An Evaluation of Ethical Concerns Raised by a Ugandan Research Ethics Committee Using the Principles and Benchmarks Proposed by Emanuel et al. (2008)

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DECLARATION

I, Claude Kirimuhuzya, declare that this dissertation titled "*An Evaluation of Ethical Concerns Raised by a Ugandan Research Ethics Committee Using the Principles and Benchmarks Proposed by Emanuel et al. (2008)"* is from my own work and where secondary sources of information have been used, they have been duly acknowledged.

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DEDICATION

I dedicate this work to my family members who had to put up with my absence when I was doing it and for the support they provided.

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LIST OF ACRONYMS AND ABBREVIATIONS

CIOMS	Council for International Organization of Medical Sciences
ICH-GCP	International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use and Good Clinical Practices
IRB	Institutional Review Board
NDA	National Drug Authority
REC	Research Ethics Committee
SAE	Serious Adverse Event
SARETI	South African Research Ethics Training Initiative
SOP	Standard Operating Procedure
UNCST	Uganda National Council for Science and Technology
UNHRO	Uganda National Health Research Organisation

ABSTRACT

Research Ethics Committees (RECs) serve several important public functions, including ensuring that research participants are protected in addition to provision of a public forum for the accountability of researchers. As such they are required to follow established national and international standards when they are carrying out protocol reviews. However, there is no standardised model on which to base their reviews. In order to help RECs in their work, Emanuel and colleagues analysed existing ethics codes and produced a framework of eight principles and benchmarks, to give eight principles to guide RECs in the process of reviewing research proposals for ethical issues. However, prior to this study, there was little empirical research into the actual issues that RECs in Uganda raise when reviewing research proposals, leave alone determining whether the issues raised during the review process were in line with those envisaged by the Emanuel and colleagues or not. This study was therefore undertaken to establish the concerns raised during the review of study protocols, using archived minutes of one REC in Uganda.

The study analysed the minutes for initial full reviews of protocols for the years 2102 to 2013 using the eight principles and benchmarks proposed by Emanuel and colleagues. Expedited and ongoing reviews were excluded.

The results indicated that of 2008 issues raised in the 28 meetings that reviewed the 110 protocols, 90.5% could be accommodated under the eight principles in Emanuel et al. (2008) framework. The most commonly raised issues were scientific validity (54.1%) and informed consent (11.4%). Other additional issues included administrative and feasibility issues at 9.5% and 6.0% respectively.

The Emanuel et al. framework provides a useful tool that can be used to categorise the issues and concerns raised during research protocol review meetings of RECs in Uganda. The results further demonstrate that it is possible to use this model to carry out comparative studies to evaluate the review outcomes of RECs in the country and other countries in Africa and the world at large.

CHAPTER ONE

1.0 INTRODUCTION

1.1 Background

The need to regulate research activities involving human participation led to the establishment of Institutional Review Boards (IRBs), also known as Research Ethics Committees (RECs) in most institutions (World Health Organisation, 2009a). It is increasingly becoming a requirement that all research studies involving human participants must be reviewed by an independent REC (Helsinki Declaration, 2013). In addition to the oversight role over health research, some RECs serve additional roles that include increasing public awareness about medical research as well as providing some form of public forum through which researchers can be made accountable to the public sector (Ashcroft & Pfeffer, 2001).

In recent years, there has been an increase in social and biomedical research activities throughout the world, with developing countries with their high disease burden, conducting more studies than before (Drain, Parker, Robine & Holmes, 2018; Luo, Wu & Chen, 2017; WHO, 2009b). This has also led to an increase in the incidence of unethical research and scientific misconduct, a situation that has necessitated the establishment of RECs in many institutions in the developing world to ensure that researchers adhere to the highest scientific and ethical standards with the ultimate goal of protecting human research participants (World Health Organisation (WHO, 2009a)).

