual lacks the mental capacity. In that case, a waiver of informed consent can be granted only if the local REC is convinced that there is reasonable justification for the research to commence without obtaining individual informed consent. Furthermore, informed consent should be free from coercion and undue influence and participants should have the right to freely refuse to consent or withdraw consent from participation at any time without any prejudice Where a participant (e.g. children) lacks the capacity to consent, consent should be obtained from the parent or a legally authorized guardian (Department of Health, 2004).

- Privacy and confidentiality

Fundamentally, the privacy and confidentiality of research participants should be protected. This involves ensuring that personal identifying information including biological samples collected during the research process, are used, stored and or discarded in culturally appropriate manner that respects the privacy and confidentiality of the individual participants and the research community (Department of Health, 2004).

- Inclusion and exclusion criteria

There should be fair participant selection. Recruitment of participants must not unfairly exclude participants because of race, gender, age, sex, ethnicity or beliefs (Department of Health, 2004).

- Risk and benefits

The guidelines require that RECs should assess the risk and benefits of the study. Assessment of risk/benefit ratio should address the potential benefits and the associated physical, social and psychological risks of the study. Furthermore, vulnerable populations whose participation in research may pose greater risk, for example pregnant women and infants, should be protected (Department of Health, 2004).

- Dissemination of study results

The dissemination of research findings or results to participants has widely gained recognition as an ethical research practice (Emanuel et al., 2004). According to the Department of Health guidelines, there is an obligation for researchers and investigators to disseminate research results in a timely and competent manner. However, there is need to ensure ethical dissemination in

order to protect vulnerable populations from risk of harm and stigmatization that may emanate from the findings (Department of Health, 2004).

- Standard of care

Standard care implies the provision of equal standards of medical care and healthcare facilities for all participants, equal respect and dignity for all participants, equal follow-up facilities (e.g. referrals and treatment for research related injuries) for all participants when the research study is completed and equal access to on-going medical care (Benatar & Singer, 2010; Shapiro & Benatar, 2005). The obligation to ensure the provision of equal standards of medical care to all participants during research is based on the fundamental ethical principles of beneficence - promoting the welfare of participants (Stobie & Slack, 2010) and reciprocal justice (Macklin, 2006). Notwithstanding debates about the appropriate standards of care in developing countries such as South Africa (Essack, 2014; Ngongo et al., 2012; Slack, 2014), it is generally accepted that the obligation to provide optimal care and treatment to research participants is an ethical imperative. There should be transparent collaborative engagement and consultative process between trial sponsors and researchers, local governments, non-governmental organizations, communities in order to agree on who will provide care and treatment and how these will be financed and sustained (UNAIDS, 2012).

- Standard of prevention in HIV prevention trials

Standard of prevention refers to the comprehensive package of HIV risk reduction methods provided to participants in HIV prevention trials. One of the heated debated about HVTs is related to the question of what prevention methods or modalities need to be included as the

standard of prevention (Essack, 2014; Essack et al., 2010). Researchers are faced with ethical dilemmas when new HIV prevention methods such as pre-exposure prophylaxis (PrEP) prove to be significantly effective. The main concern in such a scenario is that a comprehensive standard of prevention package will seriously impact the results for trials of new HIV prevention interventions (Macklin, 2008, 2009). In this case, researchers are faced with a conflict between ensuring maximum HIV risk reduction in order to promote the welfare of the trial participants and the scientific goals of the research to obtain meaningful results. Secondly, the other ethical concern would be regarding the safety and the high risk of interactional or antagonistic effects when more and more HIV prevention methods become available and used in combination (Dawson, 2012). The UNAIDS/ WHO 2007 guidelines recommend that "researchers should engage appropriate stakeholders in tailoring the design, implementation and oversight of risk-reduction interventions addressing the specific needs and risks of trial participants in a given community" (p. 46).

- Safety monitoring

The ethical guidelines necessitate monitoring of approved research in order to identify adverse events occurring during and after the research so that immediate remedial action can be taken to guarantee the safety and wellbeing of participants (Department of Health, 2004). In most cases, REC often require sponsors and the investigator to furnish in their protocol details about the Data Safety Monitoring Board (DSMB) which should independently monitor and report any adverse events occurring during and after the trial. However, literature suggests that many RECs in developing countries do not have the resources to adequately monitor approved research (Boateng, Ndebele & Mwesiga-Kayongo, 2014).

2.3.3.2 Department of Health (2015) guidelines

The Department of Health (2015) guidelines are an updated and revised version of the (2004) guidelines mentioned above. It must be noted that they were not yet in effect when the study described below was conducted; the RECs in question were subject to the Department of Health (2004) guidance. The principles of the Department of Health (2015) guidance are described below.

- Relevance and value

Research should be have relevance and be responsive to the health needs of populations of South Africa. The proposed research should describe the anticipated contribution to knowledge generation and, ideally how the results of the study can be translated into products, interventions or services likely to benefit and enhance the lives and wellbeing of people in South African.

- Scientific integrity

The study must have sound design and methodology that can reliably achieve the objectives of the study. The guidelines state that poor study design can expose participants to unnecessary risk and harm.

- Role player engagement

There should be meaningful prior engagement of relevant research stakeholders before conducting research.

- Favourable risk/benefit ratio

The proposed study should have a favourable risk/benefit ratio. In other words, the potential risk of harm to a participant should be outweighed by the likelihood of benefit to the participant or the knowledge likely to be yielded from the research.

- Fair selection of participants

There should be fair and just selection of research participants based on objective criteria. No persons or groups should be included or excluded as research participants merely on the grounds discrimination, for example according to race and religion.

- Informed consent

Voluntary informed consent should be obtained from an individual before they can be enrolled into research.

- Ongoing respect for enrolled participants

This includes for example the need to guarantee the privacy and confidentiality of enrolled research participants.

- Researcher competence and expertise

Researchers must be appropriately qualified and competent to carry out the proposed research. Principal investigators should ensure that the safety and wellbeing of participants is guaranteed throughout the study. Furthermore it is the principal investigator's responsibility to ensure that the research is of high scientific validity.

2.3.3.3 Department of Health (2006) Good Clinical Practice guidelines

The Department of Health guidelines for good clinical practice (GCP) were first established in 2000 and then revised in 2006 (Cleaton-Jones & Wassenaar, 2010). The guidelines describe the following guiding principles:

- Study rationale and motivation

The rationale and motivation of proposed research should ask relevant and important questions.

- Study design

The study design in the research proposal should demonstrate a high probability for providing answers to specific research questions.

- Investigator competence

The principal investigator should be technically competent to conduct the proposed research.

- Balance of harm and benefit

There should be a risk/benefit assessment to ensure that there is a favourable risk/benefit ratio.

- Transparency

Researchers have an ethical obligation to register the trial and report on the study results with honesty and transparency.

- Privacy and confidentiality

Measures should be implemented to protect the privacy and confidentiality of research participants.

- Ethical review

There should be prior independent ethical review of proposed research by local RECs.

- Informed consent

Researchers must ensure that voluntary informed consent is obtained from each prospective research participant before enrolling them into research.

- Safety monitoring

It is an ethical requirement to ensure ongoing monitoring of the safety of participants during and after a clinical trial. This involves monitoring and reporting and appropriate management of serious adverse events.

- Multi-centre studies

The design of multi-centre studies should be appropriate for the local setting. Furthermore, the study should ensure similar standards of care for both the sponsoring country participants and South African participants. Additionally, there should be appropriate incentives for trial participants (Department of Health, 2006).

This section has briefly described the South African research ethics system, highlighting its history, legislative context and the applicable national ethical guidelines used by RECs and researchers in ensuring that research with human participants conducted in the country is of high ethical and scientific standards. While many countries, including South Africa, have implemented laws and guidelines mandating ethics review of research with human participants (Department of Health and Human Services, 2016), there have been numerous complaints and criticisms of mandatory ethics review (Mamotte & Wassenaar, 2009). The following section will review some of the literature on this debate.

2.4 Resistance to mandatory REC ethics review

Mandatory ethics review for human participant research does not always result in satisfaction, at least from researchers. While only a handful would categorically argue against the value of independent ethics review, there is considerable literature and scholarly commentary indicating researchers' frustrations and complaints in navigating the ethics approval process by RECs (Abbott & Grady, 2011). For example, RECs are often criticized for being too bureaucratic (Israel, 2013), with cumbersome paperwork (Jamrozik, 2004) and stifling research (Snooks et al., 2012). Furthermore, RECs have often been criticized for variability and inconsistency in interpreting ethical guidelines and the decisions they make when reviewing protocols (Abbott & Grady, 2011; Angell, Sutton, Windridge & Dixon-Woods, 2006; Edwards, Stone & Swift, 2007; Lux, Edwards & Osborne, 2000; Stark, Tyson & Hibberd, 2010). RECs have also been criticized for lacking appropriate ethics expertise and training to adequately review protocols, for too much tinkering with consent documents and requesting trivial amendments (Whitney et al., 2008), and

not adequately dealing with the main ethical issues that such committees were actually put in place to address (Emanuel et al., 2004; Iltis, 2009a) and idiosyncratic decision-making (Stark, 2012; Tolich, 2014).

Similarly, mandatory ethics review of social science has also been heavily criticized (de Vries, de Bruin & Goodgame, 2004; Schrag, 2011; Wassenaar & Mamotte, 2012). One of the criticisms levelled against RECs is the power that they have to reshape proposed research, in particular, although not at all exclusively, for qualitative research designs (Librett & Perrone, 2010; Tolich & Fitzgerald, 2006). Several reports describe how research proposals have been disapproved because of inappropriate interpretations of ethical norms that were applied incorrectly to the proposed research (Dingwall, 2008; Librett & Perrone, 2010). For instance, Librett and Perrone (2010) decry how their proposals were disapproved by an REC and how the review process fundamentally reshaped the original methodology and direction of the research. Furthermore, some have complained about how the medical model has extended into such areas as social science, a consequence of so-called “ethics creep” (Haggerty, 2004).

Some social scientists have also criticized ethics review in disciplines such as journalism. For example, Dash (2007) in his paper titled, “Journalism and institutional review boards”, opposes any IRB oversight for academic work on journalism done by professors and journalism students in any academic institution, arguing that the tendency for IRBs to require anonymity for persons interviewed immediately reduces the credibility of any journalistic story. The main concern here is the perception by social scientists academics that they are being subjected to stringent rules

over how and what they can investigate, and hence infringing on their academic freedom (Dingwall, 2008; Hamburger, 2005; Hammersley, 2009; Hedgecoe, 2015; Katz, 2007; Scott & Fonseca, 2010; Tierney & Corwin, 2007).

Another concern expressed by opponents of ethics review of social science research is the perception that social science research has relatively low risk or no risk and that these risks are different from the risks posed by biomedical research (Dingwall, 2008; Haggerty, 2004; Hammersley, 2009). Furthermore, RECs are sometimes viewed as a barrier which blocks responsive research as a result of the cumbersome administrative burden created by ethics application, considering the already limited time that academics have to conduct research within timeframes and funding periods. Opponents argue that this restrictive administrative burden placed on them drastically limits the capability of social science researchers to respond to and investigate rapid social changes, particularly during social crisis (Hemmings, 2006; Hammersley, 2009).

Another criticism raised by opponents of ethics review of qualitative research is that RECs lack an understanding of and sensitivity towards the unique research designs and methodological underpinnings of qualitative research studies (Librett & Perrone, 2010; Tolich & Fitzgerald, 2006; Van Den Hoonaard, 2003; Wynn, 2011). The key concern here is that some ethical principles are difficult to implement, for example, in ethnographic study designs, which makes such qualitative methods less likely to be approved using a one-size-fits-all model of ethics review. For example, Van Den Hoonaard (2003) maintains that while anonymity is a widely

recognized ethical requirement highlighted in several research ethics guidance, it is a practically unattainable in ethnographic and qualitative research designs. In addition, some commentators argue that the informed consent requirements render ethnography generally impossible as it 'denaturalises' the research settings and environment being researched, converting it into a formal research encounter instead of its intended goal, which is to explore people and culture as it occurs naturally (Murphy & Dingwall, 2007). Consequently, there have been suggestions that, owing to the substantial methodological differences between qualitative research and the positivistic paradigm, ethnographic studies be assessed for ethical suitability using a different review process to the quantitative positivistic approach (Librett & Perrone, 2010).

An additional argument raised by opponents of ethics review of social science research is that there is substantial lack of consensus in research communities regarding 'appropriate ethical practice', criticizing the idea that RECs – a gathering of members constituted to review and approve research - are well suited to make determinations on ethical decisions (Hammersley, 2009). He further argues that the interpretation of general ethical principles must be context-dependent, i.e., consideration should be given to the specifics of a local research setting and methodological expertise. In his view it is not RECs who possesses this knowledge, rather it is the researchers themselves. For these reasons, Hammersley argues that RECs are unsuited to conduct ethics review. In his view, the regulatory framework on which RECs are grounded is counterproductive when, or because, it prevents researchers from the need and the practical process of reflecting on the ethical considerations raised by, and during, their own research (Hammersley, 2009). More recently, Dyck and Allen (2012) argued that mandatory ethics review

is in itself unethical because “review boards do not respect researchers or each other, lack merit and integrity, are not just and are not beneficent” (p. 1).

While it is beyond the scope of this study to rebut arguments against mandatory ethics review of social science – or any research for that matter, the present researcher is of the view that some arguments by social scientists against ethics review may be misguided. For example, arguments by social scientists resisting ethics review of psychology research on the view that research ethics is meant only for biomedical research are “simplistic and overlook the fact that biomedical research and psychological research cannot be judged by different moral standards” (Wassenaar & Slack, 2016, p. 307). In addition, closer analysis of cases raised by critics suggest that complaints arise out of single cases, rather than out of consistent attempts to evaluate criticisms of REC processes across a representative sample of cases.

Several proposals have been made to deal with some of the criticisms levelled against RECs (Emanuel et al., 2004; Klitzman, 2015). For instance, centralized ethics review (Abbott & Grady, 2011) has been proposed to address the allegedly unnecessary delays and costs, and variations experienced by investigators submitting similar protocols in multi-site studies. Proponents of a centralized system of ethics review argue that this will result in more efficient reviews in multisite studies (Fitzgerald & Phillips, 2006). Under the new proposed changes to the US regulations for human research, certain types of research will no longer require REC review (Emanuel, 2015).

The current section has reviewed some of the literature critiquing mandatory ethics review. This section highlighted that while the importance of ethics review and protecting human participants is acknowledged, there are several complaints regarding mandatory ethics review of research, particularly by social scientists whom continue to debate the suitability and relevance of research ethics/and or ethics review to social science research (Mamotte & Wassenaar, 2009). The next section reviews literature on the ethical issues of international biomedical research (Emanuel et al. 2004, 2008; Lavery et al., 2007). For the purposes of this present study, that is, to facilitate clear discussion of the findings (see Chapter 7), these topics will be set out below as follows: collaborative partnership, social value, informed consent, vulnerability, scientific validity, favourable risk/benefit ratio, payment of research participants, standards of care, ancillary care, post-trial access, compensation for research-related injury, post-approval monitoring of studies and dissemination of results.

2.5 Ethical issues in international biomedical research

2.5.1 Collaborative partnership

The principle of collaborative partnership in international biomedical research has gained wide recognition as an important ethical requirement (Emanuel et al., 2004; Lavery et al., 2007; Mamotte, Wassenaar, Koen & Essack, 2010; UNAIDS/AVAC, 2011). Advocates of collaborative partnership between key stakeholders in health research in developed countries with investigators, sponsors, researchers, policy makers and host communities argue that such consultation and engagement may help to minimize concerns about exploitation (Emanuel et al., 2004). Such collaborative partnership involves ensuring that research stakeholders in the

developing country are allowed to determine for themselves whether proposed research sponsored by developed countries and conducted with human participants in developing countries is relevant and responsive to the host community's health needs (Emanuel et al., 2004; Lavery et al., 2007). This means that, first and foremost, there should be no exploitation of the research communities in less developing countries. That is, the host country in which research could be conducted ought to autonomously determine if the proposed research is acceptable and relevant to the health problems of the community (Emanuel et al. 2004; Lavery et al., 2007). This can be achieved through establishing meaningful partnerships and engagement with the research enterprise- including communities in assessing health problems to be solved, determining the significance of proposed research, as well as the actual planning and implementation of research, and incorporating results and products emanating from research into local healthcare system (Benatar & Singer, 2010; Emanuel et al., 2004; UNAIDS/AVAC, 2011).

Furthermore, collaborative partnership involves strengthening of local research stakeholder capacity to synthesise and disseminate evidence to be used for policy making and health care. Furthermore, the local community's values, culture, traditions, language as well as the social context, and differences thereof, should be respected (Dickert & Sugarman, 2005). Additionally, a collaborative partnership entails the sustainable development of local capacity so that there is equal and full partnership in order to circumvent pervasive inequalities between developed and less developed countries (Benatar & Singer, 2010).

Weijer and Emanuel (2000) argue that the ethical goal of community engagement in research is to ensure the protection if research participants and communities. Other commentators have also

argued that the main goals for community engagement are to ensure protection, respect, empowerment and partnership building (Dickert & Sugarman, 2005; Participants in the community engagement and consent workshop, Kilifi, Kenya, 2013; Tindana et al., 2007).

Dickert and Sugarman (2005) proposed four ethical goals that provide a framework which can be used by various stakeholders (researchers, sponsors, RECs, and communities) to evaluate community engagement processes. These include "(1) enhanced protection, (2) enhanced benefits, (3) legitimacy, and (4) shared responsibility". First, community engagement processes must be designed and carried out in order to help identify risks for individual research participants and communities as well as to identify additional measures for ensuring the protection and safety of research participants. Furthermore, community engagement can enhance the protection of non-participants through the identification of potential risks for community members who are not enrolled in the research project.

Community engagement, for example through community advisory boards (CABs), should help to enhance benefits to individual research participants in accord with the principle of beneficence. In addition, community engagement can also benefit local communities from which research participants are recruited. Third, by allowing various stakeholders to express their views and concerns, community engagement may help to "confer ethical and political legitimacy" on a particular research study. However, achieving this goal may encounter a number of unresolved complex questions such as, what counts as a community? Who counts as a representative? What level of community support is needed to legitimize a particular study? Fourth, community engagement enables shared responsibility between researchers and the

community. For example, CABs may play an active role in assisting investigators to recruit participants and ensure that the informed consent process is conducted in a linguistically and culturally sensitive manner (Dickert & Sugarman, 2005).

King, Kolopacket, Merritt and Lavery (2014) propose an ethical framework for community engagement which seeks to clarify what kinds of community engagement strategies contributes to the ethical quality of research. The framework is premised on the view that relationships between health researchers and community stakeholders in international health research studies are the foundation of meaningful engagement. The authors argue that it is primarily through the researcher-community stakeholder relationships that investigators are able to address three core ethical responsibilities: "1) identifying and managing non-obvious risks; 2) extending respect beyond the individual to the stakeholder community; and building legitimacy for the research project" (p. 3). In their view, King et al (2014) maintain that these three ethical goals collectively characterize a logical and comprehensive framework that elucidates the important role of community engagement in international health research, and may perhaps serve as a useful reference for the on-going debate about how to evaluate the quality and impact of community engagement.

While the concept of community engagement has received much attention (Lavery et al., 2010; Marsh, Kamuya, Rowa, Gikonyo & Molyneux, 2008; Nakibinge et al., 2009; Newman, 2006; Newman & Rubincam, 2014; Newman et al., 2015; Participants, 2011; Tindana et al., 2007), there is a lack of consensus on the metrics for systematically evaluating community engagement (MacQueen et al., 2015). Furthermore, there is less empirical research on the salient aspects of

community engagement (Marsh et al., 2008, 2010) and there are unresolved questions about what makes a meaningful community engagement (King et al., 2014; MacQueen et al., 2015). Several authors in African countries, particularly at the Kenya Medical Research Institute-Welcome Trust Programme have conducted empirical studies on community engagement. For instance, Marsh et al. (2008) reported a case study in which they attempted to initiate community engagement in Kilifi, Kenya. They report that one of the important components of their community engagement strategy established through a series of consultative activities was the establishment of a representative local resident network in different geographic locations commonly involved in research, to supplement existing communication channels (Marsh et al., 2008).

A recent review of community engagement strategies used in research in three African countries (Botswana, South Africa, and Zimbabwe) found that there were various strategies used such as formative research activities, traditional or community leaders support, community stakeholder partnership, community sensitisation and education, community advisory mechanisms, and community empowerment (Musesengwa & Chimbari, 2016). Another review of the community engagement for biomedical and genomic research in Africa by Tindana et al. (2015) found that there was a lack of uniformity on how the concept of community engagement is defined in literature. The authors report found that there was the concept of community engagement was sometimes used interchangeably with community based participatory research to engage the target community and actively participating in the identification and planning of relevant research and disseminating the findings. The review found that CABs were commonly used as a community engagement strategy (Tindana et al., 2015). For genomic research, the review also

found that there was a range of strategies for community engagement such as the use of community representatives, CABs, and direct engagement with potential research participants and their communities (Tindana et al., 2015).

Several empirical studies have been conducted to investigate the role of African CABs in community engagement (Morin, Maiorana, Koester, Sheon & Richards, 2003; Reddy, Buchanan, Sifunda, Shamagonam & Naidoo, 2010). One qualitative study conducted in South Africa aimed at investigating the views of investigators, CAB members, research staff and RECs found that there were differences in stakeholders' views of the roles and responsibilities of CABs (Reddy et al., 2010). Another study by Morin et al. (2003) involving 6 research sites of the HIV Prevention Trials Network (HPTN) in US, Zimbabwe, Peru and Thailand found that there were two models, i.e. the "broad community" and "population-specific" models for the involvement of CABs in representing research participants in HIV prevention trials in these settings. Furthermore, the study found that CABs believed that their role was to act like a bridge between the researchers and trial participants. Additionally, the study found that CABs actively played a meaningful role in improving HIV prevention clinical trials by assisting in protocol development, recruitment, and retention, as well as involvement in identifying and resolving ethical issues in clinical trials (Morin et al., 2003).

2.5.2 Social Value

Social value has gained wide recognition as a benchmark of ethical research (Emanuel et al., 2004; Habets, van Delden & Bredenoord, 2014). According to Emanuel et al. (2004), social value in health research has four characteristics 1) specifying who the beneficiaries of research are, 2) outlining the potential value of the research for each of the prospective beneficiaries, 3) enhancing the value of research through, for example, dissemination of knowledge, product development, long term research collaboration and health systems improvements, and 4) ensuring that the conduct of research does not supplant the host country's existing healthcare system (Benatar & Fleischer, 2007; Emanuel et al., 2004).

Despite its acceptance as a benchmark of ethical research (Emanuel et al., 2004), there is considerable disagreement about the notion of social value, for example, how social value can be achieved and who is responsible for ensuring that it is attained (Lairumbi et al., 2008). Further unsolved questions include: Is social value a necessary requirement for ethical research? What makes research socially valuable? How does the social value of research relate to its scientific value? Does the social value of research pertain to the potential value of study interventions, research studies or research programs? Should social value be considered as a threshold condition for research to proceed, or should a given project's social value be reasonable in relation to other considerations, such as the risks to participants? (Rid & Shah, 2015). In the absence of clear-cut guidance from existing research ethics guidelines, such questions are likely to continue posing challenges for sponsors, investigators, RECs and regulatory bodies particularly where the justification for the proposed research may not necessarily be for the benefit of individual participants, but for the general population (Lairumbi et al., 2008).

There is a growing literature exploring social value in African settings (Lairumbi et al., 2008; Lairumbi, Parker, Fitzpatrick & English, 2011a; Lairumbi, Parker, Fitzpatrick & English, 2012; Lairumbi, Parker, Fitzpatrick & Mike, 2011b). One study in Kenya found that stakeholders viewed social value as benefit-sharing, for example, through post-trial access to research products and medical care, technology transfer and building local capacity, and societal benefits emanating from the successful completion of research (Lairumbi et al., 2011a). In a separate study, Lairumbi et al. (2011b) reviewed existing research ethics guidelines and found considerable inconsistency in how guidelines address the issue of social value and benefits entitled to participants and host communities in international biomedical research. Another Kenyan study by Kamunya et al. (2014) found that research participants were gratified by the benefits, particularly health care benefits, derived from participation in research. Furthermore, research participants viewed fieldworkers and researchers as the gatekeepers and conduits of benefits. The same study found that fieldworkers and researchers had difficulty ignoring participant and community requests for more benefits, especially in situations of extreme poverty (Kamunya et al., 2014).

Habets, van Delden and Bredenoord (2014) proposed that the concept of social value be limited to denote the anticipated improvement resulting from a particular intervention. The authors propose to use the concept “anticipated social value” which implies that the social value lies in the nature and magnitude of the improvement the intervention is expected to have on the wellbeing of patients, individuals in society, or society. Wenner (2015) criticized the existing guidelines for not distinguishing between those benefits which can justify the conduct of research in LMICs and those which cannot. The author argues that the justification for research

with human participants is primarily grounded in the value of the knowledge pursued, and that this social value of research generated knowledge should be contextualized, and that existing ethical guidance and frameworks on the concept of social value and benefits fails to appreciate that the value is highly context-dependent. The authors propose a framework for the assessment of benefits deriving from research assigned to host communities in developing countries in which the types of research conducted in such settings is limited (Wenner, 2015).

2.5.3 Informed Consent

Informed consent is widely recognized as the cornerstone for ethical clinical research involving human participants (Grady, 2015; Lindegger & Richter, 2000; Emanuel et al., 2004). Informed consent has its origins in the 1947 Nuremberg Code which states that "the voluntary consent of the human subject is absolutely essential" (p. 1). The principle of respect for persons underpins the requirement for informed consent (Belmont Report, 1979). Appelbaum, Lidz and Klitzman (2009) maintain that the informed consent process allows a potential research participant to make a meaningful choice whether or not to participate in research and should thus reflect the will or intention of the individual providing consent, not of other persons. The following are essential components of valid informed consent: information disclosure, understanding and voluntariness (Lindegger & Richter, 2000).

2.5.3.1 Information disclosure

Complete, accurate and understandable information should be appropriately provided to participants prior to participation in clinical trials. In other words, participants should receive the

necessary information to make an informed choice about their participation. According to the US Common Rule, 45 CFR 46 guidance on informed consent, the informed consent documents should have a clear description of information containing the following minimum requirements; (1) A statement that the study involves research, an explanation of the research, and the expected duration of the subject's participation, a description of the procedures to be followed, identification of any procedures that are experimental, (2) a description of any reasonably foreseeable risks or discomforts to the research participant, (3) benefits anticipated from research, (4) any alternative procedures or treatments to study participation, (5) a statement describing the extent, if any, to which confidentiality of records identifying the research participant will be maintained, (6) an explanation as to whether any compensation and/or medical treatment are available if injury occurs and, if so, what they consist of, or where further information may be obtained, (7) contact details of the relevant persons to ask questions or report serious adverse events, and (8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the research participant is otherwise entitled, and the participant may discontinue participation at any time without penalty or loss of benefits to which the participant is otherwise entitled (DHHS, 1991).

However, for the informed consent process to be truly ethical and valid, it demands more than just disclosure of the eight pieces of information (Flory & Emanuel, 2004). The information should be disclosed in a culturally and linguistically appropriate manner (Emanuel et al., 2004). Moreover, the need for additional community and familial consent procedures where it is culturally appropriate and necessary should be respected; however this should not override individual consent (Emanuel et al., 2004; Lindegger & Richter, 2000).

2.5.3.2 Comprehension of informed consent

Understanding of consent information is a condition that must be adequately satisfied before potential research participants can give their informed consent (CIOMS, 2002; Department of Health, 2015, WMA, 2013). However, several empirical studies have suggested that participants often do not fully understand information provided during the informed consent process, both in developed (Falagas, Korbila, Giannopoulou, Kondilis & Peppas, 2009; Flory & Emanuel, 2004; Joffe, Cook, Cleary, Clark & Weeks, 2001; Sanchini, Reni, Calori, Riva & Reichlin, 2014; Smith & Fogarty, 2016; Tam et al., 2015) and developing countries (Afolabi et al., 2014; Chaisson, Kass, Chengeta, Mathebula & Samandari, 2011; Krosin, Klitzman, Levin, Cheng & Ranney, 2006; Lynoe, Hyder, Chowdhury & Ekstrom, 2001; Molyneux, Peshu & Marsh, 2004; Molyneux, Wassenaar & Peshu, 2005; Naanyu, Some & Siika, 2014; Ndebele, Wassenaar, Masiye & Munalula-Nkandu, 2014c; Taiwo & Kass, 2009; Pace et al., 2005a, 2005b).

Participants' understanding of the terms randomization, double-blinding, and placebo was investigated and it was found that the approximately 85% of respondents showed understanding of randomization, placebo use (72%), and double-blinding (68%). Overall, the study found that 61% of respondents attained low scores on a collective understanding of all the three concepts (Ndebele et al., 2014c). Another study in Uganda assessed parents' understanding of the trial and found that while a substantial percentage (77%) of respondents reported remembering being told about the study's purpose, the required number of visits (88%), the risks involved (61%), treatment allocation (84%), and their ability to discontinue their children's participation (64%). Only 18% could name the possible side-effects of the study drugs, and only 19% knew that children would be randomized to different treatment arms (Pace et al., 2005b).

Furthermore, reports have also suggested that research participants may often fail to understand that the trial may not benefit them personally even when they have been informed that they are participating in a research study which is not part of routine clinical care, the so-called therapeutic misconception (Lidz, Appelbaum, Grisso, & Renaud, 2004; Miller & Joffe, 2006). Several commentators have also raised concerns that the increasing length and complexity of participant information sheets and informed consent forms are impeding understanding (Franck & Winter, 2004; Pilgaard & Ravn, 2012; Taylor & Bramley, 2012). For instance, a study by Kass, Chaisson, Taylor and Lohse (2011) found that adult HIV trial consent forms had median length of 27 pages and the mean readability was 9.2 grade level. Klitzman (2013a) qualitatively studied 60 US IRB chairs on how they view and make decisions about informed consent. He found that IRBs encountered challenges and dilemmas regarding consent documents, particularly when deciding what and how much should be included in the consent forms.

Several investigators have reported on mechanisms to help improve participant understanding of the informed consent information in settings where factors such as cultural background, illiteracy and language barriers hinder sufficient understanding of consent information by participants (Penn & Evans, 2010; Fitzgerald, Marotte, Verdier, Johnson & Pape, 2002; Flory & Emanuel, 2004; Lindegger et al., 2006; Molyneux, Gikonyo, Marsh & Bejon, 2007; Ndebele, Wassenaar, Munalula-Nkandu & Masiye, 2012; Nishimura et al., 2013; Vallely et al., 2010. A study by Ndebele et al. (2012) implemented a mixed narrative intervention (such use of vignettes in explaining the trial concepts and colourful pictures to supplement written information) to improve participant understanding. Their intervention was effective in improving participant understanding of trial concepts, namely randomization, double-blinding and placebo.

Another study assessed the impact of three different interventions i.e., 1) enhanced standard consent forms, 2) context-specific consent forms, and 3) context-specific counselling cards on participant understanding of informed consent by 297 pregnant women enrolled in an HIV prevention trial in Malawi. The study found that, both immediately post intervention and at 1-week follow-up, participants assigned to groups 2 and 3 understood more about research concepts and study procedures compared with group 1, suggesting that context-specific approaches contributed to improved participant understanding of consent information when compared to enhanced standard consent form (Corneli et al., 2012). Three consent interventions were developed and their effectiveness in improving participant understanding of the consent information was assessed. Group 1 participants received a bulleted fact sheet summarizing key study information, group 2 received the bulleted fact sheet in addition to engaging in a feedback question and answer (Q&A) session and the control group received standard consent procedures. The study reported that participants receiving the second intervention scored 7.6 % points higher on open-ended questions about understanding than participants in the control group, suggesting that both bulleted fact sheets and Q&A sessions can significantly contribute to improving participant understanding compared to standard consent (Kass et al., 2015).

However, a study by Paris et al. (2015) assigned 241 patients to receive a standard informed consent document and 240 patients a modified informed consent. The authors reported that there was no difference between the two groups for the score of objective comprehension, suggesting that enhancing informed consent documents had no effect on participants' understanding. The authors noted that rate of enrolment in the clinical study was lower in the group that received the modified informed consent than for the standard informed consent. The authors concluded that,

“In attempts at improving potential participants' understanding of clinical research information, efforts and future trials should focus on other ways to improve comprehension” (Paris et al., 2015, p. 1010).

2.5.3.3 Voluntariness

Voluntary informed consent is a requirement in several ethical guidelines (Nuremberg Code, 1947; Belmont Report, 1979; CIOMS, 2002; Department of Health, 2015; WMA, 2013). For instance, the Nuremburg Code (1947) states that, “The voluntary consent of the human subject is absolutely essential. This means that the person involved should … be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion” (p. 1).

Although several international and national guidelines emphasize the need for voluntary consent, their definition of voluntariness is somewhat inconsistent and there is limited guidance on how to assess voluntariness (Mamotte & Wassenaar, 2015, 2016). Firstly, these guidelines generally regard voluntariness as the absence of coercion and undue inducement, yet fail to explicitly define either term or set out the critical features of such terms (Emanuel, 2005; Mamotte & Wassenaar, 2015). Such a deficiency in clarity could further exacerbate the ongoing controversy about coercion and undue influence in research (Emanuel, 2005; Klitzman, 2013c). Furthermore, some guidelines, for example the SA MRC (1993) and SA GCP (2006) regard financial incentives as factors undermining voluntariness, but without clear articulation of how these incentives actually reduce voluntary consent.

For some commentators, the use of incentives *per se* does not automatically constitute undue inducement. (Emanuel, 2005) argues that compensation is coercive only when it distorts a participant's reasoning to the extent that they take risks they would not ordinarily be willing to take. Similarly, Largent, Grady, Miller and Wertheimer (2012) argue that misplaced concerns about money ad inducements may inadvertently distort ethically acceptable incentives and impede valuable research.

While there is a substantial body of literature on the concept of voluntariness (Appelbaum, 2011; Appelbaum, Lidz & Klitzman, 2009; Mamotte & Wassenaar, 2015, 2016; Miller et al., 2011; Nelson et al., 2011, Nelson & Merz, 2002; Pace & Emanuel, 2005), there is a lack of consensus in the ethical models or frameworks on the standards for assessing voluntariness of consent (Mamotte & Wassenaar, 2015). There are various conceptualizations of what exactly constitutes voluntary consent (Mamotte & Wassenaar, 2015, 2016). For instance, Beauchamp and Childress (2009) define voluntariness as when a person "wills the action without being under the control of another's influence" (p. 132). Nelson et al. (2011) theorizes voluntariness as constituting intentional action and substantial freedom from internal (e.g. mental illness) and external controlling influences (e.g., payments, threats, deceit, manipulation, persuasion and coercion). Furthermore, the model posits that constraining situations (e.g., lack of resources, powerlessness and severe illness) may unintentionally cause a person to act involuntarily.

However, some commentators have critiqued Nelson et al.'s (2011) approach. For instance, Bull and Lindegger (2011) argue that voluntariness must, in addition to external influences, take into consideration the participant's subjective experiences of voluntary consenting, given the

complex political, cultural, social, and economic factors and power relations between researcher and participant, which may impact the voluntariness of decision-making process. Similarly, some authors also suggested that social norms and culture (e.g., decision-making by community leaders or family members) and social relationships (e.g., patient-researcher trust) are, indeed, common contextual correlates of voluntary informed consent in Kenya and other low resource settings (Kamunya, Marsh & Molyneux, 2011), and developed countries (Miller & Nelson, 2012).

Factors that have been implicated as possibly negating voluntariness include financial compensation in return for research participation (Kass, Maman & Atkinson, 2005; Koen, Slack, Barsdorf & Essack, 2008; Kwagala, Wassenaar & Ecuru, 2010; Mamotte & Wassenaar, 2016), recruitment of participants by their health care providers (Appelbaum, Lidz & Klitzman 2009), and limited access to medical care and treatment (Kass et al., 2005; Mamotte & Wassenaar, 2016; Nelson & Merz, 2002; Pace et al., 2005a). For instance, a study conducted in Thailand by Pace et al. (2005a) reported that approximately 43 of 141 participants enrolled in randomized HIV treatment trial felt under pressure to participate because of their health status. Of these, 10 respondents reported that the trial was the only way for them to access treatment (Pace et al., 2005a).

Another study reported that 75% of participants felt moderate or a lot of pressure to participate in the phase I study due to their growing cancer, whereas 7% said they felt pressure to participate from the study investigators and 9% felt such pressure from their families (Agrawal et al., 2006). A South African study by Barsdorf and Wassenaar (2005) assessing the perceptions on the

voluntariness of research participants found that black respondents perceived consent to be less voluntary than did white or Indian respondents. Another recent South African study assessing voluntariness in HIV clinical trials found high levels of perceived voluntariness with the majority of participants reporting an absence of controlling influences from other people. The authors reported that there was a significant association between lower perceived voluntariness and feeling of having no choice but to participate (Mamotte & Wassenaar, 2016).

2.5.4 Vulnerability

Vulnerability is a widely recognized ethical concern in biomedical research involving human participants (Ballantyne & Rogers, 2007; Coleman, 2009; DuBois, 2006; Horn, 2007; Horn, Sleem & Ndebele, 2014; Hurst, 2008; Iltis, 2009b; Lange, Rogers & Dodds, 2013; Macklin, 2012; Tangwa, 2009). Several research ethics guidance (e.g., CIOMS, 2002; Department of Health, 2015; WMA, 2013) have a section on vulnerable populations and emphasize the need to protect vulnerable populations in research. For instance, the Declaration of Helsinki (2013) states that, "Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm. All vulnerable groups and individuals should receive specifically considered protection…" (p. 3). Although several international and national guidelines mention vulnerable populations, there is seemingly lack of consensus on the definition of vulnerability and standards for identifying and addressing the concept of vulnerability (Coleman, 2009; DuBois, 2006; Lange et al., 2013). Furthermore, there is little empirical research on the concept of vulnerability and what constitutes vulnerability (Lange et al., 2013; Levine et al., 2004). Macklin (2003) maintains that besides individuals or

groups, the entire community or country can be vulnerable to exploitation particularly in international clinical research funded by wealthier countries and conducted with human participants in developing countries.

RECs are required to ensure that investigators justify the recruitment of vulnerable populations and to ensure that there are additional measures in place to safeguard the rights, safety and wellbeing of vulnerable populations from coercion or undue influence (Horn et al., 2014). The National Bioethics Advisory Commission (NBAC, 2001) proposed a framework involving six specific characteristics that might create vulnerability of an individual research participant, i.e., (i) cognitive or communicative vulnerability: cognitive incapacity may cause participants not to be able to sufficiently understand information, deliberate and make informed decisions, (ii) institutional vulnerability: people in dependent relationships with authority figures, e.g., students and prisoners may be exploited for convenience, hence negating or undermining their voluntary consent, (iii) deferential vulnerability: cultural or societal norms such as in the case of women whose cultural norm is to defer to the husband for decisions regarding participation in research may be vulnerable to exploitation , (iv) medical vulnerability: an individual suffering from a serious health condition for which there is no satisfactory standard treatment may have the perception that research is the only hope to which may negate the voluntariness of their participation in research , (v) economic vulnerability: conditions of poverty may cause less privileged participants to enrol in research when such research appears to offer benefits that are much needed and only available to the participant through research participation and (vi) social vulnerability: some societal groups or individuals may be viewed as less valuable by others such that researchers may unfairly treat them e.g., by giving them inadequate information during the

informed consent process or by recruiting them into a study with a risk/benefit ratio that would not be acceptable to more privileged people (DuBois, 2006).

Kipnis (2001) offers a taxonomy delineating six types of vulnerability, i.e., cognitive (ability to understand and make decisions), juridic (being under a dependent relationship with a person with legal authority), deferential (customary obedience to medial or other authority), medical (having an illness without treatment), allocational (poverty educational deprivation) infrastructural (limitations of the research setting to carry out proposed research), and social vulnerability (belonging to a disadvantaged group). He argues that these six types of vulnerability may limit the ability to provide informed consent. However, while accepting the usefulness of the taxonomy, Levine et al. (2004) criticize it for two reasons. First the taxonomy makes an assumption that everyone who fits in any of these categories is vulnerable. Second, the taxonomy implies that everyone capable of autonomous consent is not vulnerable (Levine et al., 2004).

Ballantyne and Rogers (2007) argue that vulnerability exists as a spectrum rather than a simple (present or absent) dichotomy. They propose a conceptual framework outlining two types of vulnerability, i.e., extrinsic and intrinsic vulnerability. In their view, extrinsic vulnerability is caused by external situations, e.g., low socio-economic status or education, while intrinsic vulnerability is as a result of internal characteristics of individuals themselves, e.g., medical illnesses, mental disabilities and extremes of age (for example in children and some elderly). The authors recommended that RECs should distinguish between intrinsic and extrinsic vulnerabilities, as these may require different mechanisms to protect the rights, dignity and safety of potential research participants (Ballantyne & Rogers, 2007).

Luna (2009) argues that vulnerability should not be a label assigned to certain subpopulations, but rather proposes a conceptual framework of "layers of vulnerability" (p. 128). In other words, Luna suggests that the notion of vulnerability is highly contextual and that RECs can only determine if participants are vulnerable by considering the contextual details of the proposed research (Luna, 2009). Dhai (2015) proposes a Vulnerability Assessment Scale to assist RECs and researchers identify research participants with vulnerabilities and develop focused safeguards for their protections. According to her scale, the REC would need to ask the following eight questions, i.e., "1) Has the essential minimum standard afforded all participants in light of universal vulnerability been met? 2) Has the baseline for respecting human dignity been met? 3) Will any participant be used in the research as a means to an ends she/he may not endorse? 4) Will all the research participants in this study be able to safeguard their own needs and interests? 5) If no, is there an increased likelihood of any of them being identifiably wronged as a result of their participation in the study? 6) Is there an increased likelihood of any participant being identifiably wronged to a greater degree than other participants? 7) Have the identifiable wrongs been recognised? and 8) Have special safeguards been developed to protect those participants in need of such safeguards?" (p. 221).

2.5.5 Scientific validity

The obligation to conduct scientifically valid research is one of the fundamental ethical principles in research ethics (Emanuel et al., 2004). Almost all major international and national ethics guidance specifies that for studies to be ethical, they must be scientifically sound and have valid resigns that will properly answer the research question (Department of Health, 2015; Nuffield Council on Bioethics, 2002). According to the Emanuel et al. (2004) framework, the

design, sample, method, and analysis of the study should be rigorous, justifiable, feasible, and lead to valid answers to the research question. However, there is also much controversy and debate regarding the role of RECs in evaluating the scientific merit of research proposals with some critics arguing that scientific reviews falls outside the remit of RECs (Amdur, 2006; Angell et al., 2008; Edwards, 2010; Humphreys, Thomas & Martin, 2014a).

Supporters of scientific review by RECs argue that one of the fundamental pillars of ethical research is the principle of scientific validity (Emanuel et al., 2004). In other words, those supporting scientific review by RECs often argue that it is unethical to expose participants to risks and burden and enrol participants in research that is poorly designed and inconsistent with the expectations of good scientific methodology (Dawson & Yentis, 2007). As stated by the Nuffield Council on Bioethics (20002) "Research which is not appropriately designed will fail to provide answers to the questions posed by the research, and thus will have limited benefit or no benefit either to the participants, or to the wider community" (p. 102).

This suggests that, regardless of whether it is quantitative or qualitative, proposed research should have scientific validity and rigor to avoid investing human and financial resources in a research study that will not yield any beneficial outcomes. The scientific validity of qualitative social science research should be assured and assessed using criteria appropriate to qualitative research. Furthermore, it is important for the PIs and research team to have suitable expertise and competence to undertake proposed research; otherwise this might easily undermine the scientific validity of a research study (Tsoka-Gwegweni & Wassenaar, 2014). Molyneux et al. (2009) argue that in social science research, the positionality of the researcher in relation to participants

might influence data quality. They argue that it is therefore also important to have well trained fieldworkers when conducting interviews and observations to ensure scientifically valid research.

2.5.6 Favourable risk/benefit ratio

The risk/benefit assessment of research protocols by RECs is an important component of ethics review in accordance with the ethical principles of beneficence and nonmaleficence (Emanuel et al., 2004; Weijer, 2000). RECs are required to conduct a systematic, non-arbitrary assessment of the potential risks and benefits of a research protocol insofar as these are foreseeable (Belmont Report, 1979). The US Common Rule requires that in order for research to be approved, IRBs should ensure that "(1) Risks to subjects are minimized: (i) by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes. (2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility" (DHHS, 1991 p. 40).

While the importance of favourable risk/benefit ratio is highlighted by several international and national ethical guidelines and frameworks (Emanuel et al., 2004), there is considerable debate regarding when are research risks reasonable in relation to anticipated benefits (Weijer & Miller, 2004), and what conceptual framework should guide the ethical analysis of risk (Weijer, 2000). There are two leading models that have been proposed for a systematic approach to risk/benefit assessment, i.e., the component analysis and the net risks analysis (Weijer, 2000; Weijer & Miller, 2004). According to Weijer (2000) a component-based approach to risk/benefit assessment involves analysis of both a) the magnitude of the harm and b) its probability of occurrence. The component analysis approach is premised on the recognition that biomedical research often consists of a combination of therapeutic and non-therapeutic components, and as such there is need for separate moral standards for the assessment of individual study components or research intervention or procedure involved in a particular study instead of conducting a global risk benefit analysis profile of the overall study (Weijer, 2000).

However, opponents of the component approach have argued that the approach is flawed for several reasons. They argue that, equipoise, one of the concepts of the component analysis approach, conflates ethics of research with ethics of clinical care (Miller & Brody, 2003). Furthermore, opponents argue that the component approach is inappropriately applied in the ethical analysis of placebo-controls (Emanuel & Miller, 2001). Wendler and Miller (2007) proposed the net risks test as an alternative approach for risk/benefit assessment. Similar to the component analysis, the net risks test's emphasis is on consideration of the risks and benefits of individual research procedures or interventions instead of the overall study. However, there is a fundamental difference in the normative foundation of the net risks test which distinguishes it

from the component analysis. The net risks test is premised on the fundamental principle of non-exploitation, a central concept in the ethics of clinical research. Thus, the primary objective of the net risks test (and risk/benefit assessment in general) is to safeguard the protection of research participants from being exposed to excessive risks of harm for the benefit of others.

There are four ethical requirements articulated by the net risks test. First, the risks posed by each individual study procedure should be minimized, and the potential benefits of each procedure must be enhanced. Second, a research procedure should not pose an excessive increase in risk or an excessive decrease in potential clinical benefit for the participant when compared to available alternatives. In other words, this second requirement encompasses an assessment of whether a particular research procedure presents net risk to the individual research participant, followed by an assessment of whether these risks are excessive (Wendler & Miller, 2007). Net risks could occur in at least two scenarios. For instance, where the risks of a particular study procedure or intervention exceed its potential clinical benefits for the participant, then there is a net risk. An example of this scenario is in Phase I oncology trials, where the drugs often pose more risks to the participant than they offer potential benefits (Rid & Wendler, 2010). Another scenario of net risks occurs when a research procedure poses risks that do not exceed the procedure's potential clinical benefits, but the procedure's risk/benefit profile is lower than the risk/benefit profile of one or more of the available alternatives. For example, some older generation drugs offer a favourable risk/benefit ratio, but then it is lower than the risk/benefit ratio of newer drugs with which they have been replaced. Where a particular study procedure poses net risks to participants (as in the examples above), the net risks test necessitates that these risks are sufficiently low (Rid & Wendler, 2010).

The third requirement of the net risks test is that where a study procedure poses net risk, this should be justified by the knowledge expected to be gained from using that particular study procedure. This requirement is important in ensuring that the net risks to an individual research participant, on the provision that they are not excessive, are reasonable in relation to potential societal benefits (Wendler & Miller, 2007). The last requirement of the net risks test is that the 'cumulative' net risks of all the combined research procedures (regardless of whether each procedure poses low net risks to participants) in a study should not be excessive (Wendler & Miller, 2007, p. 484).

Critics of the net risk test argue that the approach has limitations in that it fails to align the ethics that govern clinical research with those of clinical care, subsequently allowing research that violates patients' rights to appropriate care (Weijer & Miller, 2007). Another criticism of the net risks test is that it permits any level of risk, as long as the anticipated benefits to society are reasonable, and thus may undermine the public trust of the medical research enterprise (Weijer & Miller, 2007). Furthermore, the net risks test is criticized for its apparent lack of definition of 'excessive' risk, hence leaving it to the discretion of RECs to make the determination of what risks are excessive (Weijer & Miller, 2007). This may cause variability in how RECs make decisions regarding the risk/benefit ratio of a study (Shah et al., 2004).

Bernabe, van Thiel, Raaijmakers and van Delden (2012) argue that both procedure-level approaches conflate the various risk/benefit assessment tasks of RECs.This conflation, the authors claim, makes the REC's task of assessing the risk/benefit of a research "confusing, if not impossible" (p.8). Rid (2014) argues that the current model for risk/benefit assessment is not

comprehensive and arguably places too much emphasis on informed consent as a condition of acceptable net risk to participants. Rid proposes that the scientific and social value of biomedical research is likely to be fundamental to the acceptability of exposing participants to net research risks. This implies that when a particular study is scientifically valid and socially valuable, then it may be justifiable to expose participants to net risks of research (Rid, 2014).

2.5.7 Payment of research participants

It is common practise to offer participants payments for their participation in biomedical research (Dickert, Emanuel & Grady, 2002; Fry et al., 2005; Grant & Sugarman, 2004; Ripley, Macrina & Markowitz, 2006). In order to help IRBs and investigators, several approaches to payments have been proposed (Ackerman, 1989; Anderson & Weijer, 2002; Dickert & Grady, 1999; Macklin, 1981). For instance, Dickert and Grady (1999) described the market model, wage payment model and reimbursement model. The wage model is recommended by Dickert and Grady (1999) for three main reasons: (1) it reduces concerns about undue inducement, (2) it standardises payment schedules, and (3) it establishes a system in which payment is based on the contribution made by each participant, consistent with the principle of justice, i.e., equals should be treated equally.

However, there is considerable debate regarding the ethics of paying research participants (Grady, 2005a; Gordon, Brown, Kratocvil, Schonfeld & Prentice, 2006; Horn, 2008; Koen et al., 2008). McNeill (1997) argues that it is unethical to offer payment to participants, claiming such payments may cause participants to not be able to adequately assess the risks of participating in research. He further argues that offering payments to participate in research would further

increase the inequity of research conducted on the impecunious for the benefit of the well-off. The main concerns raised by some commentators in relation to payment of participants are coercion and undue inducement which undermine free and voluntary consent (Grady, 2001, 2005a). In a paper titled *The paradoxical case of payment as benefit to research subjects*, Macklin (1989) argues that ‘‘the reason for holding that it is ethically inappropriate to pay patients to be research subjects is that it is likely to be coercive, violating the ethical requirement that participation in research should be fully voluntary” (p. 3).

Some commentators have also argued that payments do not constitute coercion and undue inducement (Emanuel, 2004; Emanuel 2005; Emanuel, Currie, & Herman, 2005; Grady, 2005a; Largent et al., 2012; Largent et al., 2013; Wertheimer & Miller, 2008). For instance, Emanuel (2005) argues that in order for an inducement to be undue, there are four necessary conditions that must be met. First, a desirable good has to be offered in return for a specified action. Second, the offered good must be so excessive that it cannot be resisted. Third, the offer has to result in a person making a poor judgment in relation to the specified action. Finally, the person’s poor judgment must result in a high probability that they will experience serious harm that threatens their interests. In his view, undue inducements apply only when risks are undoubtedly unreasonable. The author concludes that if a research proposal fulfils all the other ethical requirements and an efficient and competent REC has found the risk/benefit ratio to be favourable, then undue inducement cannot occur as long as the risk of serious harm that is precluded, even if participants exercise poor judgment (Emanuel, 2005). Similarly, Emanuel and Miller (2007) argue that instead of relying on financial considerations as indicators of ethical problems, ethical analysis should focus on relevant substantive issues, such as the research

design, the risk/benefit ratio and the informed consent process.

Horn (2008) argues that determination of whether or not to pay participants is dependent on several factors, such as the nature of the study, degree of risk involved, profile of participants, funding source, and issues related to the potential public health implications of the study. Payment should thus be considered on a case-by-case basis. Generally, the literature on the ethics of paying research participants has concluded that while issues may arise, offering payments to participants does not constitute coercion or undue inducement (Emanuel, 2004, 2005; Emanuel et al., 2005; Grady, 2001, 2005a; Largent et al., 2012, 2013; Wertheimer & Miller, 2008).

Little is known about how RECs view and deal with such issues (Ripley et al., 2006, 2010). A qualitative study by Klitzman (2013c) explored how IRBs view and make decisions about coercion and undue influence and found that IRBs often encountered difficulties with defining the concepts of coercion and undue inducement, especially in deciding about participant compensation. Another study by Largent, Grady, Miller and Wertheimer (2012) explored the views of IRB members about whether payments constitute coercion and undue inducement. They found that the majority (61%) of respondents expressed concern that payment of any amount might influence participants' decisions or behaviours regarding research participation. The authors reported that there was variation in how IRBs viewed coercion and undue influence to the extent that these inconsistences could needlessly interfere with important research (Largent et al., 2012, 2013). In 2012, The South African NHREC developed guidelines for the ethical payment of research participants. The proposed model is payment for time, inconvenience and expenses (NHREC, 2012).

2.5.8 Standard of Care

The growth of externally-sponsored clinical research in developing countries has, over the recent years, fuelled debates about the issue of standard of care, i.e., the level of treatment that should be offered to participants assigned to the control group (Ehni, 2006; Lavery et al., 2007; Lie, Emanuel, Grady & Wendler, 2004; Miller & Silverman, 2004; Schüklenk, 2004; Schüklenk & Ashcroft, 2000; Selgelid, 2005; Wendler, Emanuel & Lie, 2004). At the centre of the standard of care debate is the question of what standard reference point should be used to compare the efficacy of an investigational drug? Should it be the best current treatment or should it be the universal standards of care or should it be the locally available standard of care – even if it is close to nothing? (Hawkins, 2008). Distinguishing between these two viewpoints of standard is essential and leaves the concept of standard of care subject to different interpretations (Macklin, 2004).

The standard of care debate came to the fore following a number of cases of placebo-controlled trials of zidovudine (AZT), referred to as the ACTG 076 regimen - AIDS Control Trial Group 076 protocol - for the prevention of perinatal transmission of HIV infection in different developing countries, namely Côte d'Ivoire, Uganda, Tanzania, South Africa, Malawi, Thailand, Ethiopia, Burkina Faso, Zimbabwe, Kenya, and the Dominican Republic (Annas & Grodin, 1994; Selgelid, 2005). A brief history of AZT is given here: in 1994, clinical research in wealthy developed countries showed that treatment with zidovudine (AZT) significantly reduced by one-third, from 25% to 8%, the risk of mother-to-child transmission of HIV in the developed world (Connor et al., 1994). After these persuasive results were published, AZT received the U.S Food and Drug Administration's (FDA) approval and became the standard of care for the prevention

of HIV transmission from infected pregnant women to babies in wealthy developed countries (Schüklenk, 2000). However, AZT was expensive, costing approximately US $800 per pregnancy, and thus unaffordable in poor developing countries such as those in Sub-Saharan Africa where governmental healthcare budgets are often less than $10 per person per year (Resnik, 2001). Yet it is in those less developing countries where the prevalence of HIV is high with approximately more than 60% of new HIV infections and 90% of all maternal-foetal HIV transmission occurring in sub-Saharan Africa (UNAIDS, 2015). Therefore it is clear that Sub-Saharan Africa is where safe, effective and affordable HIV prevention interventions are much needed.

In 1994 international agencies such as the US National Institutes of Health, WHO and UNAIDS designed placebo-controlled controlled trials aimed at testing the effectiveness of a short-course treatment of AZT (which would cost only $80 per infected woman), compared to the standard of care in developing countries, of no intervention at all to prevent HIV infection of new-born babies (Lavery et al., 2007; Schüklenk, 2000). In these trials, control participants were offered placebo treatments, despite the existence of effective AZT therapy in developed wealthy countries (Angell, 2000; Lavery et al., 2007). Lurie and Wolfe (1997) heavily criticized these placebo-controlled trials (Angell, 1997). Their primary argument was the use of double standards for poor and wealthy populations, implying that researchers from developed countries were using trial designs (i.e., placebo controlled trials) for HIV pregnant woman in developing countries when the very same design would have been deemed unacceptable in the sponsoring developed country (Angell, 1997; Crouch & Arras, 1998; Lurie & Wolfe, 1997).

However, other commentators argued that the critics failed to understand the scientific, social and economic contextual complexities of the AZT trials in developing countries (Forster, Emanuel & Grady, 2001; Lie et al., 2004; Varmus & Satcher, 1997). For instance, Resnik (1998) argued that these placebo-controlled trials for AZT in 1997 were morally justifiable based on the local standards of care for those countries. In other words, it was ethically permissible to provide placebo to the control group since no alternative treatment was available locally.

Furthermore, supporters of the placebo controlled AZT trials maintained that the use of placebo control posed potential benefits rather than risks to the trial participants. Considering that no treatment was the standard of care for the prevention of mother to child transmission of HIV in those developing countries where AZT trials were conducted, proponents argued that participants assigned to the control arm were not deprived of any treatment they would otherwise have received (Selgelid, 2005; Varmus & Satcher, 1997). That is to say, if the participants had not enrolled in the AZT trials, ordinarily they would not have received any interventions to prevent HIV transmission to their babies in any case, given the existing economic and infrastructural constraints of the local contexts. Indeed, the participants who were assigned to the treatment arm in addition to free HIV counselling, benefited by receiving treatment that could reduce the risk of HIV transmission to their babies. On the other hand, those in the placebo group also benefited from free HIV counselling and education. In addition, they were not harmed because they were not denied any effective treatment entitled to them had they not participated in the AZT trial (Selgelid, 2005).

Abdool Karim (1998), in his South African viewpoint paper published in the *American Journal of Public Health*, argued that the use of placebo in the AZT trials in South Africa was ethically justifiable given the local economic and infrastructural constraints. Abdool Karim was emphasizing one of the arguments in defence of the AZT placebo controlled trials –that no locally available therapy was being withheld from participants in the placebo control group.

While many commentators advocate for best available standard of care worldwide to research participants (Angell, 1997, 2000; Lurie & Wolfe, 1997; Rothman & Michels, 1994; Shapiro & Meslin, 2001), others argue that this may impede valuable research in developing countries (Studdert & Brennan, 1998). Wendler et al. (2004) proposed a framework delineating the conditions under which it is acceptable to provide research participants with less than the best methods. They recommend that IRBs or RECs should apply a default of requiring the best interventions available anywhere in the world, in all cases. However, the authors concede that there are exceptions to this default requirement in certain circumstances, specifically when proposed research satisfies four conditions: "(1) scientific necessity: investigators must use less than the worldwide best methods to answer the scientific question posed by the trial, (2) relevance for the host community: answering the scientific question posed by the trial will help address an important health need of the host community, (3) sufficient host community benefit : the trial will produce a fair level of benefit for the host community, and (4) participant and host community nonmaleficence: participants and the host community will not be made prospectively worse off than they would be in the absence of the trial" (Wendler et al., 2004, p. 927).

Lignou (2011) argued that the fundamental human right to health and the moral principle of justice should form the moral basis for the standard of care debate in developing countries. Similarly, Marouf and Esplin (2015) argued that the duty of justice and the basic human right to health as international human rights principles are pertinent to the standard of care debate in developing countries, particularly where limited resources mean that the local standard of care is no care at all. The authors maintain that applying a human rights framework may help define a middle ground that recognizes the practical challenges arising in providing the best worldwide intervention while also setting a minimum standard of care for control groups. In the authors' view, the framework of human rights law, in particular the core obligations of the right to health, might help establish a minimum standard of care (Marouf & Esplin, 2015).