RECs rely on international and national guidelines for the review of research protocols and, as such, there are several international guidelines all of which strive to promote the dignity and maximise the protection of research participants and communities from potential harm and exploitation (Helsinki Declaration, 2103; CIOMS, 2016; ICH-GCP, 1996). Such review should be conducted by competent independent ethics review committees commonly known as Research Ethics Committees (RECs) or Institutional Review Boards (IRBs) (WHO, 2011). However, application of research ethics guidelines, most of which are based on the principles and philosophies from western countries, can become a challenge to RECs in different settings in the world, due to lack of a standardised model on which to base their review processes. In order to help RECs in their work, Emanuel and colleagues (2000; 2004; 2008) analysed the major

existing ethical codes and produced a framework of seven principles and benchmarks, which were revised in 2008, to give eight principles to guide RECs in the process of reviewing research proposals for ethical correctness (Emanuel, Wendler, Killen & Grady, 2008).

However, there has been little empirical research into the actual issues that RECs in Uganda raise when reviewing research proposals, leave alone determining whether the issues raised during the review process are in line with those envisaged Emanuel et al. (2004; 2008) or not. The first attempt to conduct this kind of research was by Tsoka-Gwegweni and Wassenaar (2014) on one South African REC. Prior to this study, there were no other data with which to compare such findings with the Tsoka-Gwegweni and Wassenaar (2014) study. A closer and systematic examination of the ethical issues raised by RECs in selected African countries, using Uganda, as one of the cases, was undertaken to shed more comparative light on this and reveal areas of concerns raised during the review of study protocols, which ultimately leads the REC to arrive at a particular decision. Using both a qualitative and some quantitative approaches, the minutes of REC meetings were analysed to evaluate their decision-making processes, according to the Emanuel et al. (2008). As part of a multinational study taking place in Cameroon, Ghana, Malawi, Nigeria, South Africa, Uganda and Zimbabwe, this study also considered the applicability of the framework in an African context.

1.2 Problem statement

From research reports about the functioning of the RECs in Africa, several inadequacies were reported (Kass, Hyder, Ajuwon, Appiah-Poku, Barsdorf, Elsayed, Mokhachane, Mupenda, Ndebele, Ndossi, Sikateyo, Tangwa and Tindana, 2007; Ajuwon & Kass, 2008; Abbott & Grady, 2011) This prompted several research ethics training initiatives to be started in Africa and these attracted a lot of funding for capacity building especially for RECs' establishment (Ali, Kass, Sewankambo, White & Hyder, 2014; Ndebele, Wassenaar, Benatar, Fleischer, Kruger, Adebamowo, Kass, Hyder & Meslin, 2014). As a result, many countries in Africa now have functional RECs which are tasked with the responsibility of conducting scientific and initial and ongoing ethical reviews of research protocols. However, prior to this study there was paucity of data when it came to how the RECs conduct their business of protocol review. Very little was known about what kind of issues were being raised during the review meetings and how they related to the framework developed by Emanuel et al. (2008), and whether the framework was

applicable in the African setting or not. This study tried to address these two issues using a selected REC in Uganda. Therefore, a study like this one, which targets RECs in different countries of Africa, goes some way to address some of the issues related to the review outcomes of RECs in these countries.

1.3 Aim and objectives

1.3.1 Aim

The study aimed to identify the main ethical issues raised during ethics review of research proposals by RECs and assess their relative weight using the principles of ethical review of clinical research recommended by Emanuel et al. (2008) framework.

1.3.2 Objectives

i. To study the minutes of a selected Ugandan RECs' review meetings to identify and describe the pattern of ethical concerns and issues raised in their reviews of research proposals.
ii. To analyse the ethical issues and concerns using the Emanuel et al. (2008) framework ranking them and identifying how they do or do not fit the framework.