2.5.9 Ancillary care

Ancillary care refers to medical care that research participants need during a trial, but which is not related to the research question (Richardson & Belsky, 2004). Investigators conducting research with participants in developing countries where there is inadequate healthcare access often encounter ethical dilemmas of having to provide additional healthcare beyond the scope of their research projects (Participants in the 2006 Georgetown University workshop on the ancillary care obligations of medical researchers working in developing countries, 2008; Richardson, 2007). A number of case studies have been reported where researchers discover unmet health needs not related to the study in which participants have been enrolled. For example, Dickert and Wendler (2009) mention a project conducted to investigate whether children with severe Malaria develop hypertension, with the aim of understanding morbidity and mortality related to Malaria. The investigators found that the children also had unmet health

problems such as eye infections, upper respiratory infections and one heart defect requiring surgery. In another example described by Merritt, Taylor and Mullany (2010), researchers enrolled 17,306 mother-infant pairs into the Nepal Newborn Washing Study, a community-based trial to test the efficacy of a one-time chlorhexidine skin cleansing for promoting infant survival in a district of Nepal where the majority of participants are impoverished, more than 95% of mothers give birth at home, with very limited access to antenatal, obstetric, postnatal, and neonatal care. In that study, researchers encountered other unmet health needs of participants such as high prevalence of hookworm infections among pregnant women, unhygienic home birth environments, and common treatable diseases among infants (Merritt et al., 2010).

The scenarios above highlight challenging ethical questions regarding ancillary care. Do researchers have a responsibility to provide ancillary care? When do researchers have a duty or responsibility to provide medical care beyond their research scope to research participants? What is the nature and extent of researchers' obligations to respond to such needs? (Belsky & Richardson, 2004; Merritt, 2011). Unfortunately existing guidelines say little, if anything, about ancillary care and thus provide limited guidance on the questions raised above (Belsky & Richardson, 2004; Krubiner, Syed & Merritt, 2015; Participants, 2008). Those that do mention ancillary care obligations emphasize the need for planning and engagement with various stakeholders in order to share responsibilities (CIOMS, 2002; HPTN, 2009; Nuffield Council on Bioethics, 2002; UNAIDS/WHO, 2007; UNAIDS/AVAC, 2011). For instance, the Nuffield Council on Bioethics (2002) states that, "During research into some diseases, participants may develop a condition that is related to the condition under study or an entirely unrelated condition…We recommend that before research begins, agreement should be reached about the

standard of care that should be provided to participants in research who already have or who develop diseases other than the disease being studied" (p. 139).

The debate about ancillary care has been viewed from two extreme endpoints. On one hand, some commentators believe that researchers in developing countries have an obligation to provide ancillary care needs of participants (Belsky & Richardson, 2004). Advocates for ancillary care obligations invoke principles such as social justice (Shapiro & Benatar, 2005), reciprocity (Macklin, 2006), and beneficence (Stobie & Slack, 2010). On the other hand, opponents argue that researchers have no obligation to provide ancillary care because medical research – aimed at generating scientific knowledge – is different from medical care (Belsky & Richardson, 2004). Furthermore, investigators may not have the expertise to address all the ancillary care needs of participants. Moreover, costs for providing ancillary care can exceed the planned budget for the study and this may jeopardise the study (Dickert & Wendler, 2009). Additionally, concerns about fairness may emerge when research participants receive priority care for other unmet needs while nonparticipants do not have access to medical care. This is particularly true if the provision of ancillary care utilizes the already scarce healthcare resources of the host country (Dickert & Wendler, 2009). In addition, placing the obligations for ancillary care provision on investigators could be seen as misplaced responsibility which is unfair to investigators, particularly if that responsibility does not reflect the nature of their work or relationships with participants (Dickert & Wendler, 2009).

Some commentators have reported practical examples demonstrating the feasibility of providing sustainable ancillary care to trial participants through shared responsibilities amongst various stakeholders – e.g., sponsors, researchers, local healthcare providers and NGOs (Participants, 2008). An example is a trial of preventive regimens for tuberculosis in HIV infected adults in a poor township in South Africa. As part of ancillary care obligations, researchers and local healthcare providers collaborated and provided all participants with free HIV care and follow-up. Another example of ancillary care involves a trial of vaginal microbicide in sex workers in Benin. The researchers organized for sponsors to provide healthcare to participants with extra uterine pregnancy not related to enrolment in the trial (Participants, 2008). Ancillary care obligations will vary from one study to another, hence RECs need to exercise caution and make recommendations based on a case-by-case review of protocols. For instance, an observational study in which the participant will be assessed only once, will present different practical ethical challenges compared to an interventional study with long term assessment of participants (Participants, 2008).

There is a considerable body of literature on ancillary care (Dickert & Wendler, 2009; Merritt (2011); Oslon, 2015; Richardson & Belksy, 2004). Several frameworks have been proposed to assist investigators in making ancillary care determinations (Belsky & Richardson, 2004; Bright & Nelson, 2012; Brownsword, 2007; Dickert et al., 2007). For instance, Richardson and Belsky (2004) proposed a partial-entrustment model which is premised on the notion that the relationship between participant and researcher involves a partial and limited entrustment of participants' health to researchers. In other words, when participants allow investigators to access their personal health information and perform research procedures, they entrust certain aspects of

their health needs to researchers, and can be affected by how investigators use such personal information, hence they become vulnerable. As a result of this vulnerability and entrustment, investigators have an obligation to assume some responsibility for certain health aspects of participants related to the study procedures. So, for example, in the Malaria case study described earlier, participants allow investigators to perform certain procedures and entrust investigators with their health needs. Consequently, according to the partial-entrustment model, the investigators have an obligation to address only Malaria-related needs of the participants (Richardson & Belsky, 2004).

However this partial-entrustment model has been criticized by some commentators for its problematic restraint on the scope of health needs for which investigators can be obligated to provide ancillary care (Dickert & Wendler, 2009; Olson, 2015). For instance, Dickert and Wendler (2007) argue that there should be no restriction on the scope of ancillary care obligations to the specific aspects of participants' health needs. They argue investigators have an obligation to provide ancillary care to a variety of health needs even sometimes they are not related to study procedures. The authors maintain that the obligation to provide ancillary care is limited by the "depth of the investigator's relationship with participants and the resource demands of providing such care" (Dickert & Wendler, 2009, p. 425). Similarly elsewhere, the authors criticize the partial-entrustment model and argue that several factors, for example, the existence of need, the capacity to help, and particularly the investigators' level of engagement such as duration and intensity of interactions with participants, are essential factors in determining the scope of the investigator's ancillary care responsibility (Dickert et al., 2007).

Tshikala et al. (2008) criticized Belsky and Richardson's model on ancillary care obligations. For instance, it is argued that not providing ancillary care for a serious but not urgent medical need would be unacceptable. Yet this would be acceptable according to the model proposed by Belsky and Richardson (2004). Weijer and Le Blanc (2006) argued that researchers do not have a moral obligation to provide ancillary care. The authors concluded by saying "…our analysis concludes that there is as of yet no robust moral argument supporting a moral obligation to provide treatment to participants in HIV prevention trials who seroconvert" (Weijer & Blanc, 2006, p. 806). However, the authors also recommend that there should be moral negotiation to allow meaningful researcher-community negotiation on the expected benefits of research participation including ancillary care (Weijer & Blanc, 2006).

Bright and Nelson (2012) proposed a capacity-based model for identifying ancillary care obligations that entail giving considerations to the urgency, the capacity of the local healthcare infrastructure and the capacity of the research infrastructure to provide ancillary care. Pratt et al. (2013) suggest that the need to meet ancillary care obligations derives from the health capability paradigm which requires the delivery of ancillary care to trial participants for a limited and specified subset of conditions that cause severe morbidity and mortality. The model is based on the idea that every person has a duty of justice to do what they can to bring individuals worldwide up to the optimal level of health achieved globally. This theory gives priority to addressing shortfalls in the health of people who are worst-off in the sense that they are farthest from the optimal level of health (Pratt et al., 2013).

Olson (2015) proposes a relationship-based approach. In this view, this approach provides a principled basis for differentiating investigators' obligations from those of clinicians' without putting restrictions on the scope of ancillary care needs for which investigators may have a responsibility (as in the partial-entrustment model). Furthermore, the relationship-based approach locates ancillary care obligations in a variety of morally pertinent factors of the researcher-participant relationship, such as the engagement level between researchers and participants, and weighs these factors against each other. The author argues that the duration and intensity of engagement between researchers and participants is important for determining investigators responsibilities on ancillary care (Oslon, 2015).

There are few empirical studies that have reported on the current practices regarding the provision of ancillary care (Krubiner, Syed, & Merritt, 2015; Taylor et al., 2011). A recent review of existing institutional guidance on health researchers' ancillary-care responsibilities in low-resource settings found that many institutions (34/57) as well as international and national ethical guidelines (54/71) did not mention ancillary care responsibilities (Krubiner et al., 2015). Another qualitative survey of researchers' practices regarding the provision of ancillary care in public health intervention research found that investigators conducting research in the community setting were more likely to identify and plan for the ancillary care needs of potential research participants in advance prior to commencement of the research project, while those affiliated with a permanent facility were more likely to provide ancillary care to research participants on an ad hoc basis (Taylor et al., 2011). Some commentators supporting ancillary care have argued that the provision of ancillary care is one way in which trial participants can receive direct benefits from their participation in research. Slack (2014) investigated whether

recommendations regarding ancillary care in HIV vaccine trials in existing ethical guidelines were being achieved, and whether stakeholders encountered challenges. She concluded that all five sites surveyed had mostly met the guideline recommendations for engaging host community in which research is conducted, and recommendations for "moral negotiation" were met to a lesser extent.

2.5.10 Post-trial access

There is increasing international concern about what happens to participants and host communities once the research is over. The requirement to ensure post-trial access to treatment for research participants is widely highlighted by key international and national guidelines (CIOMS, 2002; WMA, 2013; UNAIDS/WHO, 2012). For example, the Declaration of Helsinki (2013) recommends that "In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial…" (p. 7).

The issue of post-trial access when a research study completes has generated considerable debate in the research ethics literature (Grady, 2005b; Millum, 2011; Sofaer & Strech, 2011; Zong, 2008). At the heart of the debate is the key question: what, if anything, is owed to research participants after their participation in a clinical trial ends and whether sponsors and investigators have an obligation to provide ongoing treatment to participants or host community after the trial has ended (NBAC, 2001; Pace et al., 2006; Sofaer & Strech, 2011; Sofaer et al., 2009).

A systematic review by Sofaer and Strech (2011) assessed the reasons why post-trial access to trial drugs should, or need not be provided to research participants. The authors identified a range of reasons broadly based on morality, legality, interests/incentives, or practicality of offering post-trial access. Proponents of post-trial access invoke the ethical principles of beneficence (an obligation to help others further their important and legitimate interests), nonmaleficence (an obligation not to inflict ham on others) (Grady, 2005b; NBAC, 2001) and justice (NBAC, 2001; Macklin, 2006; Shapiro & Benatar, 2005).

The NBAC (2001) supported post-trial access based on the principle of justice as reciprocity, implying that because participants enrolled in research assume some risk and burdens for altruistic reasons for the good of society and scientific advancement, certain things are owed to them in return for their participation. According to NBAC (2001), "justice as reciprocity is concerned with what people deserve as a function of what they have contributed to an enterprise or to society. In the context of clinical trials, justice as reciprocity could mean that something is owed to research participants even after their participation in a trial has ended, because it is only through their acceptance of risk and inconvenience that researchers are able to generate findings necessary to advance knowledge and develop new medical interventions" (p. 59).

However, Merritt and Grady (2006) question the reciprocity-based justification for offering priority access to ART trial participants when ART must be rationed. They argue that justifying the provision of ART on the principle of reciprocity depends on several variables, including the quantity of ART available, the number of people in the country who need ART, and whether the country's concurrent allocation policy selects specific subpopulations (such as HIV-infected

mothers of young children) for priority. They conclude that the reciprocity-based justification for giving ART trial participants priority over equally needy HIV-infected citizens is relevant only under some circumstances, at best. In other words, they are cautioning against the prioritizing the provision of post-trial access to trial participants based on reciprocal justice without giving due consideration to the possible burden on people who did not participate in the trial (Merritt & Grady, 2006).

While the principle of providing post-trial access is recognized by various research ethics guidelines (CIOMS, 2002; Department of Health, 2015; UNAIDS/WHO 2012; WMA, 2013), there is little empirical research about how RECs, investigators and research participants deal with issues of post-trial access in practice. One study in the US surveyed 65 IRB/REC chairs, 117 investigators, and 500 research participants in a multinational HIV trial in 25 countries to assess their views about post-trial access to interventions proven effective in the study. The authors reported that 29% of IRB/REC chairs, 42% of researchers and 83% of research participants believed the study product should be guaranteed for every HIV-infected person in the world if proven effective (Pace et al., 2006). They also found different views in terms of availability of the product, with most European and Latin American research participants saying it should be provided freely, while North American, Australian, and Thai participants felt it should be provided at a price affordable to the average person. Furthermore, REC chairs and researchers believed that the "reasonable availability" requirement (CIOMS, 2002, p. 51) is meant for people in the country where the study was conducted and meant a drug should be available at a price the average person could afford and that host country governments had primary responsibility for making it available (Pace et al., 2006).

Another US study investigating how closely researchers followed NIH guidance on post-trial access found that all 18 research protocols included plans for post-trial access for trial participants and more than 13 of the 18 (70%) had specific mechanisms for post-trial access, but none guaranteed long-term sponsor funding after the trials (Shah, Elmer & Grady, 2009). The views and attitudes of trial participants in the US about whether or not, and why, they should receive post-trial access were investigated and it was found that the majority of respondents believed that various stakeholders (investigators, sponsors, health insurers, and others) have a shared obligation to facilitate post-trial access to the trial drug (or to a therapeutic equivalent) if it benefited the participant. Furthermore, the same study found that while some believed post-trial access obligations include providing transition care (referrals to non-trial physicians or other trials, limited follow-up, short-term drug supply) or care for long-term adverse events, others said, that there should be no post-trial access obligations on drugs or care. Additionally, they found that participants frequently expressed reasons such as health needs, cost, reciprocity, free choice, and sponsor self-interest to justify their views on post-trial access (Sofaer et al., 2009).

A systematic review by Cohen, O'Neill, Joffres, Upshur and Mills (2009) investigating the extent to which registered international RCTs report the use of standard of care and post-trial obligations found that out of 312 studies identified, only 4 (1.3%) mentioned provisions for post-trial access. Of those, one stated that the post-trial drug would be provided by the governments of the respective countries; another mentioned that participants who became infected with HIV during the trial would be provided with free HIV counselling and education and access to required healthcare, as well as free antiretroviral drugs, if clinically indicated. The same study noted, however, that there was no mentioning of who will offer these provisions and who will

ensure that these are provided (Cohen et al., 2009). Another US study by Ciaranello et al. (2009) investigated how details about post-trial access were included in the trial's protocols and informed consent forms. They found that post-trial access was mentioned in 14 of 31 trials (45%), access to medications in 12 of 31 (39%) and access to medical care in 5 of 31 (16%) trials.

The views of HIV/AIDS clinical trial participants, researchers and research administrators were investigated in Kenya and it was found that most research participants expressed a desire for post-trial access to drug therapy, most often life long, after their participation in a clinical trial. Furthermore, participants felt that subsidisation of drug therapies and education were essential forms of compensation for clinical trial participation. Similarly, clinician researchers and administrators believed that there was a moral obligation from researchers to facilitate continued post-trial access of the drug to participants (Shaffer et al., 2006). The views of twenty-nine South African community members regarding the provision of treatment in HIV prevention trials were investigated and the study reported that most respondents believed that researchers should facilitate access of treatment and care to participants. The same study found that respondents felt that researchers can help through referrals until such time that participants are capable of accessing care and treatment on their own (Barsdorf et al., 2010). In a study aimed at investigating post-trial access in HIV prevention trials, it was reported that , found that while all nine biomedical prevention trials they analysed had offered post-trial access, there was considerable variation in the mechanisms, duration and timeliness of post-trial access (Haire & Jorderns, 2015).

2.5.11 Compensation for research-related injury

There is wide ethical consensus that research participants should be provided with medical care and compensation for research-related injury (Cleaton-Jones, 2014; Cleaton-Jones et al., 2006; Mamotte, Wassenaar & Singh, 2013; Resnik, 2006; Slack, Singh, Strode & Essack, 2012). RECs have an obligation to ensure adequate provision of free or compensated medical care for research-related injury (Cleaton-Jones, 2014; Cleaton-Jones et al., 2006; Vasgird, 2006). Advocates supporting compensation for research-related injury invoke principles of beneficence, distributive justice, compensatory justice and reciprocity (Childress, 1976; Pike, 2014; Resnik, 2006; Vasgird, 2006). Furthermore, some commentators have argued that participants are morally entitled to compensation (U.S. Presidential Commission for the Study of Bioethics, 2011) and participating in research ought not to leave participants worse off than they were prior to enrolling in a research (Beauchamp & Childress, 2001).

Several international (cf. CIOMS, 2002; HPTN, 2009), and national guidelines (Department of Health, 2015; Uganda National Council for Science and Technology, 2014), recommend or require that participants receive compensation for research-related injuries. For example the Ugandan guidelines for research involving humans as research participants explicitly states that, "the sponsor should provide care until complete cure or stabilization of a research related injury. The injured research participant shall be given the best care available within the country for the research related injury. Research participants shall not be required to waive their legal rights for redress in courts of law" (Ugandan National Council for Science and Technology, 2014, p. 20). Furthermore, some guidelines recommend that where no compensation will be provided, this should be explicitly stated during the informed consent process (HPTN, 2009). Where such

compensation will be provided to participants, the consent process should adequately describe the nature of the compensation available to research participants for harms incurred during the study, the medical treatment to be provided for research-related injury and information about possible compensation for physical, social and economic harms attributable to research participation (HPTN, 2009).

However, according to US Federal policy, compensation is not mandatory for US sponsored studies (e.g., NIH sponsored research) and this has been criticized by several commentators both in the US (Henry, Larkin & Pike, 2015; Pike, 2014) and developing countries such as in Africa (Cleaton-Jones et al., 2006; Cleaton-Jones, 2014; Mamotte, Wassenaar & Singh, 2013). The failure to provide compensation is particularly problematic for research conducted in developing countries where injured research participants are unlikely to have health insurance and therefore cannot afford to pay for care for research-related injury (Mamotte et al., 2013). Commentators have proposed a systematic no-fault compensation in the US in order to bring US law in alignment with international ethical norms regarding compensation and ensure that injured research participants are adequately protected (Henry et al., 2015; Pike, 2014).

While compensation for research-related injury is widely accepted as an ethical practice in research with human participants, it remains a subject of ongoing debate (Mamotte et al., 2013; Pandya & Desai, 2013) and few empirical studies have examined the issue (Bavdekar & Thatte, 2009; Mamotte et al., 2013; Thatte, Kulkarni-Munshi & Kalekar, 2009). A retrospective study of 138 protocols submitted to two RECs in India found that 46 (33.33%) of protocols mentioned the provision of free treatment for a trial-related injury, 42 (30.43%) did not have any policy

regarding the provision of treatment for research-related injury, whereas others included statements that intended to provide treatment, but with certain restrictions. In relation to informed consent documents, 33 (23.91%) stated that compensation would not be provided while 65(47.10%) did not mention anything about compensation for research-related injury (Bavdekar & Thatte, 2009). The author concluded that informed consent documents submitted to Indian RECs sometimes do not conform to national guideline requirement for compensation of research-related injury (Bavdekar & Thatte, 2009). Another Indian study by Thatte et al. (2009) found that almost half (47%) of investigators expressed either ignorance or misunderstanding of the legal requirements for compensation and depended on sponsors to manage these issues. On the other hand, most (74%) of REC members expressed awareness of the requirements. While fewer than half of investigators (40%), and REC members (30%) and all sponsors had policies to manage compensation issues, the policies mainly addressed the provision of immediate free medical care or reimbursement of expenses incurred for the acute management of an adverse event. None of the policies included compensation for loss of time/wages, death, physical disability or long term incapacitation. Furthermore, informed consent and insurance documents did not adequately address issues regarding compensation, with only insurance certificates submitted to RECs (Thatte et al., 2009).

A South African study by Mamotte et al. (2013) surveyed RECs and investigators regarding the practice of compensation for research injury in US NIH-funded research, despite contrary NIH policy, described above. They found that nine of 12 principal investigators provided financial compensation to cover treatment for research-related injuries, and the other three did not. Furthermore the study found that more than half (9/14) of the REC chairs mentioned that their

REC reviewed compensation plans for research-related. Of those, eight REC chairs indicated that their ethics application form consisted of a section specifically requesting details regarding medical care and/or financial compensation for research-related injuries. Only a few chairs stated that while their REC considers the issue, their ethics application form does not specifically ask for information regarding compensation for research injury (Mamotte et al., 2013).

2.5.12 Post-approval monitoring of research

RECs are required to ensure there is monitoring of research and adverse events in order to ensure ongoing protection of participants safety and wellbeing (Boateng, Ndebele & Mwesiga-Kayongo, 2014; Department of Health, 2015). Accordingly, RECs need assurance that as the study progresses, the risks are minimized, the benefits are maximized and the risk/benefit ratio of the study continues to be favourable (Kratochvil, Prentice, Epperson & Gordon, 2006). Data safety and monitoring boards (DSMBs) play a crucial role in monitoring participants' safety data and adverse event monitoring in a clinical trial (McCutchan, 2006; Musesengwa, 2014). RECs can monitor research in several ways including through continuing reviews of approved research, reviewing informed consent processes, adherence to protocols, and unapproved activities (Heath, 1979). Monitoring of research by RECs is important in avoiding research scandals, and in enhancing public trust in the biomedical research enterprise (Weijer, Shapiro, Fuks, Glass & Skrutkowska, 1995).

While some ethical guidelines necessitate post-approval monitoring of research by RECs, there is limited guidance on the frequency, scope or operational methods for monitoring research (Ochieng, Ecuru, Nakwagala & Kutyabami, 2013). Furthermore, existing reports suggests that

while post-approval monitoring of research is considered necessary and important, there is inadequate monitoring taking place because of limited resources and expertise to efficiently conduct monitoring of approved research, and lack of clear frameworks for undertaking site monitoring (Ochieng et al., 2013).

A qualitative study with 14 REC members in Nigeria found that there was inadequate monitoring of approved research protocols to ensure strict compliance by researchers due to financial constraints (Agunloye, Salami & Lawan, 2014). Similarly, a recent review of empirical research on the structure, functioning and outcomes of African RECs found that many RECs had limited financial resources and capacity to monitor approved research (Silaigwana & Wassenaar, 2015).

There are divergent views in the research ethics literature concerning whether RECs should actively monitor research (Christakis, 1988). Those who support post-approval monitoring by RECs argue that such monitoring enhances protection of research participants. For example, Robertson (1982) maintained that an "IRB should monitor the consent process, test subject understanding, and modify its requirements accordingly" (p. 31). Furthermore, he recommended that IRBs should take steps to monitor investigator compliance with consent requirements, on a sample or comprehensive basis, and hold accountable investigators who do not comply (Robertson, 1979).

Some commentators argue that monitoring of REC decisions and approved research can rapidly result in the transformation of the ethics review system from a review and advisory body into some kind of policing system and could erode the trust between researchers and RECs (Levine,

1980). Similarly, Heath (1979) argues that, "IRB activity to ensure adherence to an approved protocol would invade the trust established between the IRB and an investigator…The IRB members seem ill-suited for this job" (p. 3).

Heath (1979) proposes a framework of monitoring which involves four concepts: (1) continuing review; (2) review of the consent process: (3) review for adherence to an approved protocol; and (4) review to identify unapproved activities. Continuing ethics review is one approach that can be used by RECs to ensure that there is ongoing protection of the rights and wellbeing of research participants throughout the course of a research study. RECs can conduct continuing reviews through either a passive or active process. Passive continuing review involves the reviewing research reports about the project's status compiled by the principal investigators. The report would typically include information such as details about participant enrolment, serious adverse events, protocol violations, and other problems encountered during the study. Active continuing review, on the other hand, could encompass formal review of the informed consent process, data and safety-monitoring by DSMBs, and periodic review of study-related documentation (Boateng et al., 2014; Musesengwa, 2014).

There have been few empirical research studies investigating how RECs implement continuing reviews in practice. A study by McNeil, Berglund and Webster (1990) reported that of 101 Austrian RECs they surveyed, only less than half said they monitored approved research. A separate 2008 survey of 103 Canadian RECs by Norton and Wilson (2008) found that 88% performed continuing ethics review while the other 12% did not. Furthermore, the study found that the most common type of continuing ethics review were reviews of ongoing study reports

completed by the investigator (84%), adverse events reported by the investigator (81%), end-of-study reports completed by the researcher (76%) and informed consent documents and the informed consent process (50%) (Norton & Wilson, 2008).

Ochieng et al. (2013) proposed a model for monitoring which includes seven elements: regulatory issues (availability of study related documents), site facilities (availability and the amount of space compared to the participant population), informed consent process and documentation (observe the process of obtaining consent), participant's welfare, reporting and management of adverse events, study related training and working practices.

2.5.13 Dissemination of study results

The dissemination of research results to participants is widely recognized as an ethical research practice according with the principles of respect for persons and beneficence (Dixon-Woods, Jackson, Windridge & Kenyon, 2006; Emanuel et al., 2004; Fernandez, Kodish & Weijer, 2003; Keens, 2006; Miller, Giacomini, Robert & Christensen, 2008; Shalowitz & Miller, 2008). Fernandez et al. (2003b) argue that offering research results to participants is an ethical imperative and that "fulfilling respect for participants obligates the researchers to offer to provide a summary of research results on completion of the study" (p. 9). RECs often require researchers to furnish plans of how they will disseminate results of their research (MacNeil & Fernandez, 2007). Indeed, a Canadian study of examining the policies of Canadian university based research ethics boards (REBs) regarding returning results to research participants found that of the 34 REBs surveyed, only 2 (9.1%) had a policy that governed the return of research

results while on a study, and seven (31.8%) following the completion of a study. No REBs had specific guidelines describing how participants should be informed of results (MacNeil & Fernandez, 2007). A 2014 study of one South African REC found that of the total 144 ethical queries raised under the principle of respect for participants, 17.3% concerned dissemination of study results to participants (Tsoka-Gwegweni & Wassenaar, 2014).

While several commentators have advocated for the dissemination of research results to participants (Fernandez et al., 2003b; Partridge, Burstein, Gelman, Marcom & Winer, 2003; Partridge & Winer, 2009; Partridge et al., 2005; Shalowitz & Miller, 2005), it remains unclear what is the scope and limits of researchers' responsibility in offering results to participants (Shalowitz & Miller, 2008). For instance current ethical guidelines are inconsistent about (1) whether investigators should proactively re-contact participants, (2) the type of results to be offered, (3) the need for clinical relevance before disclosure, and (4) the stage of research at which results should be offered (Shalowitz & Miller, 2008).

There are number of empirical studies on the views of participants on receiving research findings (Partridge et al., 2003; Shalowitz & Miller, 2008). Empirical findings suggest that most participants wish to receive results of their trial participation (Dixon-Woods et al., 2006; Partridge et al., 2003; Snowdon et al., 1998). Other studies have also reported on the views of investigators (Fernandez et al., 2003; Partridge et al., 2004) and RECs (MacNeil & Fernandez, 2006, 2007) regarding the provision of research results to participants. Fernandez et al. (2003) surveyed 150 principal investigators and found 69.3% supported or strongly supported the development of a guideline mandating provision of research results to participants. However the

respondents raised some seemingly trivial impediments to offering results to participants, namely difficulties of preparing lay summaries, time constraints, the cumbersome task of contacting participants, and potential distress for the participants. There was variation regarding when results should be offered with 30% favouring after the study was closed while 24% felt it should be at the time of publication of results. It would seem prudent to do so only after peer-review of the main findings.

Another study by Partridge et al. (2004) surveyed 796 oncology physicians and nurses and found that more than half (62.4%) indicated that they offer trial results to participants less than 20% of the time. The majority (72.4%) of responders felt that most of their patients wanted to be informed of the study results, and 79.7% of responders indicated willingness to offer results to most study participants in the future, believing that in most cases their patients want to know results of the trial and provided that routinely offering results would not cause negative effects on patients. Surprisingly, few (16.2%) responders felt that an obligation to offer results to research participants would make such patients less likely to enrol in studies (Partridge et al., 2004), suggesting that PIs might be resistant to the extra post-trial workload even though beneficence would be maximised. A study of Canadian REB chairs found that 94.8% of REB chairs supported offering research results to participants after study completion. While only 19.5% of chairs mentioned that a policy or guideline governing the return of research results to participants existed at their institution, most chairs (72.0%) supported the idea of their REB instituting a set of guidelines recommending that researchers offer results to participants in a lay format (MacNeil & Fernandez, 2007).

This section has attempted to outline some of the typical ethical issues in biomedical research, noting that these issues, reviewed for the purpose of this thesis, are by no means exhaustive. The issues highlighted above were purposively selected from the framework (Emanuel et al., 2004, 8) on which the current study is premised with the goal of facilitating the discussion of findings/ results of the present study. Having described some of the typical ethical issues arising in biomedical research, the next section focuses on studies conducted in both developed and developing countries aimed at investigating RECs and the ethical issues typically raised during their review activities.

2.6 Studies evaluating ethical issues raised by RECs internationally

There is substantial literature on ethical issues raised by developed country RECs. Several papers suggest that UK RECs frequently raise concerns about informed consent (Angell, Biggs, Gahleitner & Dixon-Woods, 2010; Boyce, 2002; Dixon-Woods, Angell, Tarrant & Thomas, 2008). One study found that, of the 339 applications reviewed by a REC in UK, 85% had queries about the participant information sheet (such as inadequate information, jargon, poor clarity, need for proofreading) and 50%) had queries about study design (Boyce, 2002).

A study of cancer trials reported that RECs mostly raised the issue of informed consent (96%), followed by risks to participants (95%) and scientific design (76%) (Dixon-Woods et al., 2008). In a similar study investigating issues raised in research involving human tissues, informed consent was the most frequently raised (Angell, Tarrant & Dixon-Woods, 2009). Similarly, informed consent, recruitment, care and protection of participants, scientific design and

confidentiality were the most frequent issues in applications involving research with children (Angell et al., 2010). Another study of four RECs in UK found that modifications to the participant information sheets were the most common queries raised (57%), followed by requests for further information in the protocol (33%), study design (22%) and informed consent form (21%) (Kent, 1999). Other issues such as missing information, slip-ups and discrepancies were also frequently identified by UK RECs (Angell & Dixon-Woods, 2008, 2009). A study in Brazil reported that the most frequent issues were related to methodology and statistics (77.1%), inadequate language and/or difficulty of understanding the informed consent form (32.2%), lack of detailed information about the study in the informed consent form (25.8%). Further issues raised in the same study were incorrect or incomplete documentation, funding/budget issues and details about the entire research team (Bueno et al., 2009). Similarly, the most frequent issues identified by Novaes et al. (2009) were related to informed consent (30%), methodology (20%), CVs (12%) and budget (9%).

A separate study in Thailand reported that out of 291 protocols, the most frequent queries were research methodology (80.7%), participant information sheet (62.2%), recruitment of participants (60.1%) and informed consent/assent form (51.2%). Furthermore, of the 44 studies involving minority populations in Thailand, the main issues identified included: participant information sheet and consent forms (86.4%), research methodology (84.1%), inclusion-exclusion criteria (72.7%) and treatment and care for participants (65.9%) (Adams et al., 2013). Elsewhere, Adams et al. (2015) found that issues of informed consent were most common for drug trials (93.3%) and biomedical studies (89.5%) while issues concerning privacy and confidentiality tended to be highest for laboratory and epidemiology studies. Overall, the most

common issues were scientific issues about specimen and data collection (60%), participant information sheet (56%) and informed consent (50%).

Queries related to informed consent were frequently identified (98%), in particular requests for changes in the informed consent documents (88%) when compared to other ethical criteria in the Common Rule (Lidz, et al., 2012). A separate study in the US found that stakeholders ranked the following as the most important aspects of REC reviews: (1) favourable risk/benefit ratio; (2) risk minimization; (3) clarity of consent; (4) protection of vulnerable populations; and (5) privacy and confidentiality (Geisser, Alschuler & Hutchinson, 2010). Another study in Canada found that REC members identified scientific merit, risk/benefit, quality of information sheets and consent process, confidentiality, participant selection and financial arrangements as important ethical criteria (Meslin et al., 1994). Elsewhere, a study of a REC in Spain reported that 56.8% of the comments raised in applications reviewed were related to informed consent and confidentiality, 18.9% concerned the principles of beneficence and non-maleficence and the remaining concerned process errors such as incomplete documentation (Martin-Arribas, Rodriguez-Lozano & Arias-Diaz, 2012). The most frequent issues raised by RECs in a study in the Netherlands were related to participant information and consent forms (80.5%), methodology and statistical analyses (70.8%), and supporting documentation, including trial agreements and certificates of insurance (68.1%) (van Lent, Rongen & Out, 2014). A recent study in Finland found that the most frequent reason for not approving research proposals were concerns about participant autonomy and informed consent (70.8%), followed by requests for more information/documents (34.2%) and scientific quality (31.5%) (Hemminki, Virtanen & Regushevskaya, 2015).

This section has reviewed international empirical studies that have been conducted aimed at investigating the ethical issues raised by RECs worldwide. The next section now focuses on local studies that have been conducted to investigate ethical issues raised by African RECs.

2.7 Studies reviewing ethical issues raised by RECs in Africa

There is relatively limited empirical data on the ethical concerns raised by African RECs (Cleaton-Jones, 2010; Clarke, 2014; Klitzman, 2008; Langat, 2005; Sathar, Dhai & van der Linde, 2013; Tsoka-Gwegweni & Wassenaar, 2014). Cleaton-Jones (2010) found that of the 369 protocols reviewed by a REC at the University of Witwatersrand, the top ranked issues were related to informed consent (55%), followed by missing or incomplete information (43%), confidentiality (17%) and sample size (15%). Likewise, informed consent (27.4%), scientific validity (21.3%), fair participant selection (13.9%), and respect for participants (13.8%), were the most frequent issues raised by a different REC (Tsoka-Gwegweni & Wassenaar, 2014). Similarly, Clarke (2014) found that of the 53 protocols reviewed by a REC, the most frequently raised issues were related to study design (21.8%), methodology (20.4%), statistical validity (9.9%) and informed consent (9.2%). Ethical queries about informed consent form (25.4%), methodology and statistics (24.3%), scientific rationale (15.9%), sample size (13.7%) and inclusion/exclusion criteria (6.5%) were also frequently raised by a REC in Nigeria (Eyelade, Ajuwon & Adebamowo, 2011).

The views of South African REC members regarding the content and process of HIV vaccine trials (HVT) suggested that most members believed that participants poorly understood the consent forms, risks and benefits of participating in HVT trials (Klitzman, 2008). Also, REC members frequently differed on the minimum standard of care for participants who acquired HIV infection during the trial; 63% believed it should be the best treatment available worldwide while 11% felt it should be the best available nationally (Klitzman, 2008).

Langat (2005) retrospectively analysed research protocols submitted to two Kenyan RECs in order to identify ethical issues regarding the storage, reuse and exporting of human tissue. He found that most investigators did not recognize the need for informed consent to storage and reuse of samples as most of them neither requested permission nor informed participants of plans to re-use stored samples (Langat, 2005). Another study involving a retrospective audit of protocols submitted to a South African REC evaluated whether ethical issues in collaborative research using human biological materials (HBMs) had not been adequately addressed. The authors concluded that both the REC and researchers did not sufficiently engage with the ethico-regulatory challenges in research involving collection, storage and export of HBMs (Sathar et al., 2013). Concerns about the collection and storage of human biological samples for future use were also raised by Egyptian RECs (Matar & Silverman, 2013). Nine RECs stated that export of samples would require national security clearance, whereas two of 13 RECs absolutely prohibited exportation of biological samples out of Egypt (Matar & Silverman, 2013). Furthermore, similar studies found that REC members were concerned with social value of studies under review (Milford et al., 2006), maximising benefits for local communities and ensuring appropriate informed consent process (Henderson et al., 2007).

2.8 Summary

This chapter reviewed the history and development of research ethics, including key international guidelines. It also reviewed the South African research ethics system. This was the followed by a section reviewing criticism of RECs. Thereafter, literature on ethical issues in biomedical research was reviewed. The chapter concluded with reviewing published studies aimed at investigating ethical issues raised by RECs in developed countries and in Africa. This chapter highlighted that modern-day research ethics was mostly born out of scandals and tragedies of research with human participants (Emanuel et al., 2003). The reviews also suggested that South Africa and other LMICs have since implemented and strengthened their research ethics systems by creating laws and ethical guidelines that enable them to conduct their own ethical review of research activities of both local and international collaborative research in order to protect the rights, dignity and safety of human participants. Furthermore, from the literature reviewed, it is evident that a significant amount of literature exists on the ethical issues raised by conducting biomedical research, particularly in international collaborative research sponsored by wealthy countries and conducted with human participants in less developed countries. Examples of such issues are collaborative partnership, social value, informed consent, standards of care and post-trials access, to name a few. Regarding the types of ethical issues raised by RECs, the literature review has showed that RECs raise an array of issues – although informed consent was the most frequently raised issue. The next chapter discusses the theoretical framework for the present study.

CHAPTER THREE

THEORETICAL FRAMEWORK

3.0 Introduction

This chapter includes a brief discussion of the theoretical framework underpinning this present study. The theoretical framework developed by Emanuel, Wendler, Killen and Grady (2004) is a synthesis of pre-existing international guidance and is widely recognized and very influential in research ethics (Tsoka-Gwegweni & Wassenaar, 2014). This framework provides a comprehensive model for researchers and RECs to ensure ethical conduct of research in developing countries. According to Emanuel et al.'s (2004) framework, for health research in developing countries to be ethical, consideration must be given to the following principles; (1) collaborative partnership, (2) social value, (3) scientific validity, (4) fair selection of study participants, (5) favourable risk benefit ratio, (6) independent review, (7) informed consent and (8) on-going respect for participants and the community. These are summarised briefly below.

3.1 Collaborative partnership

Collaborative partnership involves a holistic approach of establishing meaningful and sustainable local partnerships and establishing trust between researchers and the host community (Emanuel et al., 2004). The local country in which research would be conducted ought to autonomously determine if the proposed research is acceptable and relevant to the health problems of the community (Emanuel et al. 2004). This can be achieved through community engagement to assess health problems to be solved, determine the significance of proposed research, as well as

incorporating research results and products into local health-care system (Benatar & Singer, 2010; Emanuel et al., 2004). Also, collaborative partnership involves strengthening of local research stakeholder capacity to synthesise and disseminate evidence to be used for policy making and health care. Furthermore, there should be fair beneficiation from rewards (such as intellectual property rights, royalties, publications and authorship) emanating from the conduct of research, and the local values and cultural differences should be respected (Emanuel et al., 2004). The UNAIDS/AVAC (2011) guideline is an example of a "gold standard" on collaborative partnerships in biomedical research. The guidelines refers to community stakeholder engagement as a process through which stakeholders responsible for implementing trials build "transparent, meaningful, collaborative and mutually beneficial relationships" with "interested or affected" individuals or groups (UNAIDS/AVAC, 2011, p. 2).

3.2 Social value

The principle of social value is based on the premise that health research should generate knowledge that will ultimately contribute to the improvement in health needs of the participant and the research population. Therefore, it is imperative from the onset that consideration of who will benefit (e.g. participants, local community, host country) from the research should be specified (Emanuel et al., 2004). Research without social value not only wastes resources, but also needlessly exposes participants to risks and burdens for participation in research without any reasonable prospective value (Emanuel et al., 2004). Furthermore, the value of proposed research should be enhanced through appropriate dissemination of results, and use of generated knowledge and /or products to improve the health-care system. However, precautions should be

taken to prevent research that will result in depleting resources of the local health-care system (Emanuel et al., 2004).

3.3 Scientific validity

Scientific validity, in its broadest sense, is an important requirement for any meaningful research. In order to conduct a scientifically valid research, the study design should be such that the research objectives are accomplished within high quality, acceptable scientific standards (e.g. adequate sample size, statistical validity, objective outcome measurement) (Emanuel et al., 2004). Furthermore, the study should be feasible and realizable within the context of the local research community, i.e., consideration should be given to the social, political, or cultural context of the host community in which research would be conducted (Emanuel et al., 2004).

3.4 Fair participant selection

Fair participant selection is centred on the fundamental principle of justice. There should be fair and equitable selection of participants, i.e., selection of the study population should be relevant to the research objectives. For example, under-privileged participants should not be selected because of their poverty, to be exposed to risks and burdens of high-risk studies, whilst wealthy populations are preferentially enrolled in low risk studies (Emanuel et al., 2004). Additionally, vulnerable populations should be identified and protected. For example, proposed research involving vulnerable populations such as prisoners, refugees or persons engaged in illegal activities e.g., sex work or drug use, must be based on valid scientific justification, and not because of social marginalization or prejudice. Where the reasons for their inclusion are valid,

additional mechanisms such as privacy and confidentiality, and freedom to participate or withdraw from a study, should be implemented in order to protect such vulnerable populations (Emanuel et al., 2004).

3.5 Favourable risk/benefit ratio

Rooted in the fundamental principle of non-maleficence and beneficence, risk/benefit assessment ensures that the study has a favourable risk benefit ratio. In the case where the potential risks are outweighed by benefits to participants, then these risks must be justified by the social value of the research (Emanuel et al., 2004). In order to justify risks, benefits to participants should be assessed in terms of the direct benefit of the interventions being tested to the participant's health, or indirectly through scientific knowledge likely to be generated from the study or improvements in the health of the local community in general (Emanuel et al., 2004). The context of an individual (e.g. health background, genetic, social, environment) must be taken into consideration when determining a favourable risk-benefit ratio for the respective participant. Similarly, the net risks to a community (e.g. stigmatization resulting from genetic study that identifies genotype conferring undesirable traits to the community) should be justified in light of the potential benefits to the community (Emanuel et al., 2004).

3.6 Independent review

Consistent with international and national guidance, the Emanuel et al. (2004) framework emphasizes the need for independent ethics reviews mandated by local laws and regulations (Emanuel et al., 2004). For example in South Africa, approval by a REC and the Medicines Control Council (MCC) is required for clinical trials of drugs (Department of Health, 2015).

3.7 Informed consent

Informed consent is one of the cornerstones of ethical research involving human participants (Emanuel et al., 2004). Central tenets for valid informed consent processes include the following components: information disclosure, understanding, voluntariness to decide without coercion, capacity to consent (Lindegger & Richter, 2000). The information should be disclosed in a culturally appropriate manner (Emanuel et al., 2004). Furthermore, there is need to involve local community stakeholders in establishing an effective informed consent process that is locally acceptable; however, this should not override individual consent (Emanuel et al., 2004; Lindegger & Richter, 2000). Importantly, the participants should have the freedom not to participate or to withdraw from the trial without any penalties (Emanuel et al., 2004).

3.8 Respect for participants and the community

Respect for participants is an important ethical principle underpinning several ethical guidelines. The Emanuel et al. (2004) framework emphasizes the need to protect the privacy and confidentiality of research participants. Furthermore, there should be plans to ensure the timely and appropriate (culturally and linguistically) dissemination of results and information arising

from the study to the participants and their communities. Additionally, participants should be provided with medical care and interventions, including research-related injuries, and access to such interventions after the study - so-called post-trial access (Emanuel et al., 2004).

3.9 Summary

The above section has described the theoretical framework (Emanuel et al., 2004) on which the present study is based. The framework's eight principles of ethical research involving human participants have been described. These are (1) collaborative partnership, (2) social value, (3) scientific validity, (4) fair selection of study participants, (5) favourable risk-benefit ratio, (6) independent review, (7) informed consent and (8) on-going respect for participants and the community. Having described the important theoretical framework on which this study is premised, and highlighted the eight key benchmarks of ethical research, the following chapter will describe the aims and objectives of the present study.

CHAPTER FOUR

AIMS AND OBJECTIVES

The general aims of this study were to examine ethical issues raised by two South African biomedical RECs based on the theoretical framework outlined in the Chapter 3.

The specific study objectives were:

1. To identify the ethical issues typically raised by two South African biomedical RECs.
2. To apply the Emanuel et al. (2004) framework to evaluate the ethical issues raised.
3. To qualitatively explore the views of REC members regarding the issues identified in (1) above.
4. To determine whether findings in (1) align with national research ethics guidance.

The specific research questions were:

1. What specific ethical issues are raised by two South African biomedical RECs?
2. Is the theoretical framework by Emanuel et al. (2004) compatible with the ethical issues and concerns raised by two large biomedical RECs in South Africa?
3. What are the views of REC members regarding the ethical issues raised in (1) above?
4. Do ethical issues raised by RECs align with established national ethics guidance?

CHAPTER FIVE

METHODOLOGY

5.0 Overview of methods and study design

In line with the overall objective to investigate the ethical issues raised by RECs reviewing biomedical research protocols and to explore REC members' views on, and understanding of these ethical issues, this project was designed in three work packages.

Work package 1 comprised a retrospective audit of records from two biomedical RECs located at two different universities in South Africa. The data were extracted, anonymized and coded using a predetermined theoretical framework (Emanuel et al., 2004). This enabled both deductive and inductive content analysis of themes emerging from the data, whilst also yielding the frequency and ranking of ethical issues identified. Data from each REC were analysed, compared and then combined.

Work package 2 consisted of qualitative semi-structured interviews with REC members in order to explore their views and understanding of the ethical issues identified from work package (1) above.

Work package 3 was included in order to determine whether the findings from the work packages above align with national and international research ethics guidance. This included a review of national guidance (Department of Health, 2015), and a comparison with themes identified in work packages (1) and (2) above.

The implementation of the most appropriate design which adequately answers the research questions and objectives for this project was of critical importance. As such, the study adopted a largely qualitative study design encompassing document review and semi-structured interviews. The purpose of incorporating a mixture of research methods and data sources was to explore the types of ethical issues from a variety of different perspectives. This approach may be viewed as a form of triangulation (Kelly, 2006), a term used to refer to the process of comparing the results from either two or more different data collection methods (in this case, document analysis and semi-structured interviews) or, more simply, two or more data sources (in this case, records from two different RECs and semi-structured interviews with different REC members). According to Patton (2002), there are four types of triangulation: data triangulation (the use of various sources of data), investigator triangulation (the use of multiple coders, and comparing codes), theory triangulation (the use of multiple perspectives to interpret the study data) and methodological triangulation (the use of a variety of research methods within the study).

5.1 Methodology for work package 1 – analysis of REC minutes

This work package comprised a retrospective audit of minutes from two South African biomedical RECs. The aim of the audit was to identify the types of ethical issues raised by RECs reviewing biomedical research, with a twofold purpose: The intention was to review records for projects reviewed by both RECs for a five-year period (2009-2014). The researcher (in consultation with the contact person in each REC) estimated that an analysis of records over this five-year period would suffice to identify the types of ethical issues raised by both RECs. Furthermore, it was assumed that reviewing data from the past five years would yield a reasonable sample size considering that it was predominantly qualitative content analysis.

5.1.1 Sampling Strategy

After obtaining gatekeeper permissions, records for all research reviewed by the two RECs between 2009 and 2014 were accessed from the respective REC administrators. Purposive sampling was used to select minutes and decision letters for initial applications reviewed by full committee members (i.e., only more than minimal risk studies reviewed at full REC meetings were included). Thus, expedited studies that are reviewed by one or two REC members and then ratified by the committee were not included. Furthermore, applications for recertification, responses to queries, and amendments were excluded. While outright approval does not necessarily imply that there were no ethical issues identified in the research proposal, only studies given conditional approval or rejected were purposively selected since these indicate that REC has raised at least some issue(s) with the research proposal. A systematic random sampling technique was then used to select every 3rd case yielding a total of 180 protocols for analyses. Data were extracted in de-identified format to maintain confidentiality, onto a data collection sheet (Appendix 1). From the minutes of the 180 protocols reviewed by the two biomedical RECs during the years 2009 to 2014, REC queries were extracted and categorised. Two independent coders assessed REC minutes for each protocol to identify, code, and rank the frequency of ethical issues raised by the two RECs according to the eight principles and benchmarks described by Emanuel et al. (2004). The agreement between the two coders was 75%. Disagreements were addressed by discussion to reach consensus between the two coders.

5.1.2 Data analysis

Qualitative content analysis was chosen as the most suitable approach because it enables the researcher to interpret meaning from the content of the text data (Hsieh & Shannon, 2005). The Emanuel et al. (2004) framework was used to code and deductively analyse data. In order to identify salient emergent themes not described in the framework, inductive analysis was also applied (Hsieh & Shannon, 2005). The data were coded into eight broad themes based on the Emanuel et al. (2004) framework and an additional two emergent categories. Coding each protocol involved careful reading and re-reading of each query contained in the RECs' minutes and decision letters, and identifying the primary, central ethical issue. Where more than one issue emerged, these were coded into the primary category under which it seemed to best fit. Given the huge volume of the data set, it was impractical to have a second coder for all the data. However, a few random cases (n=20) were verified by a second coder with expertise in the Emanuel et al. (2004) framework and REC activities. The coding was discussed and any differences were resolved by consensus.

5.2 Methodology for Work package 2- Semi-structured interviews

5.2.1 Rationale for method

Semi-structured interviews allow in-depth understanding of how individuals experience or understand a particular phenomenon in their context (Patton, 2002). Unlike quantitative methods that focus on breadth, representativeness and generalizability, semi-structured interviews do not necessarily aim to have a representative sample, but rather focus on depth, insight and transferability of findings. The second work package of this present study, (i.e., exploring views

of REC members regarding ethical issues identified in work package 1), is best answered using semi-structured interviews. However, the main disadvantage of such interviews is that the quality and amount of data may be influenced by the interviewer's qualitative interviewing skills.

5.2.2 Participant sampling strategy

The researcher first approached the REC chairs at each respective site to request assistance with recruitment of REC members. At REC 1, the chair (after informing REC members about my study during one of their monthly meeting) granted the researcher access to the names and contact details of all REC members. Thereafter, a recruitment email was sent to each member inviting them to volunteer to participate. Initially, four out of 22 members responded and expressed willingness to participate. Follow-up reminder emails were sent to the remaining members who did not respond to the first email. Another three members responded, but two withdrew, citing time constraints and commitment to other activities. A third and final follow-up email was sent to members who had not previously responded. There was no further response. A total of five members from REC 1 consented to participate in the study. Various attempts were made to recruit members from both RECs, but most of these attempts were met with silence and refusals. This was not to be unexpected as reports have suggested that RECs are reluctant to be researched (de Jong et al., 2012; Klitzman, 2015; Stark, 2012).

At REC 2, the chair recommended that a group email be sent to all members inviting them to participate in the study. Members were requested to indicate their willingness to have their contact details shared with the researcher for follow-up direct contact from the researcher. Two

members initially consented to participate. After a month, reminder emails were sent to the members who had not initially responded. A further two responded and consented to participate. A third and final reminder email was sent to members who had not responded to the previous emails, but there was no further response. A total of four members from REC 2 agreed to have their contact details shared, and participate in the study. Overall, 9 members consented to take part in this project. Each member was then provided with graphs summarizing the data from work package 1(Figure 9). Semi-structured interviews lasting between 30-45 minutes were conducted face-to-face or by telephone using a semi-structured interview guide (Appendix 2). Probes, clarifications and follow-up questions were used to elicit broader views from respondents. The interviews were recorded and transcribed verbatim.

5.2.3 Data analysis

Thematic analysis was used to code and analyse the narrative data from the transcripts and identify salient themes emerging from the data (Hsieh & Shannon, 2005). This method allows a consistent examination of themes contained in the data. Data were analysed both inductively and deductively to identify themes grounded in the data. Emerging codes and themes were sought by disaggregating the data and constantly comparing for similarities and differences (Patton, 2002).

5.3 Methodology for work package 3- Comparison of findings with national ethics guidance

Thematic content analysis (Hsieh & Shannon, 2005) of national department of health guidelines (Department of Health, 2015) was conducted to identify emerging themes. These were compared to the findings in work package 1 to determine the level of congruence.

5.4 Reliability and Validity

Reliability refers to the degree to which a measure of a concept is stable or trustworthy (Bryman, 2004). Validity entails ensuring that an instrument measures the construct it is designed to measure (Bryman, 2004). Several strategies were implemented to maximize the reliability and validity of findings of the present study. First, the coding of minutes was done by two independent coders to ensure inter-coder reliability. The coding framework was discussed and any disagreements resolved by consensus, where appropriate. Furthermore, the interview guide for the qualitative interviews was developed in consultation with an ethics expert and qualitative researcher. This was then pilot tested with a sample of six experts before the actual data collection. Pilot testing ensured that the broad questions in the interview guide were in line with the study objectives. The data collected during the piloting was not used in the study findings.

5.5 Ethical Considerations

Following the Emanuel et al. (2004) framework for determining whether research is ethical, the following ethical issues applied to this study.

5.5.1 Collaborative partnership

Collaborative partnership requires that a researcher develop research in collaboration with the relevant local stakeholders so as to ensure that local context is respected (Emanuel et al., 2004). Taking this into consideration, the two biomedical RECs sampled in this study were selected based on prior consultation with relevant stakeholders knowledgeable in research ethics systems at the respective universities. Furthermore, gatekeeper permissions were also obtained from the relevant institutional authorities. In order to avoid revealing the identities of the RECs, the gatekeeper permission letters are not included in the Appendices section, but they are on record.

5.5.2 Social value

The principle of social value requires that proposed research should benefit the participants and community (Emanuel et al., 2004). In light of this, it is hoped that the present study has potential social value because its findings may generate novel empirical data on the actual issues typically raised by two busy South African biomedical RECs. Such information might inform training of REC members, researchers and future guideline developers.

5.5.3 Scientific validity

Scientific validity requires that proposed research uses high quality and scientifically valid study design and methodology in order to achieve the objectives of the study. In view of that, a full description of the research questions and methodology was addressed, including issues of validity and reliability. Furthermore, to ensure high quality results, data analysis was conducted by two independent coders with vast experience in empirical research ethics.

5.5.4 Fair selection of participants

This principle necessitates unbiased selection of participants based on the research objective. Firstly, the REC minutes or decision letters sampled were randomly selected. Second, the two participating RECs, and REC members, were purposively selected based on availability and willingness to participate, without any bias or unfair predetermined inclusion/exclusion criteria.

5.5.5 Favourable risk/benefit ratio

The principle of favourable risk/benefit ratio requires identification and minimization of potential risks, and maximising benefits (Emanuel et al., 2004). The present study did not have any direct risk associated with participation. The potential risk of harm to the reputation of either of the RECs and their host institutions is offset by anonymization. It is hoped that this minimal risk study has the potential of generating useful information that might benefit RECs and researchers as mentioned above. Interviewees were also anonymised.

5.5.6 Independent ethics review

This principle necessitates competent and independent review of research proposals by an accredited REC. Accordingly, this study received ethical approval from the two participating RECs. To maintain anonymity and confidentiality, the full ethics approvals obtained from the participating RECs are omitted from the Appendices, but are available on request for audit purposes.

5.5.7 Informed consent

The principle of informed consent requires that a participant should give voluntary informed consent before participating in a study. Therefore, written informed consent was obtained from REC members for their participation in semi-structured interviews. The members were informed that participation was voluntary and that they could freely choose to refuse or withdraw from the study at any time without any penalty. They were also free not to answer any questions they chose not to answer.

5.5.8 Ongoing respect for participants

According to Emanuel et al. (2004), the principle of respect for participants entails, among other things, protecting the confidentiality of participants and communities, providing participants with information that arises in the course of the research study and informing participants of the study results. In view of this and as mentioned above, the identities of the two RECs and REC members sampled in this study were kept anonymous and confidential in order to prevent

stigmatization and discrimination. Furthermore, the results from this study will be communicated to the participating RECs. Care will be taken to avoid revealing the identities of the two RECs in future publications in journals.

5.6 Summary

This chapter described the research methodology used in this study. The primary purpose of this study was to investigate the ethical issues raised by two South African biomedical RECs. Specifically this study aimed to determine the ethical issues raised by RECs using the Emanuel et al. (2004) framework, explore the views of REC members regarding the ethical issues raised and to determine the alignment of the issues identified above with existing South African national ethics guidance (Department of Health, 2015). The data collection and analysis process were described and the ethical considerations were outlined above.

CHAPTER SIX

RESULTS

6.0 Introduction

The section describes the main findings of the study. The results are divided into the three different work packages described in Chapter 5. Briefly, work package (1) focuses on the ethical issues identified through retrospective review of minutes and decision letters from the two RECs. Thereafter, work package (2) focuses on the views and perspectives of REC members regarding the issues identified in work package 1 above. The final work package (3), concludes by comparing the findings from work packages above with principles in the national guidance (Department of Health, 2015).

6.1 Results for Work package 1

6.1.1 Characteristics of the study sites

REC 1 has 22 members, while REC 2 has 44 members. The membership of the two RECs is varied, constituting both males and females from various disciplines – mostly clinicians and medical professionals, epidemiologists, public health specialists, social scientists, ethicists and one or two lay members - thus complying with the national guidelines (Department of Health, 2015). Both RECs meet on a monthly basis. The REC application forms, informed consent template and other documents relevant to ethics applications and standard operating procedures (SOPs) are available publicly online. Applicants have to submit these before a specified deadline

for consideration in the following month's meeting. For non-expedited, i.e., more than minimal risk studies, the focus of the present study, the proposal is assigned to primary and secondary reviewers, and occasionally to a third assigned reviewer. During the convened scheduled meeting, the chair declares the session open after quorum and requests any members to declare conflict of interests (so that they do not take part in the review process if there is any conflict of interest). The primary reviewer then presents a written synopsis of the study and then presents ethical issues identified in the proposals. These issues are also tabled in writing. The secondary and third reviewers repeat this process but without the synopsis. Thereafter the full committee discusses the ethical merits of each proposal on the meeting's agenda and the administrator records the discussion points and integrates them with the written reviews that comprise the minutes from which the decision letters are compiled and sent to the applicants. In this study, the researcher was given gatekeeper permission to access the minutes and decision letters from the two participating RECs. To preserve anonymity and confidentiality, the minutes and letters are not provided in the appendices but are available for audit purposes.

6.1.2 Characteristics of studies sampled

The characteristics of the studies sampled in this study are summarised in Table 2 below. At REC 1, most of the research proposals sampled in this study were clinical trials (53%) while the remaining (47%) were observational studies. At REC 2, half of the studies were clinical trials (50%) and the other 50% were observational studies (Table 2). The type of review caseload of both RECs was thus nominally similar. Overall, clinical trials constituted the majority (52%) of protocols reviewed by the two RECs included in this study. In terms of the subject area,

aggregated data from both RECs shows that the majority of research protocols were in the field of HIV/AIDS (45%) and TB (31%) With regard to the type of research participants, the research protocols sampled in this study consisted of mostly adults (48%), followed by children (31%) (Table 2).

Table 2: Characteristics of protocols sampled in this study

	REC 1 (*n*=90)	REC 2 (*n*=90)	Total
Type of study			
Clinical trials	48 (53%)	45 (50%)	93 (52%)
Observational studies	42 (47%)	45 (50%)	87 (48%)
Area of research			
HIV/AIDS	45 (50%)	36 (40%)	81 (45%)
TB	22 (24%)	33 (37%)	55 (31%)
Cancer	8 (9%)	11 (12%)	19 (11%)
Heart disease	6 (7%)	0 (0%)	6 (3%)
Diabetes	5 (6%)	0 (0%)	5 (2%)
Others/ unspecified	4 (4%)	10 (11%)	14 (8%)
Participants			
Adults	39 (43%)	48 (53%)	87 (48%)
Children	20 (22%)	36 (40%)	56 (31%)
Pregnant women	8 (9%)	0 (0%)	8 (4%)
Unknown	23 (26%)	6 (7%)	29 (16%)

6.1.3 Approval decisions on protocols reviewed

Table 3 below shows the initial decision outcomes of the studies reviewed. Of the 90 protocols included in this study that were submitted for initial review at REC 1, 84% were conditionally approved while the other 13% were not approved and 2% was deferred. On the other hand, 93%

were conditionally approved and 7% not approved. At both RECs, none of the protocols reviewed received full approval at initial review (Table 3).