1.4 Research questions

i. What ethical concerns does the selected REC in Uganda raise when reviewing protocols?
ii. Is there a systematic prioritisation of some ethical issues over others?
iii. Is there an observable pattern to the ethical concerns raised by the REC? If so, what is the pattern?
iv. Are the concerns raised consistent with the framework developed by Emanuel et al. (2008)?
v. Does any feature of the Emanuel et al. (2008) framework dominate the concerns? If so, which one?
vi. Are there other concerns raised by RECs which are not compatible with the framework discussed by Emanuel et al. (2008)?

1.5 Study rationale

During a decade of its existence, many institutions have come to accept Emanuel et al. framework as an important working document for application during the ethics review process. Nevertheless, apart from the Tsoka-Gwegweni and Wassenaar (2014) pilot study in South Africa, there was no other study aimed at examining the applicability of the Emanuel et al. (2008) framework, prior to this one. Therefore, this study was not only going to provide data on how RECs in Uganda conduct their review business but also to contribute to examining the applicability of Emanuel et al. (2008) in a Ugandan REC.

The results from this study may help to give a picture of the issues that dominate protocol review in Uganda and relate them to the Emanuel el al. (2008) framework. The results may help to reveal variations that exist in different cultural and geographical areas when it comes to application of the Emanuel et al. (2008) framework as compared with the results of Tsoka-Gwegweni and Wassenaar's (2014) study. It is envisaged that recommendations from this study may contribute towards the future adjustments that might have to be made to improve Emanuel et al. (2008) framework.

1.6 Scope of the study

One REC was selected from several Ugandan RECs to contribute to data obtained from RECs from the seven African countries involved in the broader study which included Cameroon, Ghana, Malawi, Nigeria, South Africa and Zimbabwe.

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 Introduction

There is now widespread acceptance that protocols/proposals for research involving human participants must undergo independent scientific and ethics review (World Medical Association (WMA), 2013; CIOMS, 2016; ICH-GCP, 1996). Such review should be conducted by competent independent ethics review committees commonly known as Research Ethics Committees (RECs) or Institutional Review Boards (IRBs) (WHO, 2011). One of the most important roles of these RECs is to ensure that research is conducted according to established ethical standards. However, for the desired level of efficiency to be achieved, the RECs must have the necessary capacity to conduct such reviews and to apply operational procedures that are standardised (Kruger, Ndebele & Horn, 2014).

For RECs in the low and middle income countries (LMICs), especially in Africa, the pressure on them becomes even greater when it comes to reviewing complex protocols like those for clinical trials involving international collaboration. This fact is clearly brought out when we consider the arguments by Burman, Reves, Cohn and Schooley (2001) in relation to the pressure exerted on local RECs that were not originally designed to handle the large volume of review work from multicentre clinical trials (Burman et al., 2001). All these put together, require that the responsibilities of the local REC in the oversight of multi-centre clinical trials be systematically evaluated (Burman et al., 2001). However, for such an evaluation to be carried out, we need a standardised model if we are to be able to compare results obtained from different backgrounds. This is partly what prompted Emanuel and colleagues (2008), to develop a framework that could be used globally in the review of research protocols (Emanuel et al., 2008).

2.2 Emanuel et al. (2008) framework

Although the four principles of bioethics, namely autonomy and respect for dignity of persons; non-maleficence; beneficence and the principle of justice (Beauchamp & Childress, 2013), are widely accepted principles that are applied in research ethics, these principles are difficult to interpret and apply in different settings with regard to history, geography, culture, gender-

relations and economic status, making it difficult for users to appropriately prioritise them when applying to these varying contexts (Molyneux & Geissler, 2008). It was in response to such challenges that the Emanuel et al. framework was proposed (Emanuel et al., 2008). The framework emphasises traditional codes, guidelines and literature on the ethics of research involving human participants and is based on 8 principles, namely: 1) collaborative partnership; 2) social value; 3) scientific validity; 4) fair selection of participants; 5) favourable risk/benefit ratio; 6) informed consent; 7) independent review; and 8) ongoing respect for participants and study communities (Emanuel et al., 2008). These are briefly outlined below.

Collaborative partnership: This principle aims at encouraging researchers to develop studies that engage the target community or population and other relevant stakeholders involved in the process at all stages, up to dissemination of results. It is derived from the need to reduce possible exploitation of research participants and communities. It aims at ensuring that the participating communities have established strategies for research benefit sharing before the study begins (Emanuel et al., 2008). What has not been clearly known is the emphasis the RECs put on this principle and how they ensure that researchers uphold it before, during, and after implementation of the study, and how this is catered for at the proposal stage. The emphasis the RECs put on the issue of community engagement with regard to collaborative partnerships can also be discerned from analysis of minutes and communication documents with researchers.

Social value: This principle aims at ensuring that research undertaken in any community addresses questions that are of social or clinical value to society or particular communities in society (Emanuel et al., 2008). The research protocol should specify who the beneficiaries of the research will be and in what way they might directly or indirectly benefit. The problem being studied should lead to knowledge and/or interventions that will be of value to the participants and/or society as a whole (Emanuel et al., 2008). Again, when we refer to the current state of the review process undertaken by RECs in various institutions, it is important to know how much emphasis the RECs put on this principle and how the social value of a study is evaluated during protocol review.

Scientific validity: This is aimed at ensuring that the study design, sampling procedures, methods used and the data analysis techniques used in the study are adequately rigorous, and that they are justifiable and feasible enough to provide valid answers to the research questions (Emanuel et al.,

2008). Any study that is not scientifically valid is always taken to be unethical (WMA, 2013; Freedman, 1987; Mitscherlich & Mielke , 1947) Therefore, RECs have to ensure that researchers use methodologies that meet the standards of scientific validity in both qualitative and quantitative research. Again, it is important to determine whether this is one of the principles that are stressed during ethical reviews and whether there are mechanisms and standard procedures to ensure that all approved protocols meet the criteria for scientific validity before they are subjected to ethics review.

Fair selection of participants: This is aimed at ensuring that there is fair distribution of research burdens and benefits with all potential participants having equal chance of participating in the study and if there are possible benefits then they should also have equal chance of benefiting. The framework further stipulates that the population selected for the study should be that to whom the research question applies (Emanuel et al., 2008). It further states that study samples should not be selected based on convenience, unless one is carrying out a pilot study that is intended primarily to be a training exercise. As has been mentioned for the other principles in this framework, it is important to know the extent to which this is an issue during the protocol review process in African RECs.

Favourable risk to benefit ratio: There should be clear identification of all possible harms, risks and costs of the research to the participants as well as specified measures to be undertaken to minimise risks/harm so that the risk/benefit ratio is favourable (Emanuel et al., 2008). During risk/benefit determination, the REC should consider the probability of harm occurring and the anticipated severity of the harm. RECs are warned not to stifle research in situations where there is a low probability of relatively minor harms occurring, but where the benefits to participants and society are clear. This means that any research which has potential risks outweighing potential benefits could be unethical and should not be approved unless risks are minimised and benefits maximised. Again, it is important to examine the day-to-day review process by RECs to determine the degree to which such a principle is emphasised during the review process since, there is limited data in this area.

Independent Ethics review: Any study involving participation of humans must be subjected to a review process and approval obtained from an independent and competent REC. Commencement of data collection before independent ethics review is a breach of research ethics (Emanuel et al.,

2008). This independent review should cover both science and ethics. RECs should have guidelines in place and should be empowered with the necessary skills, finance, legislation, and Standard Operating Procedures, among other things, to carry out this exercise (WHO, 2011). From the minutes of the REC meetings, one can to indirectly discern whether or not there are structures like scientific committees, biosafety committees or animal welfare committees.