Table 3: Initial review outcomes of proposals included in this study

Initial review outcome	REC 1 (*n*=90)	REC 2 (*n* =90)	Total (*n*=180)
Conditional approval	76 (84%)	84 (93%)	160 (89%)
Not approved	12 (13)%	6 (7%)	18 (10%)
Deferred	2 (2%)	0 (0%)	2 (1%)
Full approval	0 (0%)	0 (0%)	0 (0%)

6.1.4 Ethical issues raised in the protocols sampled

The section below describes the findings regarding the ethical frequency and percentages of ethical issues raised by the two RECS. In the sections which follow, data from REC 1 will be presented first, followed by data from REC 2, followed by a comparison of the two data sets.

6.1.4.1 Emanuel et al. (2004) ethical issues raised by REC 1

There were a total of 1274 queries raised in 90 protocols sampled at REC 1. The most frequent Emanuel et al. (2004) ethical issues raised by REC 1, ranked in descending order of frequency, included queries related to informed consent (23.9%), respect for participants (18.9%) and scientific validity (18%). Other ethical issues raised by REC 1 in the protocols sampled for this study included collaborative partnership (8.1%), fair participant selection (4.8%), favourable risk-benefit ratio (4.5%) and independent ethics review (3.5%). The least frequently raised issues were about social value (1.3%) (Table 4 and Figure 1).

Table 4: Emanuel et al. (2004) ethical issues raised by REC 1

Emanuel et al. (2004) principles	Number of queries (*N*)	Percentage of queries (%)	Rank of frequency
Informed consent	305	23.9	Highest
Respect for participants	241	18.9	
Scientific validity	229	18	
Collaborative partnership	103	8.1	
Fair participant selection	61	4.8	
Favourable risk-benefit ratio	57	4.5	
Independent ethics review	44	3.5	
Social value	17	1.3	Lowest

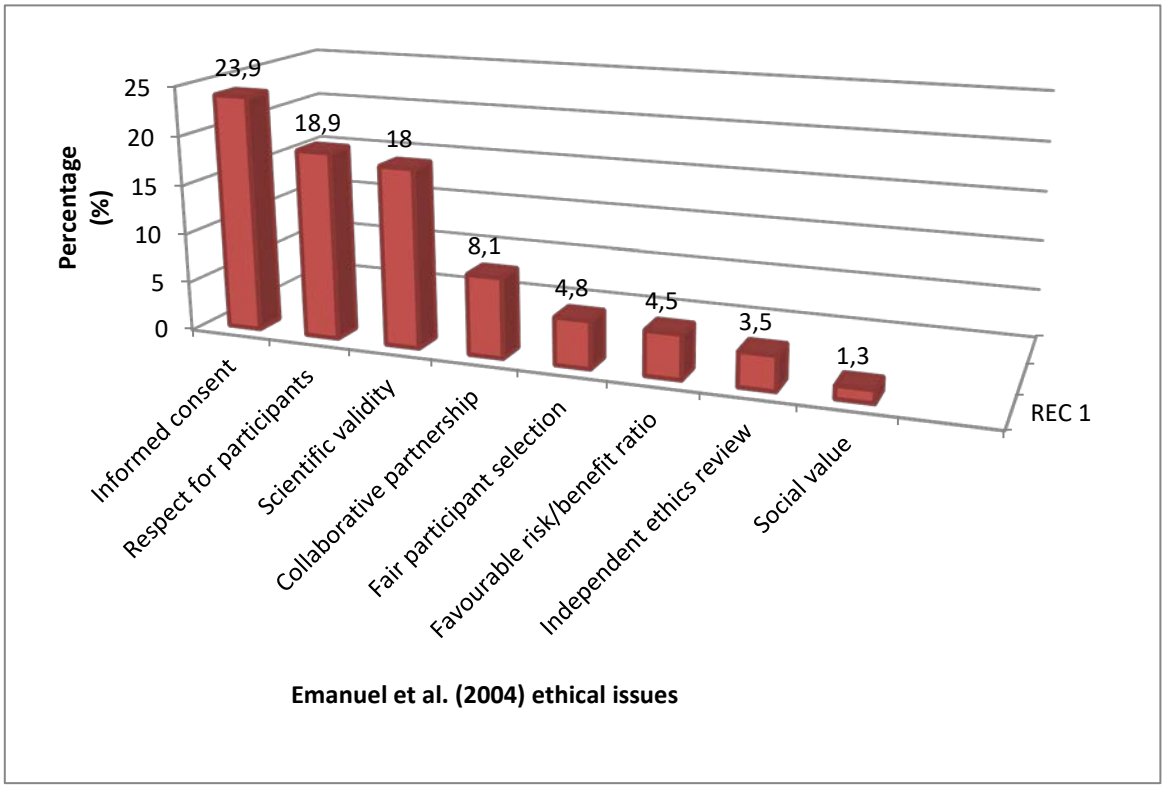

Figure 1: Ethical issues raised by REC 1

6.1.4.2 Emanuel et al. (2004) ethical issues raised by REC 2

At REC 2, there were 510 queries raised in 90 protocols sampled in this study. Informed consent issues were the most frequent (31%), followed by respect for participants (19.6%) and scientific validity (13.5%).Other ethical issues raised by REC 2 included queries related to favourable risk-benefit ratio (6.5%), independent ethics review (3.5%), fair participant selection (3.1%) and collaborative partnership (2.5%). The lowest percentage of ethical issues raised by REC 2 were about social value (1%) (Table 5 and Figure 2).

Table 5: Emanuel et al. (2004) ethical issues raised by REC 2

Emanuel et al. (2004) principles	Number of queries (*N*)	Percentage of queries (%)	Rank of frequency
Informed consent	158	31	Highest
Respect for participants	100	19.6	
Scientific validity	69	13.5	
Favourable risk-benefit ratio	33	6.5	
Independent ethics review	18	3.5	
Fair participant selection	16	3.1	
Collaborative partnership	13	2.5	
Social value	5	1.0	Lowest

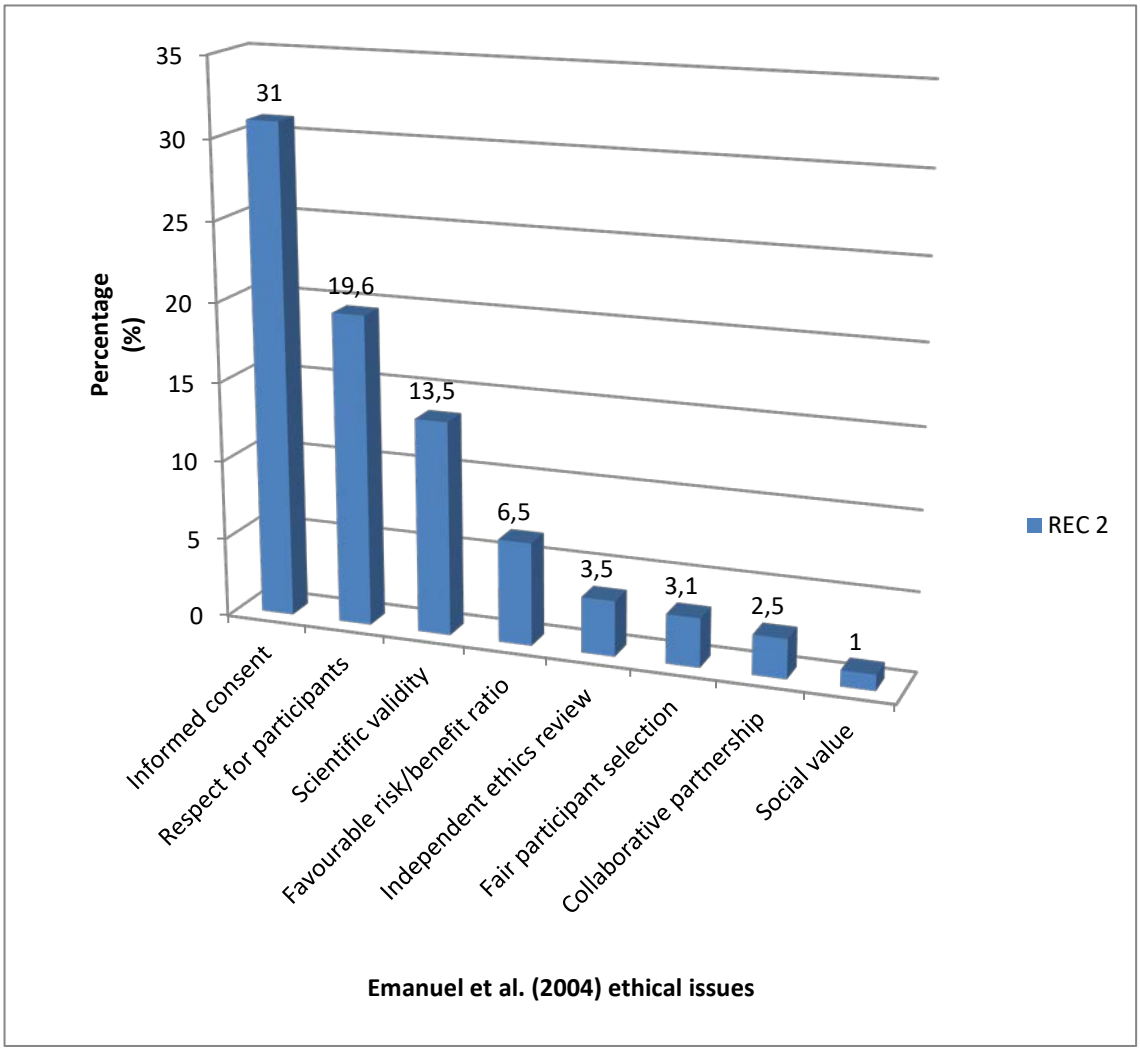

Figure 2: Ethical issues raised by REC 2

6.1.4.3 Comparison of Emanuel et al. (2004) issues raised by both RECs

A comparison of the ranking/frequency of the Emanuel et al. (2004) ethical issues raised by each REC, as shown in Figure 3, is presented below in descending order. The most frequent issues raised by both RECs were informed consent (ranked 1st), respect for participants (ranked 2nd) and scientific validity (ranked 3rd). It is clear from Figure 3, that other ethical issues were ranked differently between the two RECs. Specifically, the fourth ranked issue at REC 1 was collaborative partnership (8.1%) while at REC 2 it was favourable risk/benefit ratio (6.5%). Similarly, independent ethics review was ranked 5th at REC 2, while the 5th ranked issue at REC 1 was fair participant selection (3.1%). Furthermore, the 6th ranked issue at REC 1 was favourable risk/benefit ratio (4.5%), while it was fair participant selection (3.1%) for REC 2. The principle of independent ethics review (3.5%) was ranked 7th at REC 1, while collaborative partnership was ranked seventh (2.5%) at REC 2. Social value was the least frequent issue, ranked 8th by both RECs.

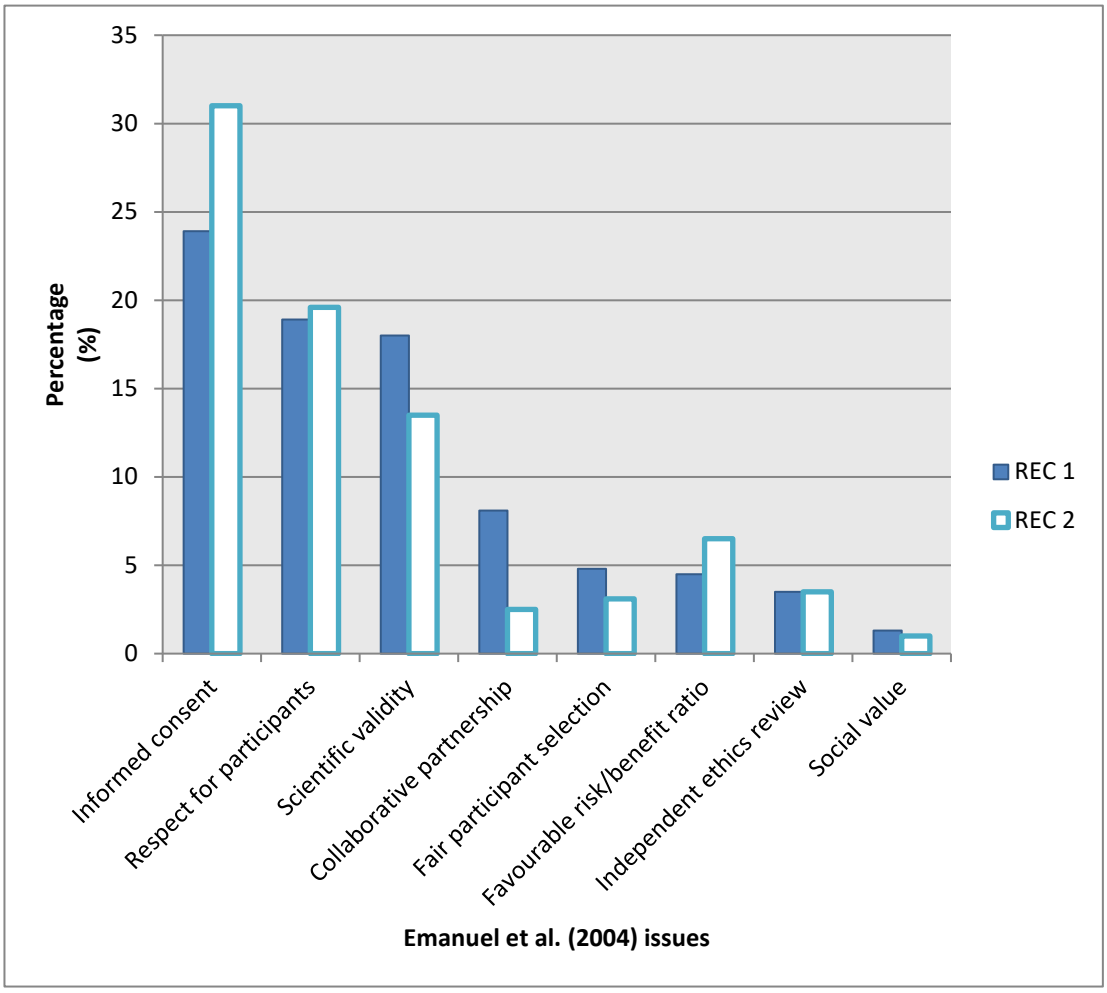

Figure 3: Comparison of ethical issues raised by both RECs

6.1.5. Sub-analysis of Emanuel et al. (2004) ethical issues raised by REC 1

Further sub-analyses of the eight broad categories of ethical issues (Emanuel et al., 2004) raised by both RECs were conducted in order to identify sub-themes and codes emerging from the data. The data for REC 1 are presented below in decreasing order of frequency.

6.1.5.1 Informed consent (23.9%)

Table 6 below shows that the most frequent queries under informed consent were requests for adequate information (e.g., study procedures, risks, benefits, contact details of investigators) (50.8%), rewording and simplification of language in the consent documents (38.7%) and ensuring voluntary participation and withdrawal from the study without any penalties (10.4%).

Table 6: Informed consent queries raised by REC 1 (n=305)

Ethical principle	Specific queries raised	Frequency	Percentage
Informed Consent	Complete information	155	50.8%
	Rewording and simplification of language	118	38.7%
	Valid and voluntary consent process	32	10.4%

6.1.5.2 Respect for participants (18.9%)

Table 7 below shows that under the principle of respect for participants, the majority of queries raised were related to participant care during and after research (29%), including post-trial access to interventions (26.1%). Additional queries that were commonly raised included issues related to privacy and confidentiality (23.2%), compensation and reimbursements (17.4%) and informing participants and the community of research findings in ways that are culturally and linguistically appropriate (4.1%).

Table 7: Respect for participants queries raised by REC 1 (n=241)

Ethical principle	Specific queries raised	Frequency	Percentage
Respect for participants	Participant care during and after research	70	29.0%
	Post-trial access	63	26.1%
	Privacy and confidentiality	56	23.2%
	Reimbursements and compensation	42	17.4%
	Dissemination of results to participants	10	4.1%

6.1.5.3 Scientific validity (18%)

Table 8 below shows that of the scientific validity issues identified, most concerns were related to methodology (34.9%), study design (25.3%), data collection instruments (15.7%), research questions and feasibility (13.1%), statistical validity (6.9%) and sample size (3.9%).

Table 8: Scientific validity queries raised by REC 1 (n=229)

Ethical principle	Specific queries raised	Frequency	Percentage
Scientific validity	Methodological clarifications	80	34.9%
	Research design	58	25.3%
	Data collection instruments	36	15.7%
	Research question/ feasibility	30	13.1%
	Statistical validity	16	6.9%
	Sample size	9	3.9%

6.1.5.4 Collaborative partnership (8.1%)

Table 9 below shows that of the overall queries under collaborative partnership, most (48.5%) of the concerns were about developing partnerships with researchers, and other research stakeholders in planning and conducting proposed research, as well as developing capacity for local researchers. This was followed by the need to respect local community cultural values and beliefs (41.7%). Other issues emerging were concerns about ensuring that research results are disseminated to relevant stakeholders and used to enhance local health systems (9.7%).

Table 9: Collaborative partnership queries raised by REC 1 (n=103)

Ethical principle	Specific queries raised	Frequency	Percentage
Collaborative partnership	Develop partnerships and build local capacity	50	48.5%
	Community consultation and respect for local culture and practices	43	41.7%
	Integrating research results into local healthcare system	10	9.7%

6.1.5.5 Fair participant selection (4.8%)

Table 10 below indicates that of the issues queried under fair participant selection, the most common were appropriate recruitment methods (50.8%), unbiased inclusion/ exclusion of study population (40.9%) and safeguarding vulnerable participant groups such as children (8.1%).

Table 10: Fair participant selection queries raised by REC 1 (n=61)

Ethical principle	Specific queries raised	Frequency	Percentage
Fair Participant selection	Appropriate recruitment method	31	50.8%
	Unbiased inclusion/exclusion	25	40.9%
	Safeguard vulnerable populations	5	8.1%

6.1.5.6 Favourable risk/benefit ratio (4.5%)

Table 11 below highlights that most of the queries under risk-benefit ratio were related to identification of study risks and burdens (50.8%) and ensuring that the risks are minimized to the greatest extent possible in relation to the potential benefits (49.1%).

Table 11: Favourable risk/benefit ratio queries raised by REC 1 (n=57)

Ethical principle	Specific queries raised	Frequency	Percentage
Favourable risk/benefit ratio	Identification of risk and burdens to participants	29	50.8%
	Mitigation of risks	28	49.2%

6.1.5.7 Independent ethics review (3.5%)

Table 12 below shows that under independent review, most of the queries were related multisite ethical approvals in collaborative studies (52.2%) and regulatory approvals, for example approvals from the Medicines Control Council (MCC) for all clinical drug trials (47.8%).

Table 12: Independent ethics review queries raised by REC 1 (n=44)

Ethical principle	Specific queries raised	Frequency	Percentage
Independent review	Ethics approval by RECs	23	52.2%
	Other regulatory approvals	21	47.8%

6.1.5.8 Social value (1.3%)

Table 13 below shows that for social value, most of the queries (12.2%) were related to the importance of proposed studies, as well as enhancing the value of research for enrolled participants and communities (4.4%).

Table 13: Social value queries raised by REC 1 (n=17)

Ethical Principle	Specific queries raised	Frequency	Percentage
Social Value	Importance and value of study	11	64.7%
	Enhance value for participants	6	35.3%

6.1.6 Sub-analysis of Emanuel et al. (2004) issues raised by REC 2

Further analyses were performed to identify sub-themes within each particular ethical category raised by REC 2. The results are described below in descending order of frequency, i.e., informed consent (31%), respect for participants (19.6%), scientific validity (13.5%), favourable risk-benefit ratio (6.5%), independent review (3.5%), fair participant selection (3.1%), collaborative partnership (2.5%) and social value (1%).

6.1.6.1 Informed consent (31%)

Table 14 below shows that the most frequently discussed queries under informed consent were requests for adequate information (e.g. study procedures, risks, benefits, contact details of investigators) (42.4%), rewording and simplification of language in the consent documents (34.2%) and ensuring voluntary participation and withdrawal from the study without any penalties (23.4%).

Table 14: Informed consent queries raised by REC 2 (n=158)

Ethical principle	Specific queries raised	Frequency	Percentage
Informed Consent	Complete information	67	42.4%
	Rewording and simplification of language	54	34.2%
	Valid and voluntary consent process	37	23.4%

6.1.6.2 Respect for participants (19.6%)

Table 15 below shows that under the principle of respect for participants, the majority of queries raised were related to participant care during and after research (36%), including post-trial access to interventions (24%). Other queries raised included privacy and confidentiality (19%), compensation and reimbursements (15%) and informing participants and the community of research findings in ways that are culturally and linguistically appropriate (6%).

Table 15: Respect for participants queries raised by REC 2 (n=100)

Ethical principle	Specific queries raised	Frequency	Percentage
Respect for participants	Participant care during and after research	36	36%
	Post-trial access	24	24%
	Privacy and confidentiality	19	19%
	Reimbursements and compensation	15	15%
	Dissemination of results to participants	6	6%

6.1.6.3 Scientific validity (13.5%)

Table 16 below shows that, of the scientific validity issues identified, the majority of concerns were related to methodology (40.6%), study design (21.7%), measuring instruments (14.5%), sample size (11.6%) and feasibility (11.6%). There was significance difference ($p < 0.05$) noted between the two RECs.

Table 16: Scientific validity queries raised by REC 2 (n=69)

Ethical principle	Specific queries raised	Frequency	Percentage
Scientific validity	Methodological clarifications	28	40.6%
	Research design	15	21.7%
	Data collection instruments	10	14.5%
	Sample size	8	11.6%
	Feasibility	8	11.6%

6.1.6.4 Favourable risk-benefit ratio (6.5%)

Table 17 below shows that the most frequent queries under risk-benefit ratio were related to identification of study risks and burdens (54.5%) and ensuring that the risks are minimized to the greatest extent possible in relation to the potential benefits (45.5%).

Table 17: Favourable risk/benefit ratio queries raised by REC 2 (n=33)

Ethical principle	Specific queries raised	Frequency	Percentage
Favourable risk/ benefit ratio	Identification of risk to participants	18	54.5%
	Mitigation of risks	15	45.5%

6.1.6.5 Independent ethics review (3.5%)

Table 18 below shows that for independent ethics review, most of the queries were related to multisite ethical approvals in collaborative studies (55.6%) and regulatory approvals, for example approvals from the Medicines Control Council for all clinical drug trials (44.4%).

Table 18: Independent ethics review queries raised by REC 2 (n=18)

Ethical principle	Specific queries raised	Frequency	Percentage
Independent review	Ethics approval by RECs	10	55.6%
	MCC approvals and other regulatory requirements	8	44.4%

6.1.6.6 Fair participant selection (3.1%)

Table 19 below indicates that of the issues queried under fair participant selection, the most common were appropriate inclusion/ exclusion study population (56.3%), recruitment methods (31.2%), and safeguarding vulnerable participant groups (12.5%).

Table 19: Fair participant selection queries raised by REC 2 (n=16)

Ethical Principle	Specific queries raised	Frequency	Percentage
Fair Participant selection	Unbiased inclusion/ exclusion	9	56.3%
	Appropriate recruitment method	5	31.2%
	Safeguard vulnerable populations	2	12.5%

6.1.6.7 Collaborative partnership (2.5%)

Table 20 below shows that, for collaborative partnership, most (13.3%) of the queries were about developing partnerships with researchers, and other research stakeholders in planning and conducting proposed research, as well as developing capacity for local researchers. This was followed by the need to respect local community cultural values and beliefs (6.6%). Other issues emerging were concerns about ensuring that research results are disseminated to relevant stakeholders and used to enhance local health systems (2.2%). There was significant difference ($p < 0.05$) noted between the two RECs.

Table 20: Collaborative partnership queries raised by REC 2 (n=13)

Ethical principle	Specific queries raised	Frequency	Percentage
Collaborative partnership	Develop meaningful partnerships and local capacity	7	53.8%
	Community consultation and respect for local culture and practices	5	38.5%
	Integrating research results into local healthcare system	1	7.7%

6.1.6.8 Social value (1%)

Table 21 below shows that, for social value, most of the queries (60%) were related to the importance of proposed studies, as well as enhancing the value of research for enrolled participants and communities (40%).

Table 21: Social value queries raised by REC 2 (n=5)

Ethical Principle	Specific queries raised	Frequency	Percentage
Social Value	Importance and value of study	3	60%
	Enhance value for participants	2	40%

6.1.7 Additional issues raised by RECs

Furthermore, there were additional queries raised by both RECs that could not be coded using the eight categories in the Emanuel et al. (2004) framework. These were mostly coded as administrative queries and errors.

6.1.7.1 Additional issues raised by REC 1

The additional issues raised by REC 1 are summarised below in Table 22 and shown in Figure 4. The findings showed that most of the additional queries were administrative queries (68.2%) related to research budgets (34.9%), investigators' CVs (34.2%), details about the research team (17.8%) and missing signatures, for example from the co-principal investigators (13%). Furthermore, the results showed that errors were identified in 31.8% (*n*=68) of the protocols sampled in this study.

Table 22: Additional queries raised by REC 1 (n=214)

Additional issues raised	Frequency	Percentage
Administrative issues	146	68.2%
Research budgets	51	34.9%
Researchers' CVs	50	34.2%
Details about the research team	26	17.8%
Missing signatures	19	13%
Errors	68	31.8%

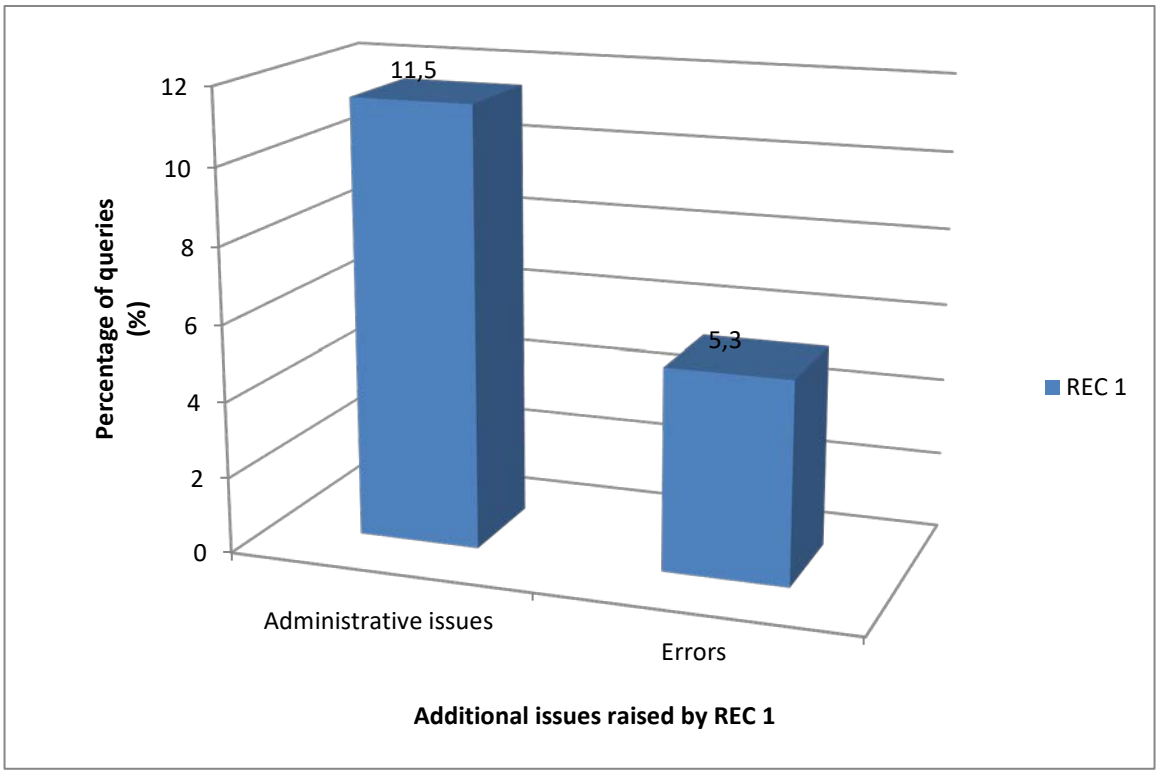

Figure 4: Percentage of additional queries raised by REC 1

6.1.7.2 Additional issues raised by REC 2

Similarly, for REC 2, most of the additional issues raised were coded as administrative queries (69%) and errors (30.9%). Table 23 below and Figure 5 below summarizes the frequency of additional issues raised by REC 2.

Table 23: Additional queries raised by REC 2 (n=97)

Additional issues raised	Frequency	Percentage
Administrative issues	67	69.0%
Researcher's CVs	23	34.3%
Research budgets	18	26.9%
Details about the research team	16	23.9%
Missing signatures	10	14.9%
Errors	30	30.9%

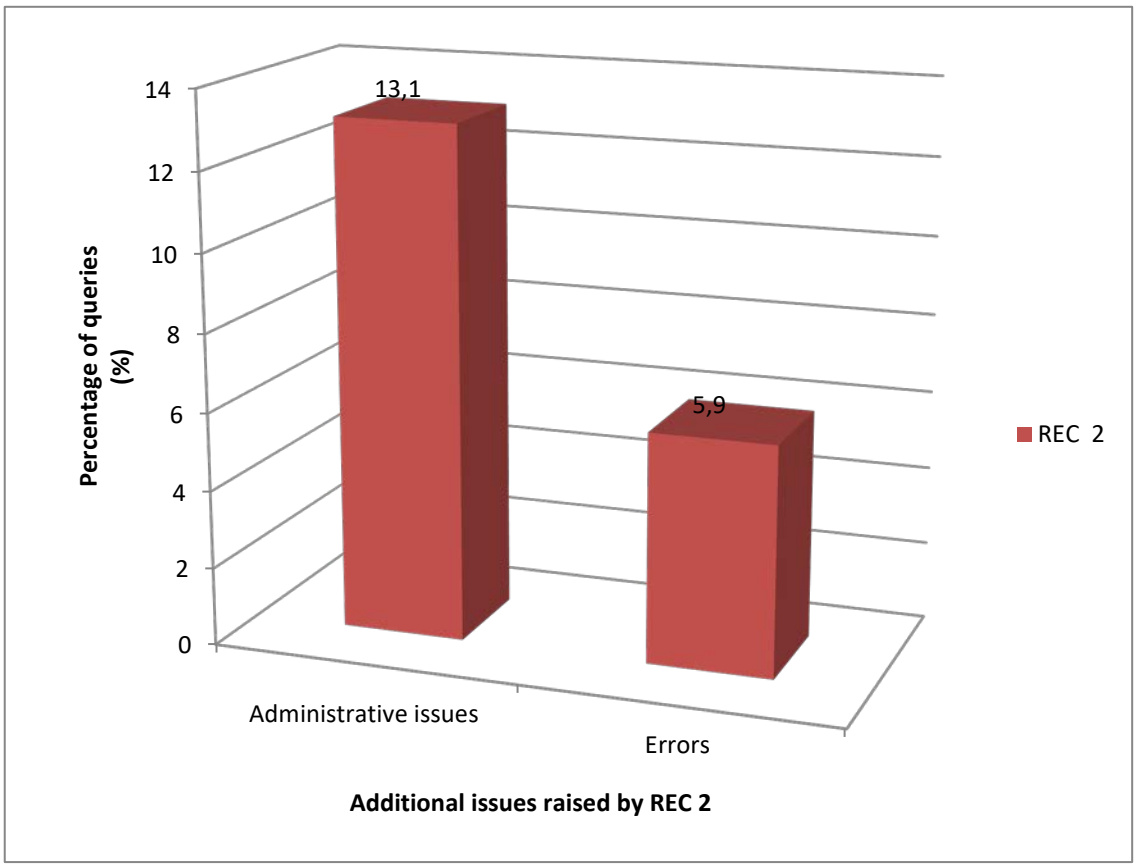

Figure 5: Percentage of additional queries raised by REC 2

6.1.8 Comparison of additional issues raised by both RECs

Figure 6 below is a comparison of the aggregated data on additional issues (i.e., not coded under the eight Emanuel et al. 2004 benchmarks) raised by the two RECs. The data shows that REC 1 most frequently raised additional queries related to administrative issues (8.1%) and errors (4%) compared to REC 2 in which administrative issues (3.8%) and errors (1.7%) were less frequently raised.