Informed consent: This is one of the principles that are usually regarded as central to the review process, a fact that has its origins in the Nuremburg Code (1947) and Declaration of Helsinki (2013). RECs are expected to have mechanisms and guidelines that ensure that, before anyone is recruited to participate in a study they, have been given appropriate information and that the participant is intellectually competent, understands the issues raised in the consent process and is capacitated to voluntarily participate (Stanford Encyclopaedia of Philosophy, 2011). To ensure that participation is voluntary and not driven by coercion or undue inducement (Kass, Maman & Atkinson, 2005), there must be guaranteed permission to withdraw without victimisation and the formalisation of consent in writing. The principle further states that in situations where minors are involved, there may also be assent where the participant's legally acceptable representative is the one giving consent. There may be extra restrictions on the informed consent process for the vulnerable groups such as the mentally challenged, prisoners, among others (Emanuel et al., 2008). Analysis of RECs' minutes can reveal issues raised about the adequacy of the informed consent process and the emphasis that is placed on informed consent as one of the major principles that are given special consideration in the ethical review process.

On-going respect for participants and study communities: The last principle of Emanuel et al. framework is that of treating research participants with respect during and after the project. RECs have to have mechanisms and procedures in in place to ensure that the researchers do not abandon the ethical principles after completion of the research (Emanuel et al., 2008). The REC's minutes can also help to bring out incidents of this principle having been underemphasised by researchers. Although the Emanuel et al. framework could be criticised for omitting concerns relating to the integrity of researchers, and perhaps of not being adaptable to all cultural settings (see below), it provides a systematic model that can be used to gain insight into the actual issues that influence decision making during the ethical review process (Emanuel et al., 2008). However, one important consideration that has to be made is that the principles have to be applied together. A

comprehensive analysis of the minutes of proceeding during the review process is one approach that can help bring out the patterns and trends in the issues raised during protocol meetings.

An area which might not be satisfactorily accommodated by the Emanuel et al. (2008) framework concerns issues to do with reciprocity and mutuality as emphasised in the San Code of Research Ethics (2017). A closer look at the San Code of Research Ethics (2017) suggests that the code emphasises that there should be respect for individual, community, culture and history as well as respecting relationship with environment. Although Emanuel et al. (2008) mention ongoing respect for participants and their communites, the San Code is more explicit especially on cultural heritage and the relationship with the environment. The San Code is also more emphatic on protection of privacy and acknowledgement of community contribution to research and the need to have comprehensive community engagement and honouring the promises made to the community after the research. The San Code, arguably, makes giving feedback to the community or allowing them access to benefits, more obligatory, an issue that is not well articulated by Emanuel et al. (2008) framework. Furthermore, the San Code recommends honesty from all researchers and this contributes to ensuring that there is research integrity (already mentioned as a shortcoming of the Emanuel framework, in the above paragraph). Researchers are also supposed to avoid exaggerated claims of inability to provide any benefits. The San code demands open and clear information exchange between the researchers and all stakeholders including honest sharing of information in a language that can clearly be understood by all stakeholders.

The San code also articulates the principle of justice beyond just distributive justice: there is mention of meaningful involvement of local communities in the proposed studies, which includes learning about the non-monetary benefits that the participants and the community might expect, including co-research opportunities, sharing of skills and research capacity, and roles for translators and research assistants, to give some examples. The San code also allows the participating communities to enforce compliance with any breach of the Code, including through the use of dispute resolution mechanisms. There is also emphasis on acknowledgement of intellectual contribution by indigenous knowledge sources and sharing of benefits accruing from use of indigenous knowledge. The code also emphasizes that research should be aligned to local needs and improve the lives of the participating communities. Although the Emanuel et al. (2008) framework emphasises favourable risk/benefit ratio and social value, the San Code of Ethics

(2017) is more explicit and emphatic on these particular points. However, it is also pointed out here that the Emanuel framework does not purport to be a comprehensive ethics guideline or code; indeed it is rather a collation of the major points made in most international guidelines into a useful set of major categories for researchers and RECs to consider. It was not designed to replace national or international ethics guidance documents. It is fair to say that it should be revised in the light of some of the above critiques.