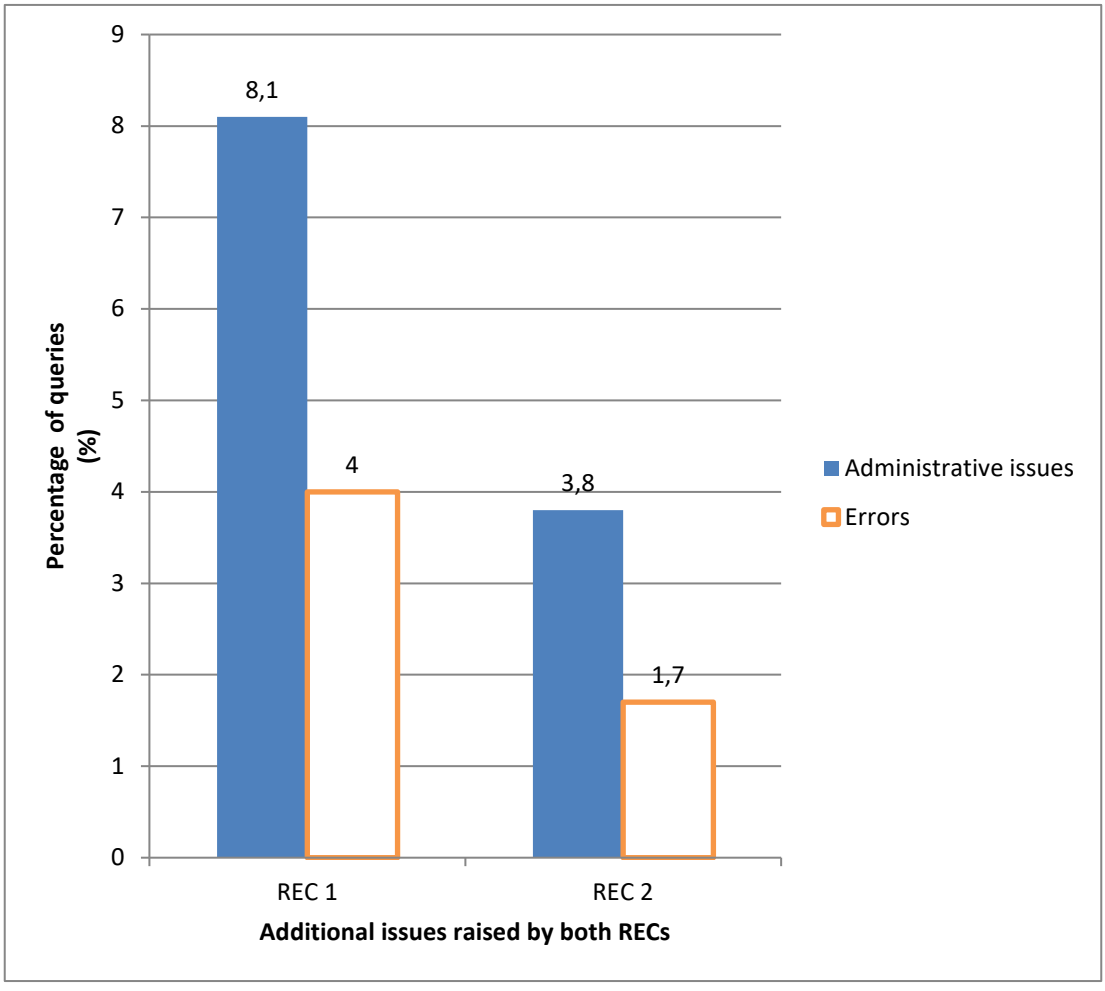

Figure 6: Comparison of additional queries raised by both RECs

6.1.9 Total issues raised by RECs

The section below describes the total issues (i.e., Emanuel et al. (2004) plus those coded under additional queries) raised by both RECs.

6.1.9.1 Total issues raised by REC 1

Analysis of the total issues raised by REC 1, as shown in Figure 7 below, showed that the most frequent issues that emerged were related to the informed consent (23.9%), respect for participants (18.9%), scientific validity (18%), administrative queries such as CVs and funding (11.5%) and collaborative partnerships (8.1%). This was then followed by queries related to editorial errors (5.3%). Other ethical issues raised by REC 1 that emerged less frequently in this study were fair participant selection (4.8%), favourable risk-benefit ratio (4.5%), independent ethics review (3.5%) and social value (1.3%) (Figure 7).

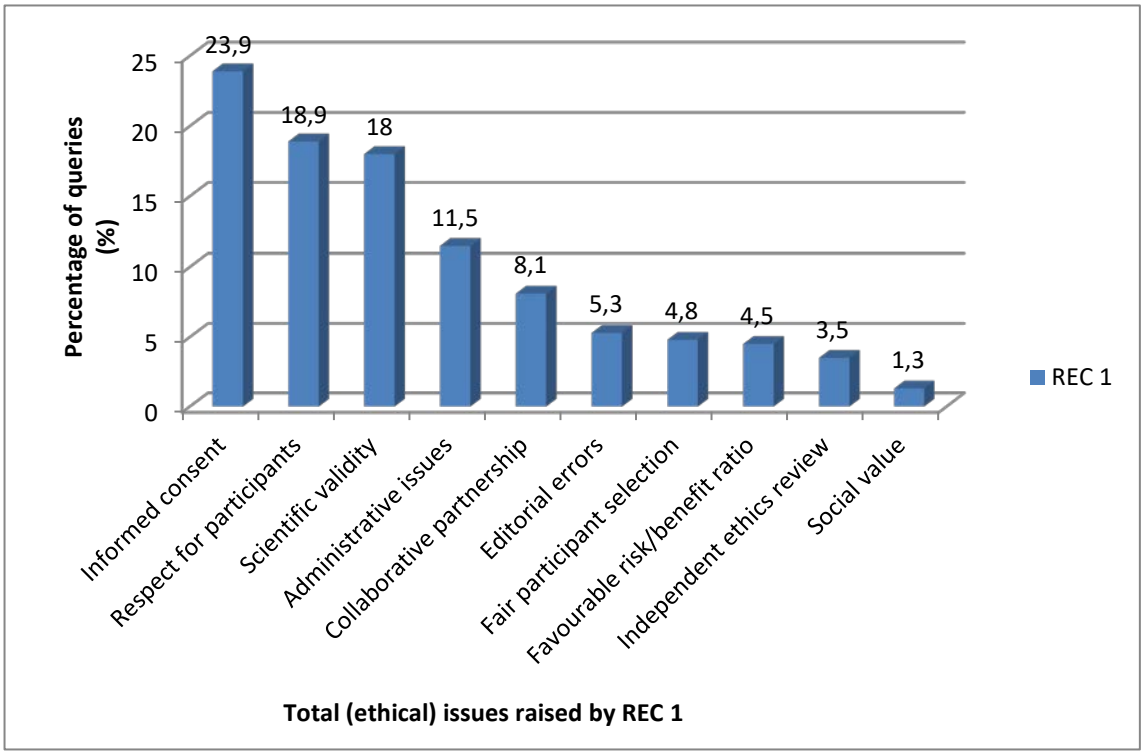

Figure 7: Percentage total queries raised by REC 1

6.1.9.2 Total issues raised by REC 2

Figure 8 below shows that of the total queries raised by REC 2, the most frequent were informed consent (31%), respect for participants (19.6%) and scientific validity (13.5%). Administrative issues emerged as fourth ranked (13.1%). Other ethical issues raised by REC 2, albeit less frequently, were queries related to favourable risk/benefit ratio (6.5%), errors (5.9%), independent ethics review (3.5%), fair participant selection (3.1%) and collaborative partnership (2.5%). Social value was the least frequent issues identified in this study (1%).

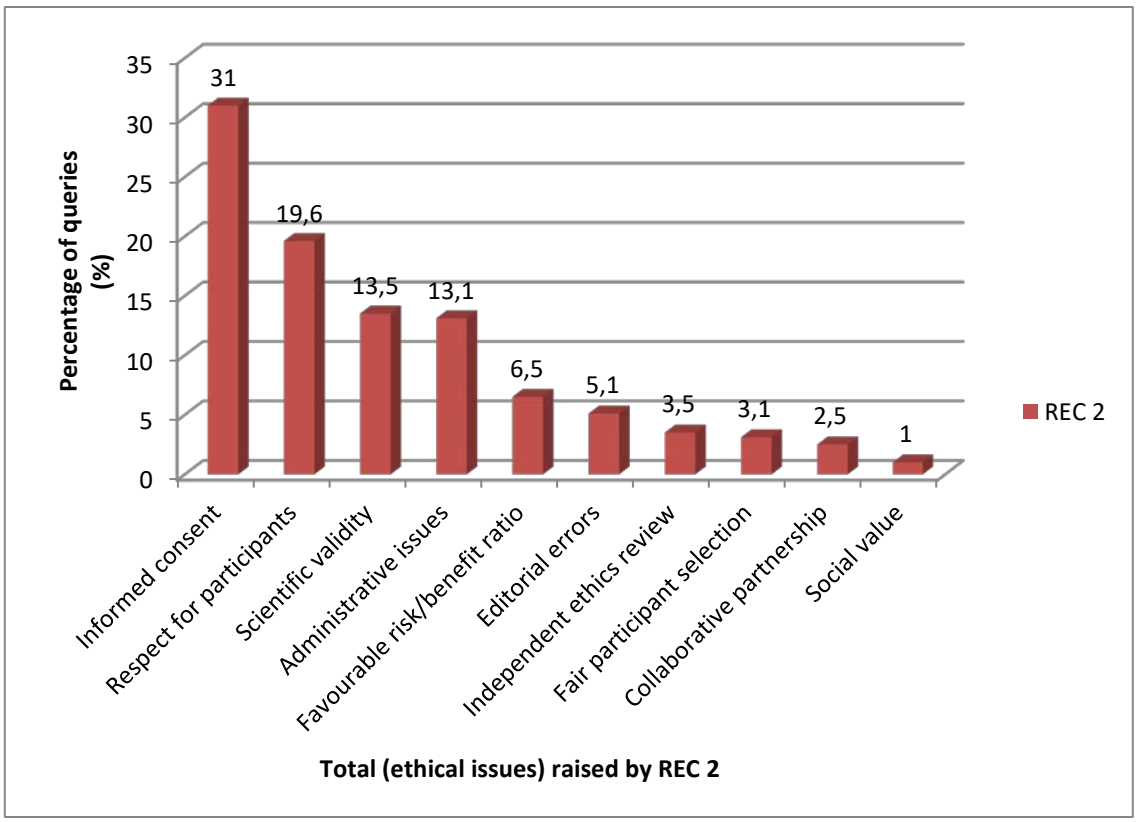

Figure 8: Percentage total queries raised by REC 2

6.1.10 Comparison of overall queries raised by both RECs

When comparing aggregated data from both RECs, Figure 9 below shows that there were similarities and differences in the ranking of the issues raised by the two RECs. The ranking of the overall issues between the two RECs was similar for the following issues: informed consent (ranked 1st), respect for participants (ranked 2nd) scientific validity (ranked 3rd), administrative issues (ranked 4th), editorial errors (ranked 6th) and social value which was the least frequent issue (ranked 10th). Differences were observed in the ranking of the other remaining issues such as collaborative partnership ranked 5th at REC 1 and 9th at REC 2. Ranked seventh at REC 1 were fair participant selection issues, which were ranked 8th for REC 2. Queries related to favourable risk/benefit ratio were eighth and 5th ranked at REC 1 and REC 2, respectively. Independent ethics review was ranked 9th for REC1, while at REC 2 they were the seventh most frequent issue overall.

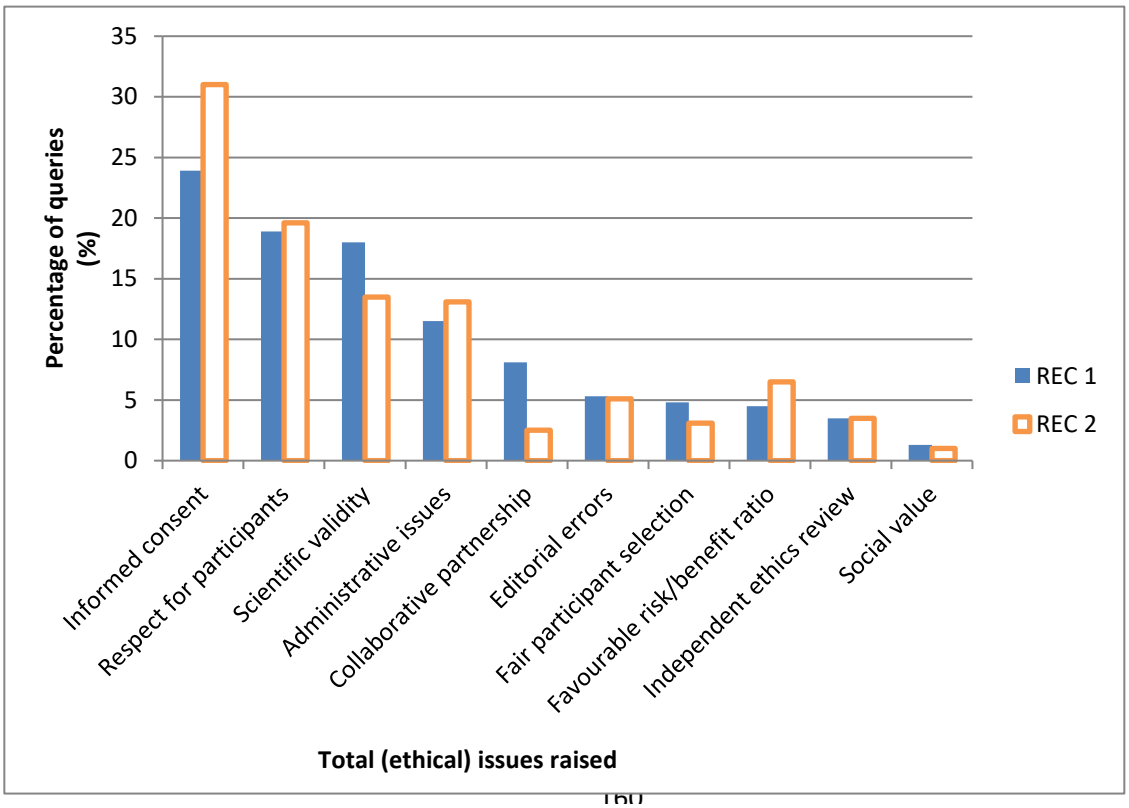

Figure 9: Comparison of total ethical issues raised by both RECs

Figure 10 below shows the average combined percentage of issues raised by both RECs are presented. The results showed that for the aggregated data averaged, the most frequent issues raised were about informed consent (26%, top ranked), respect for participants (19%, ranked 2nd), scientific validity (16.7%, ranked 3rd) and administrative queries (11.9%, ranked 4th). The other less frequent issues emerging in this study were collaborative partnership (6.5%, ranked 5th), editorial errors (5.5%, ranked 6th), favourable risk/benefit ratio (5%, ranked 7th), fair participant selection (4.3%, ranked 8th), independent ethics review (3.5%, ranked 9th) and social value (1.2%, ranked 10th).

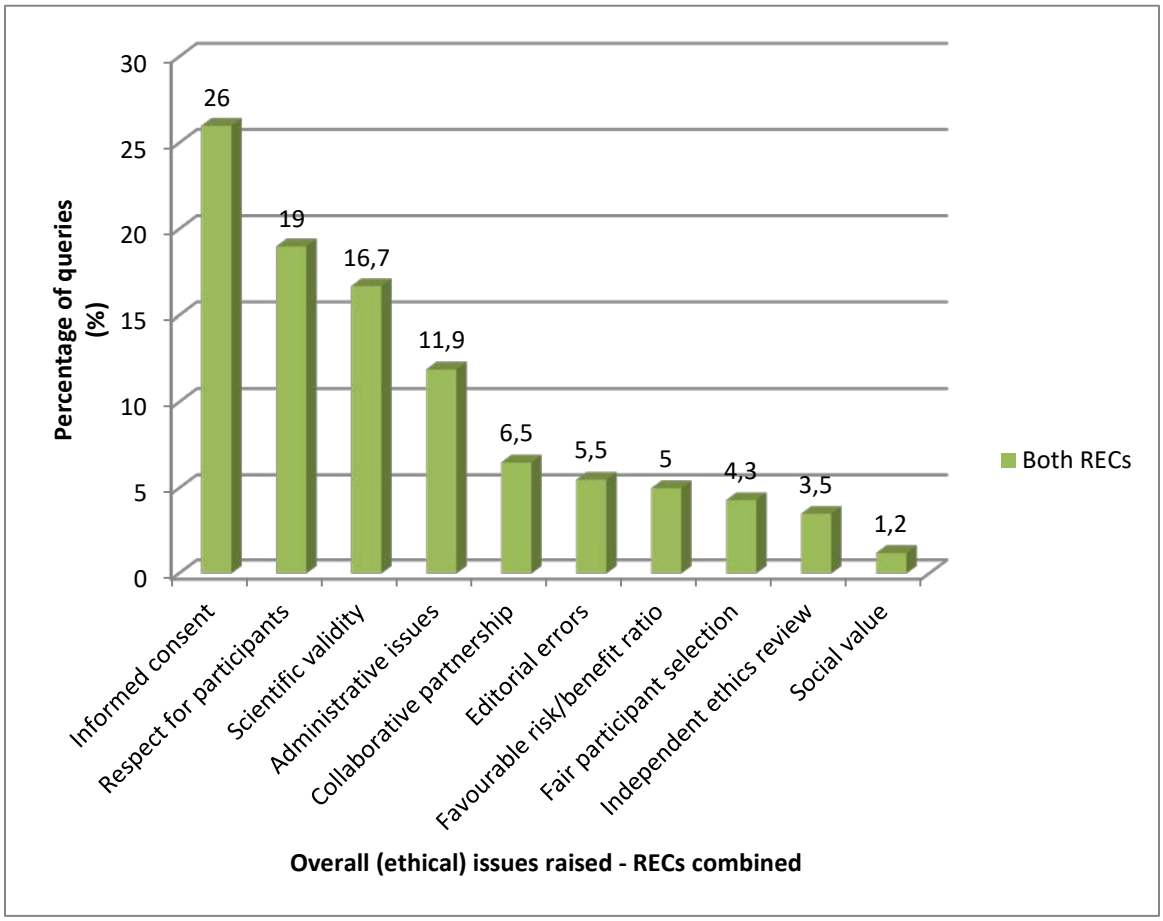

Figure 10: Overall ethical issues raised – RECs combined

6.2 Qualitative description of ethical issues raised by both RECs

In what follows, examples of anonymized quotes from the actual minutes and decision letters from both RECs are used to illustrate the types of ethical issues identified drawing from the Emanuel et al. (2004) framework. The combined data from both RECs are presented in descending order of frequency. The aggregated percentage (%) of queries in each category is displayed in brackets. Where a statistically significant difference in frequency was found between the two RECs, this is also indicated.

6.2.1 Informed consent (26%) (Significant difference, $p < 0.05$)

The top ranked issues identified by both RECs were informed consent (26%). Although ranked first by both RECs as the most frequently raised issue, there was a statistically significant difference between the frequencies of informed consent issues being raised by both RECs ($p < 0.05$). The Emanuel et al. (2004) framework calls for participant information disclosure in culturally and language appropriate formats, obtaining supplementary community or familial consent where culturally appropriate and ensuring freedom to refuse participation or withdraw from the study without any penalties. Both RECs frequently raised informed consent issues. Of these, the majority were requests to applicants to provide more complete information.

> *The consent forms should describe the intervention itself in more detail and mention that there will be non-intervention control comparisons (REC 1).*
>
> *The informed consent form should be revised to include…more information about the study and details of what will be required from participants… e.g. confidentiality, risks and/or benefits… contact details of the researcher and the REC (REC 2).*

This was followed by requests for simplification of language in these consent forms.

> *Language level of information and consent document needs to be simplified (REC 1).*
>
> *The informed consent form is too technical and more simple language should be used (REC 2).*

Finally, both RECs were concerned about ensuring appropriate and valid consent processes. This includes appropriate measures to ensure that vulnerable participants with limited or no capacity to provide valid consent are protected.

> *Can valid informed consent be obtained from acutely ill patients? (REC 1).*
>
> *This is an acutely ill study population and they are unlikely to be able to provide rational informed consent upon admission to hospital…the protocol should provide procedures for assent by the patient and proxy consent, as well as retrospective consent by patients when stabilized (REC 2).*

6.2.2 Respect for recruited participants (19%)

The second ranked issue raised by both RECs was about respect for participants (19%). There was no statistically significant difference between the two RECs. According to the Emanuel et al. (2004) framework, respect for recruited participants and study communities entails protecting their confidentiality, disseminating research results to participants and ensuring appropriate medical care during and after research, including research-related injuries. Both RECs were mostly concerned with ensuring appropriate medical care to participants, including research-related injuries.

The standard care package is not fully explained (REC 1).

Briefly explain the procedure for referral for continued treatment and care outside of the study. What happens regarding ongoing HIV treatment for babies at the end of the study (REC 2).

Furthermore, both RECs raised queries about post-trial access of the intervention to participants beyond completion of the study.

Will there be post-trial access to this drug? (REC 1).

The post-trial options as well as the recourse in case of injury should also be in the summary (REC 2).

Furthermore, RECs were also concerned about measures in place to protect the privacy and confidentiality of participants. Merely stating that confidentiality will be ensured seemed inadequate as both RECs often wanted a clear explanation or demonstration of how such confidentiality will be maintained and the sort of restrictions/measures in place to ensure that participant data is protected and not shared with third parties without appropriate consent.

Confidentiality and privacy of mother and infant-describe measures to prevent stigmatisation (REC 1).

What site-specific measures will be put in place to protect the privacy of participants and to ensure confidentiality? (REC 2).

Furthermore, both RECs wanted to ensure that participants were provided with appropriate reimbursements and compensation.

> *If the follow-up procedures for the study are more than required for routine care, participants should be reimbursed for travel (REC 1).*
>
> *You are kindly requested to clarify your remuneration or compensation of participants (REC 1).*

Finally, both RECs were also less concerned about the dissemination of study results to participants and communities in appropriate ways.

> *Describe the dissemination plan (REC 1).*
>
> *Describe how results will be reported back to these participants/this community (REC 2).*

6.2.3 Scientific validity (16.7%) (Significant difference, $p < 0.05$).

The third most frequent issue raised by both RECs concerned scientific validity (16.7%). Although this was the third most frequent issue raised by both RECs, there was a statistically significant difference ($p < 0.05$) between the RECs regarding the relative frequency of the issue being raised. According to Emanuel et al. (2004), scientific validity entails ensuring that the scientific design of the study realizes the scientific objectives. Furthermore, the research study should be feasible and realizable within the context of the local research community. Both RECs

raised many queries on the methodology and study design - in some cases even requesting the applicant to consider an alternative study, for instance:

> *The investigators plan to use a cohort study design… the proposed design will result in an unnecessary burden on the study participants… The investigators should consider using a cross-sectional design (REC 1).*

> *This is an open label study. The sponsors should indicate why it is not a double-blind study bearing in mind the greater weight which findings in these studies carry (REC 2).*

There were also frequent queries related to sample sizes and statistical validity.

> *There are a multitude of aims and objectives that cannot be justified by the sample size and methodology (REC 1).*

> *Have you consulted with a statistician to ensure that the study is powered to answer your research questions? If not, please do so before approval can be granted (REC 2).*

6.2.4 Collaborative partnership (6.5%) (Significant difference $p < 0.05$)

From the combined averaged data, collaborative partnership issues were ranked fifth by both RECs, but there was a statistically significant difference ($p < 0.05$) in the frequency of such queries being raised by both RECs. The Emanuel et al. (2004) framework defines collaborative partnerships as developing partnerships with researchers, makers of health policies, and the community. Furthermore, collaborative partnerships entail involving 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

healthcare system. Additionally, collaborative partnerships involve respecting the community's values, culture, traditions, and social practices and developing the capacity for researchers, makers of health policies, and the community to become full and equal partners in the research enterprise (Emanuel et al., 2004). This was evident in both RECs as most of the queries were about respecting the local community's values and culture, and community engagement with community representatives.

> *Principal Investigator need to get support from community leaders for support of this study as this is a low socio-economic/vulnerable group (REC* 1*).*

> *The committee recommend that researchers consult the Community Advisory Board (CAB) or equivalent community representative on appropriate entry into this community and… any cultural issues to consider (REC 2).*

Furthermore, RECs were concerned about establishing partnerships with researchers and developing the capacity for researchers, makers of health policies, and the community to become full and equal partners in the research enterprise.

> *Please justify why laboratory work will be done in the US. Is this not a missed opportunity for technology transfer and capacity building in RSA (REC 1).*

> *Could you kindly clarify….why [laboratory tests] must be done in the USA (REC 2).*

Additionally, queries about human biological samples were also raised, in particular, the exportation of samples. RECs constantly requested international investigators to obtain export permits and material transfer agreements [MTAs] from the Department of Health.

Genetic material will be exported to UK and US for further analysis…MTA and export permits must be submitted prior to shipping (REC 1).

The MTA is still pending and must be available before the transfer of study samples to non-South African labs (REC 2).

Lastly, both RECs were concerned with how the results of the study would be integrated into local healthcare system and benefit public health.

What is the likely availability of [name of drug] in RSA public health system if the study shows safety and efficacy? (REC 1)

6.2.5 Favourable risk/benefit ratio (5%)

Queries coded under the principle of favourable risk/benefit ratio were ranked seventh by both RECs. The Emanuel et al. (2004) framework says the study risks should be balanced against potential benefits to achieve a favourable risk-benefit ratio. Both RECs raised concerns with the potential risks and ways in which they can be minimized.

Has the study drug any risk of triggering or aggravating neuro-psychiatric disorders such as depression or anxiety (REC 1).

The committee is concerned that pre-term infants are being subjected to unnecessary safety risks (REC 2).

Furthermore, both RECs were also concerned about the actual conduct of the research study, for example ensuring that medical procedures are conducted by appropriately qualified researchers.

> *Venepuncture is required more than once, even in controls. Who will do it? A Phlebotomist was not identified in the proposal (REC 1).*

> *As the PI is not a medic, a clinician must be a co-investigator and be responsible for the investigation. For the purpose of this study we strongly recommend that a paediatric neurologist be recruited (REC 2).*

Additionally both RECs raised concerns about the need for independent data safety and monitoring board (DSMB) to monitor participant safety and adverse events in clinical trials.

> *Who are the members of the Safety Monitoring Committee and how is their independence guaranteed? (REC 1).*

> *In research of this nature independent monitoring and oversight will be essential to protect participants (REC 2).*

6.2.6 Fair participant selection (4.3%)

Queries related to fair participant selection were the eighth most frequent issue raised by both RECs. The Emanuel et al. (2004) framework states that there should be fair and equitable selection of participants to ensure scientific validity of the research. Moreover, vulnerable populations should be identified and protected. This was evident in the data from both RECs as they were concerned with ensuring that participants are recruited fairly and that there is clear justification of enrolling particular populations.

Why was the enrolment only subjected to black women and not other races? (REC 1).

Please state more details of how it will be decided which specific participants will be recruited/chosen (REC 2).

6.2.7 Independent ethics review (3.5%)

The principle of independent ethics review was ranked ninth for the combined averaged data from both RECs. The Emanuel et al. (2004) framework emphasizes the need for independent and competent review of research by RECs and other regulatory authorities mandated by national laws and regulations**.** As such, both RECs often wanted to see approvals mandated by law in their countries.

Has Medicines Control Council [*MCC*] *approval been obtained for the use of this drug in the phase 3 study? (REC 1).*

Kindly indicate whether the issue of [name of experimental drug] dosage been cleared up with MCC (REC 2).

6.2.8 Social value (1.2%)

The principle of social value was the least frequently raised issue by both RECs, ranked tenth (Figure 10). According to the Emanuel et al. (2004) framework, social value means the research should benefit participants and the community. This was clearly evident in data from both RECs as they were concerned about whether the research would be relevant to the well-being and

needs of the individual participants suffering from the disease under study or address the health problems of importance to the community. Essentially, both RECs were anxious that the findings emanating from the study should benefit participants and improve their health needs and the host community (35.3% vs 40%).

> *Can more be done to maximise benefits to patients and to the study site (REC 1).*
>
> *The rationale for this study is to get [drug] registered in [foreign country] for patients with COPD. It is not clear why the South African population is being studied as there is no indication that [drug] will be marketed in South Africa (REC 2).*

6.2.9 Additional issues raised

Furthermore, there were some additional REC queries that could not be accommodated by the Emanuel et al. (2004) framework. These were categorised as administrative issues –e.g., researchers' CVs and budgets (ranked 4th) and errors (ranked 6th overall).