2.3 Ethics research in Africa

An early study involving RECS in Africa was a case study conducted by Milford, Wassenaar and Slack (2006) who evaluated the resources and needs of relevant African RECs to review HIV vaccine trial protocols. Another study that targeted African RECs was by Kass et al. (2007). The study focused on the structure and function of RECs in Africa and examined the history, operations, strengths, and challenges of selected 12 African RECs (Kass et al., 2007). It reported inadequate training and funding, members often being poorly equipped to review using ethics criteria, inadequate training of staff and administrators, and tendency of some institutions to influence their RECs to grant approvals to enable the institutions secure funding without due diligence (Kass, et al., 2007). There was also mention of a lack of national guidelines and local operating procedures in some cases (Kass et al., 2007).

Based on the challenges raised by the Kass et al. (2007) case study, it was suggested that more training, funding, independence, and political commitment be accorded the RECs in Africa, to improve functioning. Suggestions were made for training workshops on how to interpret ethics principles in light of local norms; public outreach programs about research; creation of networks of African RECs to share materials, resources, and capacity building; creation of mechanisms to facilitate communication between host and sponsor country RECs; joint meetings between REC members and investigators to brainstorm solutions to shared challenges; human rights advocacy to help enhance participants' and researchers' awareness about rights in research; and more empirical research on ethics and African research (Kass et al., 2007).

From the case study it was also noted that many of the challenges described by Kass et al. (2007) were not unique to African RECs but also existed in wealthier countries. This view was supported by the results of a systematic review of empirical studies of IRBs in United States

(U.S.) which was carried out by Abbott and Grady (2011). They found that there were differences in application of federal regulations even among the IRBs within the US (Abbott & Grady, 2011). They also reported evidence of variations in multi-centre review, some inconsistencies or ambiguities in interpretation of the US Federal regulations governing research, and that there were inefficiencies in the review process (Abbott & Grady, 2011). They further reported that several studies carried out in the US, which were aimed at evaluating the structure, process, and outcome of IRB review, also documented inconsistencies and inefficiencies in the work of IRBs. As a result, they recommended that there should be deliberate efforts to address the concerns and challenges reported if the quality of reviews was to improve (Abbott & Grady, 2011). With such challenges being faced by IRBs in USA, one would expect a much worse situation with the RECs in Africa, due to training deficits and resource constraints, making such evaluation studies more imperative for African RECs. Again, knowing how important ethics review is, periodic evaluations become imperative because such evaluations can help to determine whether or not RECs are operating according to established standards (Office of the Inspector General, 1998).

There have also been concerns especially from researchers that RECs do not have sufficient capacity to review the proposals that are presented to them. For example, in a study conducted by Ajuwon and Kass (2008), though involving only one university, the authors found the following, as concerns about the quality of reviews by RECs: (1) Delay in review of proposals by the local REC; (2) weak monitoring system of approved proposals; (3) lack of training of some members of REC; (4) misunderstanding of the role of RECs; (5) lack of understanding of informed consent process by many scientists; (6) many scientists not fully understanding the role RECs ought to play in a research project; and (7) some researchers believing that members of RECs will plagiarise their ideas during the review process (Ajuwon & Kass, 2008).

Following reports about challenges faced by RECs in Africa, several projects were funded to facilitate research ethics training on the continent and to facilitate establishment of RECs, with several research ethics training initiatives being established, as well as incorporating ethics training as a component in several funded projects (Ali et al., 2014; Ndebele et al., 2014). At the moment, a substantial number of African Scientists and REC members have acquired training and countries like Uganda now have 24 fully accredited RECs (http:www.uncst.go.ug).

Other studies covering ethical issues that influence decision-making in African REC review meetings are covered in a review by Silaigwana and Wassenaar (2015) which identified six studies that provided empirical data about this issue. However, the majority of these studies were conducted in South Africa (Klitzman, 2008; Cleaton-Jones, 2010; Sathar, Dhai & van der Linde, 2013; Tsoka-Gwegweni & Wassenaar, 2014); one was in Kenya (Langat, 2005); one in Egypt (Matar & Silverman, 2013) and one in Malawi (Henderson, Corneli, Mahoney, Nelson & Mwansambo, 2007). None of the studies was done in Uganda (Silaigwana & Wassenaar, 2015). Three of the studies on African RECs, the Kenyan study (Langat, 2005), the South African study conducted by Sathar et al. (2013) and the Egyptian study by Matar and Silverman (2013), were on reviews of protocols involving storage, re-use and transfer of human biological materials (HBMs). The findings form these studies are outlined below:

The Kenyan study involved analysis of research protocols submitted to two different RECS and the finding was that most investigators did not recognise the need for informed consent to storage and reuse of samples. The reason given was that it was because most of them never raised the issue during the informed consent process. The study did not examine all the issues raised during protocol reviews (Langat, 2005).

The Henderson et al. (2007) study explored the views of members of the National REC in Malawi, and targeted reviews of protocols for international collaborative research. They investigated the criteria used during protocol reviews and how members interpreted international guidelines to fit the local context. The study used in-depth interviews with the members of the national REC. Their findings were that most members reported inadequacies in the informed consent process, and suggested improvements that would make the informed consent process by recommending that an appropriate informed consent process is one that contextualises the local community setting and responds to the local community needs (Henderson, et al., 2007). Again, this study did not examine the actual documentation of the review proceedings, to get first-hand information about the issues raised during the review meetings.

A study by Klitzman (2008) involved questionnaire interviews with REC chairs and considered the views of United States and South African REC members regarding the process and content of protocols for HIV Vaccine Trials (HVTs). The findings were that it was common for South African RECs to ask for major revisions of the protocols and that there was general agreement

that there was poor understanding of the consent forms as well as risks and benefits (Klitzman, 2008). He also reported that REC members frequently differed on the minimum standard of care for participants who acquired HIV infection during the trial, with the majority (63%) advocating for the best treatment available worldwide to be the one given to the patients in Africa and a small minority (11%) saying that it should be the best standard of care available nationally that should be given (Klitzman, 2008). Although, the findings could be taken to have important implications for various stakeholders involved in formulating policy for research ethics training, it did not bring out much about the issues raised by RECs, since it was just a questionnaire interview with REC chairs and did not involve analysis of any documentation. Besides, it was concerned only with HVTs, and on the African continent, and covered only South African RECs (Klitzman, 2008).

The Sathar et al. (2013) study was a retrospective cross-sectional audit of approved protocols submitted to one South African REC, to determine whether ethical issues in collaborative research using HBMs were being adequately raised. The finding was that both the REC and researchers gave insufficient consideration to regulations and ethical challenges in research involving HBMs (Sathar, et al., 2013).

The Egyptian study by Matar and Silverman (2013) was a survey carried out on RECs and also used in-depth interviews. It investigated the views and attitudes of the RECs about collection and storage of human biological samples for future use. The researchers found that most RECs did not support the collection and storage of HBMs for future use, and that the main reason cited was the potential for stigmatisation of the Egyptian population and that, for that reason, it was mandatory to require national security clearance before export including prohibition of exportation of HBMs in some situations (Matar & Silverman, 2013).

These studies provided limited data with regard to the functioning of RECs as they were confined to single topic (HBMs) and to single countries and sometimes one REC in the country and they did not target records of proceedings during the review process. However, one important fact that we can note from two of these studies is the way the handling of HBMs differed under different cultures and legal regimes.