> *The CVs, declarations and proof of GCP training should be submitted for all investigators and sub investigators (REC 1).*
>
> *A copy of the financial agreement for this project must be submitted to the ethics committee (REC 2).*

In summary, when data from the two South African RECs were integrated and averaged, the following emerged as the most frequent ethical issues overall in descending order: informed consent (26%, ranked 1st), respect for participants (19%, ranked 2nd), scientific validity (16.7%, ranked 3rd), administrative issues (11.9%, ranked 4th), collaborative partnership (6.5%, ranked 5th), editorial errors (5.5%, ranked 6th), favourable risk/benefit ratio (5%, ranked 7th), fair participant selection (4.3%, ranked 8th), independent ethics review (3.5%, ranked 9th) and social value (1.2%, ranked 10th). This analysis of the data suggests that the Emanuel et al. (2004) framework was compatible with 83% of the ethical issues raised by both RECs overall, supporting it's widely accepted applicability and utility for guiding research ethics training and informing ethics review systems and templates (Tsoka-Gwegweni & Wassenaar, 2014).

6.3 Results for Work package 2: Interviews with REC members about findings of work package 1

6.3.1 Response rate for semi-structured interviews

A total of 66 REC members were invited to participate. Five out of 22 (22.7%) members at REC 1 and four out of the 44 (9%) members at REC 2 consented to take part in the semi-structured interviews. Overall, there was a 14% (9 out of 66) response rate. The sample was skewed in favour of REC 1 despite efforts to increase enrolment of respondents from REC 2.

6.3.2 Demographic characteristics of respondents

Table 24 below summarizes the demographics of the respondents. In brief, the majority (77.7%) of respondents were white academics employed by the institution to which the REC is affiliated. All but one had obtained PhDs in different fields of health sciences. There were almost equal number of members from the medicine, public health and biomedical science. No lay members volunteered to take part in this study. There was a chair or co-chair at each REC sampled. In terms of gender, there were more males interviewed at REC 1 compared to REC 2. The duration as REC members was quite similar with members from both RECs having experience ranging from 2-10 years.

Table 24: Demographic characteristics of respondents

	REC 1	REC 2	Total
Race	*n* (%)	*n* (%)	*n* (%)
Black African	1 (20)	0 (0)	1 (11)
Indian	1 (20)	0 (0)	1 (11)
White	3 (60)	4 (100)	7 (78)
Gender			
Female	2 (40)	3 (75)	5 (56)
Male	3 (60)	1 (25)	4 (44)
Age group			
30-40 yrs	0 (0)	3 (75)	3 (33)
41-50 yrs	1 (20)	1 (25)	2 (22)
51-60 yrs	4 (80)	0 (0)	4 (44)
> 61 yrs	0 (0)	0 (0)	0 (0)
Highest education			
PhD	5 (100)	3 (75)	8 (89)
Masters	0 (0)	1 (25)	1 (11)
Area of specialization			
Medicine	3 (60)	2 (50)	5 (56)
Public health	1 (20)	1 (25)	2 (22)
Psychology	0 (0)	1 (25)	1 (11)
Biomedical science	1 (20)	0 (0)	1 (11)
Role in REC			
Chair/ Co-chair	1 (20)	2 (50)	3 (33)
Internal member	4 (80)	2 (50)	6 (67)
Lay member	0 (0)	0 (0)	0 (0)
Duration as REC member			
Range	(2-6 years)	(2-10 years)	

6.3.3 Research ethics experience of respondents

All respondents indicated that they had received some form of ethics training before or immediately after becoming a REC member. The research ethics training received by most (67%) members from both RECs was in the form of short course training and online courses. All respondents indicated that their training was based mostly on the Emanuel et al. (2004) framework. At REC 2, two members indicated that they had received ethics training at Masters and PhD level, respectively. When asked to rate their level of expertise/experience in research ethics review, more than half (67%) of the respondents ranked as intermediate while the remaining 33% of REC members were ranked advanced (Table 25).

Table 25: Questions of REC members' experience in research ethics review

	REC 1	REC 2	Total
Have you ever received training in research ethics/bioethics	*n* (%)	*n* (%)	*n* (%)
Yes	5 (100)	4 (100)	9 (100)
No	0 (0)	0 (0)	0 (0)
If yes, what did your training comprise of?			
Short course	4 (80)	2 (50)	6 (67)
Diploma	1 (20)	0 (0)	1 (11)
Masters	0 (0)	1 (25)	1 (11)
PhD	0 (0)	1 (25)	1 (11)
How would you perceive your level of experience/expertise in research ethics review			
Basic	0 (0)	0 (0)	0 (0)
Intermediate	4 (80)	2 (50)	6 (67)
Advanced	1 (20	2 (50)	3 (33)

6.4 Qualitative views of REC members

Semi-structured interviews using an interview guide (Appendix 2) were conducted with 9 REC members to explore ethical issues identified as previously described in detail in Chapter 5. This section presents the findings from these semi-structured interviews. The main themes emerging from the qualitative data are described below in order of decreasing frequency.

6.4.1 Role of REC

The first question asked from REC members was what they thought the main role of a REC was. All respondents clearly articulated that the primary task of REC was to protect research participants and provide adequate ethics oversight for research involving human beings. For example, two respondents said:

> *I think it's primarily to ensure participant protection, and I see it particularly from a medical point of view where there has been a history of abuse of research participants in medical science. So I think that the first reason we have research ethics committees is to protect participants. And then there are other reasons that come about to make sure that the research is of good quality, that the researchers actually know what they are doing when it comes to doing research… But I think it's about participant protection…so we have ethics now because we don't want participants to be ever abused again (REC 1).*

> *Well, I suppose the ethics committee is sort of a representative to protect the, I would say maybe the rights, but to try and use the [ethical] guidelines and legislation to protect the rights of the participants, the researcher and the institution. But the participant would be your main category that you want to provide protection (REC 2).*

However, another respondent reiterated that while RECs are there primarily to protect participants and ensure that the goals of research do not supersede the rights and safety of participants, RECs should take precaution not to stifle research (Snooks et al., 2012). The respondent said:

> *My way of looking at the ethics committee is that it's there to protect participants, but at the same time not stifle research- which is where I end up conflicting often with some of my colleagues who seem to suggest that we [RECs] should be stifling research. But, so I like to look at it from, is this study in general going to be safe, doable and practicable without putting patient or participant's identity, safety and outcome at risk (REC 2).*

In the next set of questions, respondents were asked to describe the kinds of ethical issues that they typically identify during ethics and their opinions on the findings from work package 1 (Figure 9). These data are presented below in descending order of frequency.

6.4.2 Informed consent

Although the sample was relatively small (*N*=9), all respondents identified informed consent as one of the most frequent issues they find problematic in research protocols. As such, all respondents (100%) said they were not at all surprised at the distribution of informed consent issues in this study (Figure 9). REC members repeatedly identified informed consent as one of the most important issues that they address during ethics review. For example, two respondents said:

It's almost common sense to think that if informed consent is not in place that's probably not going to be ethical research….without it you can automatically say that this study is unlikely to be ethical unless of course if there are other circumstances that allow for waivers of informed consent. So for me it [informed consent] is the first step in actually making sure that research is ethical and the others [ethical issues] follow (REC 1).

Well for me, the most important part is informed consent process and all the aspects... So I think informed consent is the most important issue that needs to be covered (REC 2).

When asked to elaborate further exactly the key elements of informed consent that they identified, almost all respondents mentioned that the most frequent problems include the use of too much technical language and/or omitting sufficient details about the study, for example the risks, benefits, and contact details of researchers and the local REC. Therefore, REC members stated that they often required changes to the informed consent document in terms of rewording and simplification of language, as well as every single detail pertinent to the research study. For example four respondents said:

I think the biggest problem that people have with the ethics application form is the ability to include in the informed consent the aspects of the study… sometimes their form is so comprehensive that it becomes many many pages and difficult for someone to read [laughter]….When they do an informed consent they may not include all the aspects that are relevant to the ethics of the study, for instance they may not reveal that it's being done for your Masters or PhD etc…, they may not say that the patient can withdraw from the study at any time that they wish, they may not say that there will be no penalties for

withdrawing, they may not say that they [participants] are not obliged to give consent, you know, that this is purely voluntary and at any stage they can withdraw their consent. And the last thing is that sometimes the investigators fail to reveal whether they are actually paying for the participants or not, and that's very important that it's noted in the consent form so that there is no perverse incentives. So those are the things that we particularly look at [in the consent form] (REC 1).

We tend to focus on informed consent it has to be thorough. Usually we receive a huge document, and the researcher says this is informed consent, and we say No, No, No! simplify it, simplify the language it's too technical. It doesn't matter whether the funders wanted it that way but we want it to be simple for the participants, so the language must be simplified and it must be shortened and list everything that that is there including the harms (REC 2).

Yeah, the kind of informed consent queries that I can remember are the language issue, and then often the information is too complex for the lay person and that it's too long. Those are the queries that come to mind that people [reviewers] ask, and those won't be addressed in a REC application (REC 1).

It is a lot about the wording and the phrasing, and sometimes it's about not including details or contact details…making sure every single element of the procedures of that trial is explained to the participant (REC 2).

REC members also believed that because of low levels of education and literacy in many South African samples, participants may not easily understand the study. Hence they often raised

comments related to understanding and comprehension of the informed consent by prospective participants. As mentioned by one respondent:

> *Issues of informed consent form one of the biggest problems that we have. Researchers think that if they explain something to the participant in terms that they themselves understand, then their potential participants automatically are going to understand, and that's a problem (REC 2).*

6.4.3 Respect for participants

When it came to the principle of respect for participants, most respondents identified the need to protect the privacy and confidentiality of participants: For example two respondents stated that:

> *Well first of all I think anonymity of data [is important] because any personal data can actually be used to harm someone. So I think if you protect the person's identity in the research documents by not having any traceable information (REC 1).*

> *For instance most studies for students are chart reviews or they use previously collected samples. So… we want to ensure that issues of privacy and confidentiality are addressed in the protocol or in the informed consent, i.e. how are they going to ensure they protect the privacy of participants if they are interviewing participants? (REC 2).*

Furthermore, REC members believed that researchers should make plans for post-trial access of interventions to participants upon completion of the study. REC members said that they are often troubled when there is no clear indication from researchers and their sponsors on plans for on-

going access to medical care for participants after the study has completed. For example one reviewer said:

> *One of the common issues in terms of participant protection is the issue of post-trial availability of test drugs, okay. And that's something I stare in horror with some of the commercial proposals that gets sent to me for review (REC 1).*

6.4.4 Scientific validity

While all REC members acknowledged the importance of good scientific validity for any research study, there were divergent views about the overall distribution of scientific queries raised by RECs in this study (Figure 9). Most (77.7%) respondents said they were not surprised by the high frequency of scientific queries because they felt strongly that scientific reviews were in the remit of ethics review. To illustrate this, three respondents said:

> *Scientific validity is at the roots of research and immediately if the scientific validity is wrong, is misinterpretable then…there is no point looking at the ethics. If it's not scientifically valid, it's immediately unethical to start the study (REC 1).*

> *We're looking at ethical issues but we're also looking at whether the study is well designed so that we can really make sure that we are not wasting participant's time and resources by doing research that has no scientific value in the end because it's been badly designed and the findings will be invalid. So we look at whether it's feasible in terms of the methodology and the design, but also whether the way that those things are being conducted is done in ethical ways (REC 2).*

The primary focus of RECs is to look at the ethics of a study. But if you have poor science you gonna end up with poor ethics, right [laughter], and one is not mutually exclusive from the other. So you have to look at both aspects, if a study has poor science then how can you ethically justify doing that study especially if its invasive (REC 1).

Interestingly, however, while acknowledging that the science of a project should be valid, a few other REC members (22.2%) strongly felt that there was often an over-emphasis on scientific issues. They believed that querying scientific issues was not the core function of an REC, hence it falls outside its purview. For example, two respondents said:

One of the biggest issues that strike me the most….is the over-emphasis on the scientific validity…We tend to lose focus that we are ethics committees reviewing ethical issues, noting that the science should be ethical. But we are not there to ask all these questions about the scientific methodology (REC 2).

As to the sort of scientific methodology, I think that's where the REC needs to often take a step back and say, look this is not our discipline, let's ask an expert to review the science and advise us, and I don't think we do that often enough especially for some of the postgraduate studies (REC 1).

When asked about their views on the criticism levelled against RECs that they lack expertise to review scientific issues for example, in qualitative designs, some respondents agreed strongly

and believed that this was fair criticism. They believed that RECs generally did not have the expertise to review qualitative designs: For example, one respondent said:

> *Absolutely. It's a very fair comment. In most medical work that gets done especially in clinical medicine schools, is quantitative…and there are limited people [REC members] that know what they are doing with qualitative research. So I think it's a responsibility of any REC to have somebody on board who can understand qualitative research, who can understand that you can get away with a sample size of 10 because you have reached saturation. But a lot of clinicians don't have the time to get their head around that. So I think that we have to look further and find people [REC members] who can grasp that work. And I have seen it in my work where I had a student's work reviewed and the two reviewers had no clue what I was doing and in front of me they slated the work almost brutally [laughter] I realized afterwards that they actually just didn't understand the work (REC 2).*

Finally, when asked to what they attribute such a high number of queries on scientific validity, it was concerning to note that most REC members attributed a high number of queries raised (for scientific validity and other ethical issues), to inadequate supervision or input from supervisors prior to submission to RECs for ethics approval particularly for postgraduate student projects: For example two respondents said:

> *I'm afraid that there is very little support given to novice researchers and some of the stuff [proposals] that gets through [REC] and that gets slated is because it's a novice researcher who hasn't got adequate assistance from the supervisor. And things are just getting rubber stamped [by postgraduate committees] for turnover (REC 1)*

It's not necessarily that we have a particularly brusque ethics committee. It may just reflect the fact that we are suddenly getting an increased numbers of submissions by relatively inexperienced students with relatively inexperienced supervisors. And it needs to be set against a postgraduate review system which just rubber-stamped the applications (REC 2).

6.4.5 Collaborative partnership

Although issues of collaborative partnerships were not as frequently mentioned as compared to other ethical issues (consent: ranked 1st, respect for participants: ranked 2nd and scientific validity: ranked 3rd), there was a general concern by some REC that they would like to see more collaborative partnerships when researchers from more developed countries conduct research in local communities. In particular, REC members wanted developing country researchers to engage in consultative process with local researchers and respect the local context and culture, as opposed to imposing their own standards on the local community in which research is being conducted. One respondent said:

There are other studies that are more internationally funded studies, and bigger sponsors. So essentially the sponsor pushes through what is applicable in their settings, and these are from developed countries, and they push through the norms and standards they use and they expect that to be done here also with little regard to the local issues and the cultural sensitivities and the local guidelines that apply here (REC 2).

6.4.6 Reasons for low frequency of certain issues

When asked for their views on perhaps why certain issues (e.g., social value) were not as frequent as others, respondents generally felt that the nature of their REC application forms influenced the distribution of ethical queries raised by reviewers. For instance, respondents believed that their application forms adequately addressed issues of risk benefit and fair participant selection, such that few queries arise from the REC deliberations. An illustration of that point was made by one respondent who said:

> *I think that the application form itself makes sure that you answer the questions on participant selection and favourable risk benefit ratio and whether there has been another independent review. So if there is a tick box that covers these, and I think there is in the [name of REC] application form, of course these issues will be lower (REC 1).*

Also, some respondents said that the data did not necessarily mean that they neglect certain issues, but it could be that the issues are well described by researchers in the protocol. For example with social value, most respondents felt that because most studies addressed issues of national importance such as HIV. Therefore, there were likely to be very few queries asked on social value because the mere fact that it's a biomedical study addressing a disease or condition affecting people in South Africa, then it means the study has social value: This was illustrated by one respondent who said:

> *The nature [of studies reviewed by REC] is biomedical research and they are public health research. So when the researchers come, they study those issues that are of national priority, so they justify why they want to do their research. Like I said HIV and*

TB is very topical in South Africa…So obviously once you[REC member] look at it [the proposal], the reviewer will know that this is a national priority and they will say ok there is social value because South Africa is battling with HIV, you know….the issues are easy to sort (REC 2).

6.4.7 Additional issues

The researcher also asked for respondents' views on the overall ranking of administrative issues (ranked 4th) compared to ethical issues such as favourable risk/benefit (ranked 7th) and social value (ranked 10th) (Figure 10). Most REC members felt that querying administrative issues, such as investigator CVs and research budget occurred for valid reasons and not because reviewers were pedantic. They said that although these are not overtly ethical issues, they have ethical and scientific implications. To illustrate this point, two respondents said:

For instance with CVs and qualifications, it comes back to, umm, are the researchers qualified or experts and experienced in what they are researching, okay. You don't want to send out a boy to do a man's job [laughter] because it's not fair on the participants; you can't send somebody [researcher] who doesn't know what they are doing to do research on these people (REC 1).

Some of the administrative issues may not be regulatory requirements, like a budget or a timeline. [But] for me again it speaks a little bit to the validity of the research (REC 2).

Importantly, most REC members reiterated that most of these administrative issues such as CVs, in fact, are regulatory requirements in accordance with national and international standards. This is what one respondent said:

> *Quite a lot of these things [CVs] actually are regulatory requirements. The NHREC [National Health Research Ethics Council] and the regulations actually require that these things [CVs] are included in the applications and ethics review- and if they are not there they invalidate the application and it means the REC is doing something wrong by keeping on file an application that is incomplete without those things (REC 2).*

Furthermore, when asked for their views on whether the ranking of the issues between the two RECs (Figure 9), was expected or surprising, and/or reflected what RECs should be attending to, most respondents stated that the ranking was not at all surprising. They felt that indeed, these are the kinds of issues they would have expected their RECs to pick up. Some REC members also believed that they do not necessarily over-scrutinize protocols, but they raise issues simply because they would not have been properly addressed or are missing in the submitted proposals. As such, REC members cannot simply cast a blind eye to those issues. One respondent said:

> *I don't think there is any terrible plot from the ethics committee to pick everybody up on these issues. It's just that they are there, if it's an issue it's an issue. You can't just say oh well I'm going to ignore this because I have been sending a lot of these queries back recently. You can't say it's wrong to pick up on it, you can't say a lot of these are going back [to applicants] let's try and decrease our numbers [of queries]…So this [data] reflects us doing our job- it's not a policing thing (REC 1).*

At the end of the semi-structured interviews, REC members were asked to suggest ways in which the protocols submitted for ethics review could have been improved. Almost all participants made specific comments about the need for better supervision in the case of student research. Furthermore, all REC members believed there is need for more research ethics training of researchers when it comes to addressing ethical issues in REC applications. Furthermore, some respondents also suggested that the use of electronic REC management review systems could improve the review process and circumvent the need for multiple submissions of documents such as CVs.

6.5 Results for Work package 3: Alignment to national research ethics guidance

This section provides an overview of results from work package 1 (Figure 10) and draws on the ethical statements in the South African national research ethics guidance (Department of Health, 2015) to illustrate whether there is consistency between the issues identified by both RECs and existing guidance.

Table 26 below shows that, when comparing the types of issues raised by both RECs (Figure 9) and the requirements of the national guidelines (Department of Health, 2004, 2015), the majority of issues identified by the RECs were compatible with the guidelines. Specifically, both RECs raised the following Emanuel et al. (2004) ethical issues in descending order of frequency: informed consent (top ranked), respect for participants, scientific validity, collaborative partnership, favourable risk/benefit ratio, fair participant selection, independent ethics review

and social value (least ranked) . Although they do not stipulate how much weight should be given to each issue, the national guidelines (Department of Health, 2004, 2015) require the work of RECs to be informed by the same principles as the Emanuel et al. (2004) principles identified in work package (1). Furthermore, Table 26 shows that in terms of the additional issues identified by both RECs, such as investigator CVs, these are requirements of the national guidelines, which states that the researcher must have the requisite qualifications and experience (Department of Health, 2015). In conclusion Table 26 shows that the issues raised by RECs in this study were in line with requirements in the national guidelines (Department of Health, 2015).

Table 26: Comparison of themes identified in work package (1) with national guidance

Ethical issues identified in work package (1)	What does the national ethical guidance say?
Emanuel et al. (2004) issues (Ranked in descending order for combined REC data)	
Informed consent (26%)	*Ensure valid and voluntary informed consent is obtained from participants or their legally authorized proxies where the participants are not competent enough to provide valid consent*
Respect for participants (19%)	*This involves respecting the participants' rights, including but not limited to rights to dignity, privacy and confidentiality…. The researchers should ensure appropriate plans for provision for compensation for research-related injury, for more than minimal risk research*
Scientific validity (16.7%)	*The research should have a valid scientific methodology and be likely to provide answers for the specific research questions that are posed*
Collaborative partnership (6.5%)	*Researchers should engage key role players at various stages of planning and conducting research to improve the quality and rigour of the research, to increase its acceptability to the*

	key role players, to harness role player expertise where possible, and to offset power differentials where these exist.
Favourable risk/ benefit ratio (5%)	*The proposed research must ensure that the research benefits outweigh the potential risks, i.e. a favourable risk-benefit analysis*
Fair participant selection (4.3%)	*Fair participant selection: The researchers should ensure that the recruitment and selection of potential participants is objective and fair*
Independent ethics review (3.5%)	*It is the obligation of the researchers to ensure that they submit protocols for independent review by a registered health research ethics committee.*
Social value (1.2%)	*Research should be responsive to the health needs or priorities of the population, participating community or proposed participants*
Additional issues	
Administrative queries e.g., CVs (11.9%)	*Researchers must be suitably qualified and technically competent to carry out the proposed research… Competence is demonstrated mainly by academic qualifications, credentials, scientific and technical competence as evidenced in previous publications or testimonials.*
Errors (5.5%)	No specific guidance

6.6 Summary

In in section, results from the three work packages were presented. In the first work package, a retrospective analysis of minutes showed that, in descending order, the two RECs in this study most frequently identified issues related to:

- Informed consent (ranked first: 26%)
- Respect for participants (ranked second: 19%), and
- Scientific validity (ranked third: 16.7%).

Although ranked first by both RECs as the most frequently raised issue, there was a statistically significant difference between the frequencies of informed consent issues being raised. Similarly, there was a statistically significant difference in the frequency of respect for participants and scientific validity queries raised by the two RECs ($p < 0.05$).

In the second work package, qualitative interviews with REC members highlighted that generally respondents were not surprised with the ranking of the ethical issues queried (Figure 9) and saw them as compatible with what was expected as REC outcomes. However, there were some different views, especially regarding scientific validity. While most respondents agreed with the frequency with which scientific issues were raised by both RECs in this study, some felt that it was outside the remit of RECs to review scientific issues. The aim of work package 3 was then to do a review of national ethical guidelines and compare it with findings in work package (1) above to determine if there is alignment between the two and showed that the majority of issues raised by RECs in this study were in accordance with the guidelines (Department of Health, 2015).

CHAPTER SEVEN

DISCUSSION

7.0 Introduction

The aim of this chapter is to relate the findings presented in the results sections to the existing relevant scholarly literature.

There have been many calls for the evaluation of RECs (Abbott & Grady, 2011; Coleman & Bouesseau, 2008). However, there is a lack of consensus on the assessment criteria for evaluating research ethics review (Nicholls et al., 2015). The present study described and evaluated the ethical issues raised by two biomedical RECs in South Africa from three perspectives: (i) content analysis of REC meeting minutes and decision letters, using the Emanuel et al. (2004) framework, (ii) semi-structured interviews with REC members, and (iii) comparison with findings in (i) above with current South African national research ethics guidance (Department of Health, 2015). Assessing the institutions' research ethics capacity (instead of RECs themselves) (Hyder et al., 2013, 2015) or the effectiveness of ethics review (Abbott & Grady, 2011) was beyond the scope of this project.

In what follows, the main findings of this study are discussed. The findings are discussed and interpreted in relation to the eight benchmarks described in the theoretical framework used in this study (Emanuel et al., 2004). The discussion is structured according to the overarching themes presented in the results sections in descending order of frequency 1) informed consent, 2) respect for participants, 3) scientific validity, 4) collaborative partnership, 5) fair participant selection, 6) favourable risk benefit ratio, 7) independent review, and 8) social value. The section concludes

with a discussion of the administrative issues and other process errors identified by the two RECs in this study.

7.1 Informed consent

The findings suggest that the two RECs in this study most frequently identified problems with informed consent (26%) when reviewing proposals. These findings are comparable with previous South African studies in which informed consent were the most frequent ethical issues identified (Clarke, 2014; Cleaton-Jones, 2010; Tsoka-Gwegweni & Wassenaar, 2014). Furthermore, similar studies conducted in the United Kingdom (Angell et al., 2010; Dixon-Woods, Angell, Tarrant & Thomas, 2008), U.S (Lidz et al., 2012), France (Decullier, Lheritier & Chapuis, 2005), Brazil (Bueno et al., 2009) and Spain (Dal-Ré et al., 2004; Martin-Arrabis et al., 2012) also reported that informed consent issues were top ranked by RECs in their settings. Another study in Germany reported that of the total 1299 queries identified, 53% concerned the patient information and consent document (Russ, Busta, Riedel, Zollner & Jost, 2009). A study of US IRBs reported that informed consent issues were discussed in 102/104 (98%) of protocols and changes to the informed consent were requested in 92/104 (88%) of protocols (Lidz et al., 2012). Similarly, a study that analysed 100 protocols submitted to two US IRBs found that 87% of those protocols had queries related to informed consent. Of those, omissions in the consent documents (40%), requests for better clarity (24%) and word-smithing (10%) were the most common queries requested (Blackwood et al., 2014). These data suggest that RECs want to ensure that participants are provided with simple but comprehensive study details, including a statement that the study has been approved by a local REC.

There are several possible explanations for such a relatively high frequency of informed consent issues observed in this present study. Firstly, informed consent is a legislative requirement enshrined in the South African Constitution and National Health Act (Strode, Toohey, Singh & Slack, 2015). It is widely recognized that informed consent is the cornerstone for ethical research with human participants, and for it to be valid, consent should include information disclosure, comprehension, competence and voluntariness (Grady, 2015; Lindegger & Richter, 2000). Therefore RECs may feel pressured to be more rigorous when reviewing informed consent forms on both legal and ethical grounds. Another possible explanation is that local RECs probably worry about the vulnerability of local participants due to high illiteracy and lower levels of education – contextual factors which may compromise voluntary informed consent (Bull & Lindegger, 2011; Kamunya et al., 2011), although there is still a lack of consensus on the standards for conceptualizing and assessing voluntariness (Mamotte & Wassenaar, 2015, 2016).

While the informed consent process should be interactive and on-going throughout the study, and not necessarily reliant on the ability to read (Horn et al., 2014), RECs may feel the need to be more vigilant when reviewing the readability of consent forms in order to ensure that potential participants are better informed through the use of simple language (Blackwood et al., 2014; Horn et al., 2014). Indeed, some empirical studies have reported limited understanding by participants during informed consent. One study found that participants had difficulties understanding technical terms such as randomization, double-blind and placebo, unless explained in simple local terms (Ndebele et al., 2014c). Another study also reported that participants' understanding of HIV research could be impeded by linguistic and cultural differences. The authors found that RECs often raised concerns about the context (e.g., low literacy and less

familiarity with research procedures), content (e.g., length of forms and translation), and aspects of the consent process such as written vs. oral consent (Hanrahan et al., 2015). Therefore, these data thus seem to have useful educational implications for researchers, i.e., they should ensure, to the greatest extent possible, the use of simple understandable language in the informed consent forms. While research ethicists have called for improved readability, several researchers have criticized RECs for too much tinkering and word-smithing, sometimes requesting unreasonable demands to the informed consent documents (Paasche- Orlow, Taylor & Brancati, 2003). Informed consent documents submitted to Australian RECs were frequently too long to read, with mean readability of 47, and were too complex to comprehend at the recommended grade 8 level (Biggs & Marchesi, 2015).

Another study in New Zealand and Australia found a mean readability score of 11.9 (higher than the recommended 8), but the authors nevertheless concluded that this was more than the average readability requirements in their countries (Taylor & Bramley, 2012). While these data are from an international context, they could possibly justify why South African RECs also frequently requested changes to simplify language in the participant information sheet and consent forms as suggested by data from the present study. The qualitative interviews with members from the two South African RECs (described in detail in the previous Chapter 5) suggested that they also require readability of consent forms to be around grade 8 level. An empirical study investigating how US IRBs viewed and made decisions about consent forms found that while IRBs generally strive to decrease the length and complexity of consent forms, some IRB members often experienced difficulty regarding what and how much the informed consent forms should include, i.e., how perfect should a consent form be? (Klitzman, 2013a).

7.2 Respect for participants

Ongoing respect for participants emerged as the second most frequent issue (19%) raised by both RECs in this study, particularly participant care during and after research, confidentiality and compensation and reimbursements. With regard to participant care, most issues were related to adequate monitoring of medical conditions including research-related injuries. These data are in accordance with the South African GCP (Department of Health, 2006), which requires RECs to assess whether insurance cover for clinical trials is in place and valid. Furthermore, RECs were concerned about plans for post-trial access to treatment beyond the duration of the study.

There is considerable debate in the literature about what is owed to participants after research completion and whether investigators have an obligation to provide post-trial access to medication and care beyond the duration of the study (Pace et al., 2006; Sofaer et al., 2011). While this argument is beyond the scope of this thesis, a possible explanation why local RECs often comment on post-trial access is because of lack of adequate healthcare systems and poor access to medical care by the majority of SA trial participants (Harris et al., 2011). Thus, based on the premise of beneficence, social justice and reciprocity (Slack, 2014), RECs may feel that participants should continue to receive medical care and treatment even after trial completion. Unfortunately, the national ethical guidelines are rather ambiguous regarding the matter (Department of Health, 2015). However, some international guidelines recommend that "sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial" (WMA, 2013, p. 7). Furthermore, participants must be provided information regarding post-trial benefits during the informed consent process (WMA, 2013).

7.3 Scientific validity

The findings highlighted that scientific validity emerged as the third frequent (16.7%) source of queries raised by both RECs in this study. Contrary to some reports that RECs do not pay sufficient attention to scientific rigor (Altman, 1994), data in this present study show that the two South African biomedical RECs in this study regularly raised scientific validity issues such as the study design, research questions, methodology, sample size, statistical validity and measuring instruments. This issue was the third most frequently ranked issue, overall.

These findings are comparable to results reported in previous studies in South Africa. One study found that 21.3% of queries raised were related to scientific validity (second after informed consent) (Tsoka-Gwegweni & Wassenaar, 2014), while in the present study issues of scientific validity were the third most frequent issue. Another study found that of 142 queries, the majority were scientific issues: study design 31 (21.8%), methodology 29 (20.4%), statistics 14 (9.9%) (Clarke, 2014). A different study analysed 306 letters and found that queries about the study sample were raised in 15% of applications (Cleaton-Jones, 2010). Elsewhere, 141 decision letters showed that scientific issues were raised in 104 (74%) of the letters. The most common issues were related to sampling (65%), methodology (50%), research question (28%), measuring instruments (27%), data analysis (22%), bias (15%) and feasibility (12%) (Angell et al., 2008). A recent study in Finland reported scientific issues, particularly the methodology, to be the most frequent queries raised by RECs in that study (Happo, Halkoaho, Lehto & Keranen, 2016).

The findings of this study showed the importance accorded to the ethical importance of scientific validity and provided some data on the types of concerns arising under this general heading. While the majority (77.7%) of REC members sampled in this study indicated that they expected a high proportion of scientific validity issues, a smaller group others (22.2%) felt that it was not the duty of their RECs to query issues related to the scientific validity of proposed research. That there are divergent views about scientific validity reflects the on-going debate on the remit of RECs in relation to scientific reviews. Perhaps a question that remains unanswered is how far RECs should go in reviewing the science of proposed research? Qualitative interviews with RECs, researchers and policy makers could help explore these questions further.

There are arguments on whether or not RECs should review the science of research proposals and the suitability of study designs and methodologies chosen by researchers to achieve their scientific objectives (Angell et al., 2008; Humphreys et al., 2014a). For some commentators, reviewing scientific validity is uncontroversial because enrolling participants in a scientifically invalid research poses unnecessary risks and burden to participants, i.e. bad science is bad ethics (Dawson & Yentis, 2007; Emanuel et al., 2004). Furthermore, most international (e.g., CIOMS, 2002; WHO, 2011; WMA, 2013) and national guidelines (Department of Health, 2015) require review of the science of research proposals.

There could be several interpretations for the high ranking and frequency of queries on scientific validity observed in this present study. That local RECs frequently raised scientific issues is in line with the national guidance (Department of Health, 2015) which explicitly obliges RECs to

ensure that propose research has scientific validity. Another possible explanation is that because of the composition of RECs, often dominated by medical scientists compared to lay members, it may be almost impossible for REC members not to comment on the scientific issues - even if they are tangential to the study (Humphreys et al., 2014b). As a result, the scientific expertise of most REC members may unintentionally dominate the deliberations of the entire REC, thus resulting in an over-emphasis on scientific issues (Humphreys et al., 2014b).

7.4 Collaborative partnership

The findings of this study showed that issues of collaborative partnership were ranked fifth (6.5%) for the combined REC data. These issues were raised particularly in international collaborative studies involving the collection, storage and export of human biological samples for future, and sometimes unknown and unspecified, research purposes. Both RECs often (ranked fourth among other categories of ethics query) requested clarifications on issues such as ownership of samples, benefit-sharing, material transfer agreement (MTAs) and export permits. Existing international ethical guidelines such as CIOMS, Declaration of Helsinki are ambiguous on several salient issues. For example, there is no specific guidance on benefit-sharing and ownership - an important ethical issue emerging from this study. Therefore, current frameworks need to be revised to provide further guidance on concerns identified by RECs in this study such as ownership, commercialization and benefit-sharing.

There are published reports suggesting that exportation of biological samples sometimes happens without appropriate REC approvals, MTAs and export permits (Langat, 2005; Sathar, Dhai & van der Linde, 2013). A study exploring the views of stakeholders about exportation of human biological samples from Ghana and Kenya found frequent concerns about developing meaningful partnerships through obtaining culturally appropriate permissions prior to exportation of samples, consideration of cultural sensitivities in the use of blood samples, and also building sustainable local scientific capacity and benefit-sharing (Tindana et al., 2014). These data emphasise the need for meaningful consultative collaborations, for example, through direct engagement with participants and communities, or involvement of community advisory boards (UNAIDS/AVAC, 2011). While there have been many efforts to produce guidance on promoting community engagement, there is a general lack of consensus on the ethical goals and strategies for community engagement, as well as appropriate indicators and metrics for evaluating the effectiveness of existing models of community engagement (MacQueen et al., 2015).

7.5 Favourable risk/benefit ratio

The findings showed that the combined REC queries related to favourable risk/benefit ratio were ranked seventh (5%). These data are comparable to previous studies in South Africa and elsewhere. One South African study found that risk/benefit queries were ranked fifth, representing (9% of the total queries raised by the REC in their study (Tsoka-Gwegweni & Wassenaar, 2014). Another study reported that of the 142 queries identified, only four (2.8%) were issues of risk/benefit (Clarke, 2014). A separate study investigating how US IRBs apply the criteria in the Common Rule guidelines, found that they did not address risk-benefit issues in

52/91 (57%) of the protocols reviewed (Lidz et al., 2012). These data raise interesting questions about how thoroughly RECs systematically assess favourable risk/benefit ratio to ensure protection of research participants from excessive risks (Rid & Wendler, 2011). Although there were relatively fewer risk/benefit issues (ranked fifth) compared to informed consent (top ranked), respect for participants (second ranked), scientific validity (third ranked third) and collaborative partnership (fourth ranked), results of the qualitative interviews suggested that REC members believed that they gave adequate consideration to risk/benefit issues because these issues are detailed in the REC application forms, forcing applicants to consider them carefully. It is therefore possible that risk-benefit issues were well addressed in the research proposals. A study by Klitzman (2013b) found that some US IRBs encounter difficulties in assessing and balancing social risks and benefits of a study, and vary in whether and how to balance these against individual risks/benefits. Another study of 188 US IRB chairs found inconsistencies in how they assessed risk/benefit issues in paediatric research, at times in ways incongruent with federal regulations (Shah et al., 2004).

7.6 Fair participant selection

The findings revealed that issues regarding fair participant selection were not as frequently raised (ranked sixth) as other previous ethical issues such as informed consent (ranked first: 26%), respect for participants (ranked second: 19%), scientific validity (ranked third: 16.7%) and collaborative partnership (ranked fourth 6.5%). These results are comparable to similar previous studies in South Africa. For example, Clarke (2014) found that of the 104 queries, only 3 (2.1%) were issues about fair participant selection. Another study reported that issues of fair participant selection were identified in 145/1040 (13.9%) of ethics queries, thus ranked third after informed

consent (27.4%) and scientific validity (21.4%) (Tsoka-Gwegweni & Wassenaar, 2014). A study in the US reported that IRBs did not consider fair participant selection in 60% of protocols (Lidz et al., 2012). That these issues were relatively infrequently raised does not mean that the RECs paid insufficient attention to fair participant selection. Qualitative data from REC members suggested that they are often concerned with ensuring that disadvantaged persons and communities are not unfairly included or excluded from ethically sound research on the sole basis of their vulnerable status, for example, supporting enrolment of homeless persons in research that otherwise stands to benefit wealthy communities only.

7.7 Independent ethics review

Independent ethics review issues were ranked ninth overall on aggregated data from both RECs (3.5% of total queries). The findings suggest that RECs in this study often requested investigators to provide relevant approvals mandated by laws in the host countries. For example in South Africa, it is mandatory to obtain MCC approval for clinical drug trials as well as approval by local RECs registered with NHREC (Department of Health, 2015). While acknowledging the value of independent ethical review, some commentators have criticized the practice of multiple REC reviews and approvals for multinational collaborative studies because the process results in duplication of effort, wastes time and resources and is often riddled with inconsistencies (Abbott & Grady, 2011). A review of African RECs identified that some RECs encounter several barriers (e.g., inadequate resources, difficulties interpreting international guidelines, limited ethics review expertise) in conducting effective and efficient ethical reviews (Silaigwana & Wassenaar, 2015).

7.8 Social value

While it was the least frequent (1%) and lowest ranked issue raised by both RECs in the present study, social value is an important ethical benchmark underscored by key national and international guidelines (Emanuel et al., 2004). The principle of social value entails ensuring that proposed research is responsive to the health needs of the researched communities and is not exploitative (Department of Health, 2015; Emanuel et al., 2004). The data from qualitative interviews with REC members suggested that no member was surprised by the low frequency of social value queries raised by both RECs. The members felt that, because most studies reviewed by their RECs addressed important public health priorities such as HIV/AIDS and TB, they already were of social value to the community. This suggests that REC members believed that issues of social value would have been adequately addressed by the investigators in the research proposal under review, hence the low frequency of queries related to social value. There are a few empirical studies that have explored stakeholder's views on social value in research. A study in Kenya found that stakeholders viewed social value as benefit-sharing, for example, through post-trial access to research products and medical care, technology transfer and building local capacity, and societal benefits emanating from the successful completion of research (Lairumbi et al., 2012).

7.9 Additional issues

Although most of the issues raised in the data analysed for the present study were compatible with principles articulated in the Emanuel et al. (2004) framework, there were additional issues raised by the two RECs that could not be accommodated by the Emanuel et al. (2004) framework. These issues were categorized into administrative queries and include CVs and certificates of investigators and funding/budget. At face value, these would seem like mere administrative queries, but qualitative data with REC members suggests that these issues have a bearing on the social value, favourable risk benefit ratio and scientific validity of a study. For example, a trial that is not sufficiently funded may suddenly come to a halt before completion-hence exposes participants to unnecessary burden and waste of time and resources (Tsoka-Gwegweni & Wassenaar, 2014). Second, a study conducted by a scientifically poorly qualified PI is unlikely to yield valid results.

Furthermore, research procedures conducted by an unqualified researcher could not only yield invalid results, but pose risk of harm to the participants. Thus, RECs have to ensure that an appropriately qualified PI oversees the research and that appropriately qualified and skilled study personnel conduct relevant research and clinical procedures. This will improve the scientific validity as well as ensure that participants are attended to by qualified study personnel. Another category was editorial queries such as grammatical errors and typos. While these should not be encouraged, an interesting question is how far should RECs go in querying editorial issues? Are they important enough a reason to not approve a study? Should these issues even be queried in the first place? Considering the seemingly antagonistic relationship between RECs and researchers, particularly social science investigators (Mamotte & Wassenaar, 2012; Wassenaar &

Slack, 2016), it would be interesting to further explore the views of both REC members and researchers on these issues. A similar study in UK analysed 100 letters and found that errors were raised in 30% of letters (Angell & Dixon-Woods, 2009). There are some reported cases in the literature where research proposals have not been approved on the basis of poor editorial work (Stark, 2012). It could be argued that editorial issues reflect poor attention to detail by researchers, which could be a predictor of similar poor oversight in the study being proposed. Alternately or in addition, RECs could be briefed to attend only to editorial issues if they obscure key meanings of ethical import. Further work is needed to articulate and refine RECs' concerns arising under this general additional category.

7.10 Summary

This chapter has interpreted and discussed the study findings in light of the literature and framework underpinning this study (Emanuel et al., 2004). Comparing with results of other previous studies conducted both in South Africa (Clarke, 2014; Cleaton-Jones, 2010; Tsoka-Gwegweni & Wassenaar, 2014) and internationally (c.f., Adams et al., 2013, 2015; Angell et al., 2008, 2010; Kent, 1999; Lidz et al., 2012; Novaes et al., 2009; van Lent et al., 2014), the findings showed that the three most frequent issues identified in the present study, ranked in descending order (informed consent, respect for participants and scientific validity) were similar and comparable, except that there were some differences in the ranking of the issues. For instance, when comparing the results of the present study and findings reported by Tsoka-Gwegweni and Wassenaar (2014), issues of scientific validity were second ranked, whereas in the present study the second most frequent queries were respect for participants, followed by scientific validity in the third rank. In conclusion, the discussion chapter suggested that there is

some considerable similarity in the kinds of ethical issues raised by the two different RECs in the present study and previous studies conducted elsewhere, notwithstanding the different rankings and frequency of these issues. The next and concluding chapter highlights the limitations of the methodology and sample employed in this study, as well as the conclusions and recommendations for future consideration.

CHAPTER EIGHT

CONCLUSIONS AND RECOMMENDATIONS

This final chapter provides a summary of the study as a whole and concluding remarks. The chapter begins by highlighting the limitations of this study. This is then followed by the major conclusions and recommendations for further research.

8.1 Limitations of the study

This study has several limitations. The study sampled only two South African biomedical RECs. Results may therefore not be generalizable to all 44 biomedical RECs in South Africa (NHREC, 2015). However, both RECs are based at major South African universities that have highly active biomedical research portfolios, including many large clinical trials. Further, this study was a retrospective analysis of previous REC minutes and decision letters. The researcher did not prospectively observe the actual REC meetings. Thus, salient ethical issues raised by REC members during the rich conversational deliberations could have been omitted in the minutes analysed – even though many of the points in the minutes are transcribed by REC staff directly into the minutes, which in turn are extracted into decision letters to applicants. An ethnographic approach would possibly allow the more richly deliberated ethical issues be identified and provide in-depth insights into the review process (de Jong et al., 2012; Klitzman, 2015; Stark, 2012; Tolich, 2014).

Additionally, there was an untested assumption that the two RECs had comparable types of applications reviewed. Different workloads and types of protocols reviewed could influence the nature and frequency of ethical issues raised by RECs. Another limitation was that it was not possible to determine whether the low ranked ethical issues such as social value (ranked tenth overall), were well addressed in the research protocols or were thoroughly addressed through comprehensive ethics application forms, as suggested by some of the interviewees, or were caused by reviewers' blind spots. Furthermore, there is no agreed upon normative framework to interpret the ranking or frequency of queries, hence one of the reasons for qualitative interviews with REC members who confirmed that the distribution of the ethical issues was roughly what they would expect from such an analysis. A further critique of their commentary might be that they knew that they were indirectly reviewing their own REC's work (plus that of one other anonymous REC) which could have inclined interviewees to be uncritical. A future study should seek commentary from independent REC members or research ethics experts.

A further limitation is that members from both RECs stated that they had been trained using the Emanuel et al. (2004) framework, thus contributing to review outcomes compatible with this framework. Future work will explore REC outcomes from RECs whose members have not been trained using this popular framework. Hopefully these data would contribute to the development of a normative framework on how frequently these queries should be raised by RECs. A further multinational study is underway to collect, compare and aggregate similar data from several African countries. In addition, the coding of the minutes into the Emanuel et al. (2004) categories might have been unreliable, even though a co-rater attained 75% concordance with the researcher and differences were managed by discussion until consensus was attained.

8.2 Conclusions

The analyses of REC minutes using the Emanuel et al. (2004) framework presented in this study focused on ethical issues raised by two South African biomedical RECs. The findings of this present study suggest that while the relative weight given to ethical principles varied slightly across the two different RECs, the core issues raised were very similar and consistent with established national guidance (Department of Health, 2004, 2015). For instance, the findings highlighted that informed consent was the most frequent ethical issue raised by both RECs, followed by ongoing respect for participants (ranked second) and scientific validity (ranked third). The other remaining Emanuel et al. (2004) issues were ranked differently by the two RECs (see Figure 9). For example, collaborative partnership was the fourth most frequent issue raised by REC 1, while it was seventh at REC 2. Similarly, fair participant selection was ranked fifth and sixth at REC 1 and 2 respectively. Likewise, favourable risk/ benefit ratio was the sixth most frequent issue raised at REC 1, but was ranked fourth at REC 2. Social value was the least frequent issue raised by both RECs in this study. The frequencies of ethical issues raised by the two RECs sampled in this study largely resemble the findings reported in a similar previous study (Tsoka-Gwegweni & Wassenaar, 2014).

Furthermore, the present study also found that the frequency of additional queries raised by both RECs, coded as administrative queries e.g., funding and CVs (4^{th} ranked) and editorial errors (ranked 6^{th} overall) was higher compared to, perhaps more important, ethical issues such as favourable risk/benefit ratio and fair participant selection. This suggests that researchers really need to proof-read their ethics applications and check all of the information and additional documentation required before submission because the likelihood is that RECs will find

something in the application that is of (ethical) concern to them or that they want further information about. Similar studies in the UK have also reported that RECs frequently identify errors such as missing information and discrepancies in applications for ethics approval (Angell & Dixon-Woods, 2009).

The findings of the present study hopefully provide valuable empirical insight into some of the ethical issues raised by two South African biomedical RECs. Researchers submitting protocols need to be aware of, and address in advance, concerns about informed consent (ranked first), respect for participants (ranked second) and scientific validity (ranked third), as these were frequently raised and ranked highest by both RECs. While they were not as highly ranked in the present study, other ethical issues such as collaborative partnership (ranked 5th), favourable risk/benefit ratio (ranked 7th), fair participant selection (ranked 8th) and social value (ranked 10th), are equally important and should be thoroughly addressed in applications for ethics approval. The data shows that, overall, the Emanuel et al. (2004) framework seems compatible (83%) with the type of ethical issues identified by both RECs in this study. Almost all respondents regarded the framework as an adequate, concise and comprehensive research ethics framework compatible with review activities of local RECs.

However, certain limitations of the framework were noted. The framework does not explicitly mention issues related to storage and use of biological samples such as the need to have export permits or MTAs, yet these requirements are required by the South African national guidelines

(Department of Health, 2015). As such, this could be added as a benchmark of collaborative partnership in the Emanuel et al. (2004) framework.

Secondly, the framework does not explicitly address administrative issues, such as funding and investigator CVs. These issues have a considerable bearing on the social value, favourable risk/benefit ratio and scientific validity of proposals as previously described and could be added as benchmarks under these respective headings in the Emanuel et al. (2004) framework. The South African (Department of Health, 2015) and most international ethical guidelines such as CIOMS (2002) and Declaration of Helsinki (2013) explicitly require that research be conducted by a competent investigator - reflected in their certification, knowledge and experience. This concern could probably be included as a subsection of scientific validity.

Overall, it is reassuring that the majority of ethical issues raised by the two index RECs in this study resonated well with principles in the national research ethics guidance (Department of Health, 2004, 2015) as well as international guidelines such as the Declaration of Helsinki (WMA, 2013). Nonetheless, there is need for RECs to be constantly re-trained and kept abreast with ethical issues in international biomedical research to be able to apply the Emanuel et al. (2004) framework and national guidance (Department of Health, 2015) optimally in their important ethics review activities.

This study has hopefully generated empirical data and highlighted some of the important ethical issues typically considered by two South African biomedical RECs during their ethics review work. It is hoped that findings of this thesis could be used to alert future investigators about the concerns raised by local RECs reviewing biomedical research and what issues should be addressed in their applications for ethics approval. It is also hoped that the findings will be of use in training REC members with regard to common and possibly neglected issues in ethics review.

8.3 Recommendations for future research

First, the study was based on a retrospective analysis of REC minutes. Further ethnographic studies of ethical issues raised during REC meetings would be very useful as they are more likely to give in depth insight into the kinds of issues discussed and the decision-making process (Klitzman, 2015; Stark, 2012). Secondly, the study involved only two South African RECs. Future studies comparing a bigger sample of RECs in South Africa would be worthwhile. Such a study is currently underway in about ten additional African countries.

Second, the RECs sampled in this study stated that they mainly depend on the Emanuel et al, (2004) framework for ethics training of their REC members. This could have contributed to why the ethical issues identified in this study were compatible with this framework. Therefore future studies could explore ethical issues raised by RECs whose members have not been trained using this popular framework. Perhaps such studies might uncover a different pattern of ethical issues from those reported in this study.

Furthermore, it was interesting to note the high ranking of certain issues e.g., informed consent and respect for participants. This may perhaps be due to lack of knowledge or limited understanding of these ethical issues among researchers or inadequate specification of requirements in the RECs' application forms. It remains unclear how researchers view and understand the ethical issues identified in this study. Further in-depth interviews about these findings with such stakeholders will be useful. Importantly, researchers need to familiarise themselves with their institutional REC's framework and national (Department of Health, 2015) and international ethical standards governing biomedical research such as the Declaration of Helsinki (WMA, 2013). When researchers familiarise themselves with principles of ethical research and really think about these ethical issues, and work closely with their local RECs, there is increased likelihood for fewer ethical queries on their applications because they would have submitted well-written protocols and improved informed consent documents that better address the ethical issues typically raised by RECs in the first place (Wassenaar & Slack, 2016).

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APPENDICES

Appendix 1: Data collection form

Title: ***An empirical investigation of ethical issues raised by two Research Ethics Committees reviewing biomedical research in South Africa.***

1. General

1.1 Research protocol unique code: ----------

1.2 REC unique code: ----------

1.3 Year of ethical review

A. 2009

B. 2010

C. 2011

D. 2012

E. 2013

1.4 Type of research

A. Cross-sectional

B. Clinical Trial

C. Cohort

D. Case-control

E. Descriptive

F. Other: ----------

1.5 Area of Research: ----------

1.6 Research participants

A. Children

B. Adults

C. Other: _____

1.7 Vulnerable group

A. Pregnant women

B. Children

C. Prisoners

D. Mentally ill

Other _____

2. Checklist based on Emanuel et al. (2004) Principles and benchmarks

	Issue raised by REC	Issue not raised by REC	Comments
PRINCIPLE 1: COLLABORATIVE PARTNERSHIP			
Develop partnerships with researchers, makers of health policies, and the community			
Involve partners in sharing responsibilities for determining the importance of health problem, assessing the value of research, planning, conducting, and overseeing research, and integrating research into the health-care system			
Respect the community's values, culture, traditions, and social practices			
Develop the capacity for researchers, makers of health policies, and the community to become full and equal partners in the research enterprise.			
Ensure that recruited participants and communities receive benefits from the conduct and results of research.			
Share fairly financial and other rewards of the research.			
PRINCIPLE 2. SOCIAL VALUE			
Specify the beneficiaries of the research—who.			
Assess the importance of the health problems being investigated and the prospective value of the research for			

each of the beneficiaries—what			
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			
PRINCIPLE 3. SCIENTIFIC VALIDITY			
Ensure that the scientific design of the research realizes social value for the primary beneficiaries of the research			
Applicability of results- 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			
PRINCIPLE 4. FAIR PARTICIPANT SELECTION			
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.			
PRINCIPLE 5. FAVOURABLE RISK-BENEFIT RATIO			
Assess the potential risks and benefits of the research to the study population in the context of its health risks.			
Assess the risk-benefit ratio by comparing the net risks of the research project with the potential benefits derived from collaborative partnership, social value, and respect for study populations.			
PRINCIPLE 6. INDEPENDENT REVIEW			
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.			
PRINCIPLE 7. INFORMED CONSENT			
Involve the community in establishing recruitment procedures and incentives			
Disclose information in culturally and linguistically appropriate formats.			
Implement supplementary community and familial consent procedures where culturally appropriate			

Obtain consent in culturally and linguistically appropriate formats.			
Ensure the freedom to refuse or withdraw.			
PRINCIPLE 8. RESPECT FOR PARTICIPANTS			
Develop and implement procedures to protect the privacy and 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.			

3. Additional Comments

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Appendix 2: Interview guide

Topic guide: Semi-structured interviews with REC members

General experience and views about REC ethics review

1. Can you tell me about your experience with REC reviews?

    - What do you think is the core function of your REC? Can you tell me about issues/ benchmarks that you associate with ethical research?
    - Based on your experience reviewing research protocols, please identify common (ethical) issues or concerns that you see in proposals. *[Probe for all types of ethical issues known]*. *Can you think of any other issues?*
    - Can you please define/ tell me more about the categories/issues raised above. What are the most important considerations/indicators e.g. collaborative, social value, informed consent, respect for participants. etc.
    - What do you think are the main ethical issues that local RECs should consider when reviewing research? [*Why should these be raised or not*?]
    - In general, what kind of issues (of those you have just mentioned) do you see as more important than others? Would you even argue that there are important issues than others? Why are these important?
    - Do you think all the relevant ethical issues are given adequate consideration by your REC?
    - Do you feel that there are issues that should be given more consideration than others during ethics review? *[Probe for reasons why or why not]*

Views about the data summary [to be shown to each interviewee]

2. What do you think about this distribution?

    - Would you expect such a distribution from your REC? [*probe for reasons*]
    - How would you compare these two sets of issues? Overall, do you think they reflect what local RECs should be doing? [*probe for reasons why or why not*]?
    - Would you argue that there are any categories overemphasized or under-emphasized?
    - Are there any surprises? [*why or why not*]
    - Do you think some issues should be queried more than others? [*probe for the type of issues and reasons why*]
    - Could the above distribution be due to a bias in the application form?
    - Do you think your REC application form captures all the main ethical issues in the shown in the data?
    - Do you think there is a REC doing a better job at protecting participants than the other? If so why do you say this? In what way do you think one REC is doing better than the other? [*draw on data explained in the graphs above*]

- What would you, as a REC member/chair/administrator, ideally like to see addressed in the proposals that you review or during REC deliberations? Is there anything missing in the data presented?

General views about the Emanuel framework

3. What are your views about the Emanuel framework?

- Are you familiar with the Emanuel framework?
- Do you think the Emanuel benchmarks are important or relevant to your work? In what way do they seem important or pertinent to your REC?
- Is the framework compatible with issues that you pick up in your typical review activities?
- Are there any types of issues raised by your REC and not covered in the framework that you would like to see in the framework? [*Why or why not. Probe around administrative queries*].

Concluding remarks and reflections

- Do you have any other thoughts/comments about these issues?

Appendix 3: Informed Consent Form

PARTICIPANT INFORMATION LEAFLET

TITLE OF THE RESEARCH PROJECT: An empirical investigation of ethical issues raised by research ethics committees reviewing biomedical research in South Africa

PRINCIPAL INVESTIGATOR: Mr Blessing Silaigwana

ADDRESS: University of KwaZulu-Natal
College of Humanities
School of Applied Human Sciences
P/Bag X01, Scottsville
Pietermaritzburg
3209
South Africa

Hello. My name is Blessing Silaigwana and I am a PhD student at the University of KwaZulu-Natal. I would like to invite you to participate in a research project that aims to investigate the views of Research Ethics Committee (REC) members on the issues typically raised by local RECs. This study will help us to understand aspects of the ethical issues that RECs typically identify in their review activities.

Please take some time to read the information presented here, which will explain the details of this project and contact me if you require further explanation or clarification of any aspect of the study. Also, your participation is **entirely voluntary** and you are free to decline to participate. If you say no, this will not affect you negatively in any way whatsoever. You are also free to withdraw from the study at any point, even if you do agree to take part.

This study has been approved by the XXXXXX **(REC) at XXXXXXX University** (Ref XXXXX) and **University of XXXXXX Research Ethics Committee** (Ref XXXXX) and will be conducted according to accepted and applicable National and International ethical guidelines and principles, including those of the international Declaration of Helsinki 2013.

What is this research study all about?

The purpose of this component of my study is to explore the views of Research Ethics Committee (REC) members on the issues raised by local RECs. The investigator will present you with materials reflecting typical queries of RECs to applications for ethics approval. This study will help us understand perspectives on the ethical issues that RECs typically identify in their review activities.

Your participating involves taking part in an in-depth interview lasting between 30-45 minutes. You will be asked some open-ended questions, based on the data presented, which will help us to

explore these ethical issues. The questions are not personal or sensitive in any nature, but you are free not to answer any specific question.

The study will be conducted at your University and one other South African University. Details of both participating institutions will be anonymised in all reports and publications. Altogether 15 participants will be recruited for this study.

Why have you been invited to participate?

You have been invited to participate because as a REC member who is familiar with the ethical review process of biomedical research studies, we would like to explore your views on the ethical issues typically raised by the two participating RECs. Your comments will help us understand the data from the first part of this study.

What will your responsibilities be?

Your responsibilities will be to voluntarily give your opinions and responses to some open-ended questions asked in the form of an in-depth interview. You will be presented with a synopsis of results obtained from the analysis minutes and letters of two South African RECs. You will be asked for your opinions and views about the ethical issues identified by RECs. I would also like to ask your permission to audio record the interviews.

Will you benefit from taking part in this research?

There are no direct benefits that you will receive from participation in this study. However, your participation in the study has potential to contribute scientific knowledge to the research being conducted. We have also offered to present our findings to the two participating RECs.

Are there in risks involved in your taking part in this research?

Presently, there are no any foreseeable risks in your participation. All data will be completely anonymized and your name and the name of your institution will not be recorded anywhere nor revealed in subsequent publications.

If you do not agree to take part, what alternatives do you have?

Please note that participation is voluntary and completely based on your willingness. You are not being forced to take part in this study. The choice of whether to participate or not, is yours alone. If you choose not to take part, you will not be affected in any way whatsoever. If you agree to participate, you may stop participating in the research at any time. You are guaranteed that there will be no penalties or any action taken against you and you will not be prejudiced in any way should you decide to withdraw from the study. If you chose not to take part or chose to withdraw from this study, your welfare will not be affected in any way.

If you are willing to participate in this study please sign the attached Declaration of Consent and hand it to the investigator.

Declaration by participant

By signing below, I ……..……. agree to take part in a research study entitled **An empirical investigation of ethical issues raised by Research Ethics Committees reviewing biomedical research in South Africa.**
.

I declare that:

- I have read the attached information leaflet and it is written in a language with which I am fluent and comfortable.
- I have had a chance to ask questions and all my questions have been adequately answered.
- I understand that taking part in this study is **voluntary** and I have not been pressurised to take part.
- I may choose to leave the study at any time and will not be penalised or prejudiced in any way.
- I may be asked to leave the study before it has finished, if the researcher feels it is in my best interests, or if I do not follow the study plan, as agreed to.

Signed at (*place*) .....….....…….. On (*date*) ……...…….. 2015.

Signature of participant

CONSENT FOR TAPE RECORDING
I hereby agree to the tape-recording of my participation in the study.

……..
Signature of participant
Date:……..

Appendix 4: Ethics approval from University 1

Withheld to retain confidentiality. Available on request for audit purposes

Appendix 5: Ethics approval from University 2

Withheld to retain confidentiality. Available on request for audit purposes