By 2014, there were only are two studies which analysed the minutes of RECs – the Cleaton-Jones (2010) study and the Tsoka-Gwegweni and Wassenaar (2014) study. In the Cleaton-Jones (2010) study an analysis of minutes of one REC for 2008 to 2009 was carried out. It showed that the committee frequently identified issues related to informed consent and also that 37% of the protocols received approval at first evaluation, 56% required minor revisions, and 4% were rejected at first consideration. The researchers reported that the problems most frequently encountered were informed consent forms (55%) and missing information (43%), and they suggested that applicants could reduce errors by first showing their draft protocol to a REC member before actual submission for approval (Cleaton-Jones, 2010). Although this was the first African study to consider the minutes of a REC and did not use a particular standardised model, and considered one REC in South Africa, it set a stage for subsequent studies and gave clues about what formed the gist of issues raised in the rest of the RECs in South Africa and the rest of Africa.

The Tsoka-Gwegweni and Wassenaar (2014) study was the first to use the Emanuel et al. (2008) framework to determine the ethical concerns raised by an African REC. It carried out an analysis of systematically sampled REC minutes from 2008 to 2012 and found that informed consent, scientific validity, fair participant selection, and respect for participants were the most frequently raised queries. The majority of ethical issues identified were compatible with the Emanuel et al. (2008) framework, an indication that the framework could be used to carry out a wider study on the African continent (Tsoka-Gwegweni & Wassenaar, 2014). The Tsoka-Gwegweni and Wassenaar (2014) study served as a model for the present study, which is part of a wider African study covering seven countries. It is envisaged that results from these seven countries in different regions of Africa will give a representative picture of the issues raised by RECs in Africa, while at the same time catering for geographical and cultural variation as well as differences in legal frameworks governing research activities in Africa. A critique of the Tsoka-Gwegweni and Wassenaar (2014) study is that it is merely descriptive and does not attempt to explain the pattern of data generated – this is left to future studies. This critique also applies to the present study.

Several other recent studies have also used the Emanuel at al. (2008) framework to analyse minutes of REC review meetings in Ghana (Frimpong, 2016; Selormey, 2015) and South Africa (Bengu, 2018; Silaigwana &Wassenaar, 2019). The study by Selormey covered minutes of 22

protocols that underwent initial review by a selected Ghanaian REC in 2012–2013. Her findings were that issues related to informed consent were the most frequently raised (35.05%) while the other issues followed in descending order: independent review (30.17%), scientific validity (24.57%), fair participant selection and respect for participants (3.88% each), favourable risk-benefit ratio (2.59%), social value (0.86%), with no query being raised about collaborative partnerships (Selormey, 2015). However, the same study found that 20% of the queries raised by the REC meetings could not be catered for by Emanuel et al. framework and the study reported that these were mainly non-ethics related issues which had to do with administration, typographic and grammatical errors, issues related to material transfer agreements other regulatory issues and insurance cover, while some related to responsible conduct of research (Selormey, 2015).

The study by Frimpong (2016) also covered a REC in Ghana. According to the findings of this study, the most commonly raised queries were those related to scientific validity (51.3%) followed by issues related to informed consent (20.6%). These were followed by respect for participants (8.2%); independent review (5.9%), favourable risk benefit ratio (4.4%) collaborative partnerships (4.0%), fair participant selection (2.7%) and finally social value (0.6%) in that order. However, unlike the case with the study by Selormey (2015), this study found that only 2.3% of the queries raised could not be accommodated under the benchmarks of Emanuel et al. (2008).

A study by Bengu (2018) examined minutes of social science REC and found that the ethical concerns raised, in descending order, were: informed consent (31%); scientific validity (21%); respect for participants (14%); fair participant selection (11%); other (10%); social value (7%); favourable risk to benefit ratio (4%); independent ethics review (1%); and collaborative partnerships (1%) (Bengu, 2018). On the other hand, a summary of the integrated results from the Silaigwana and Wassenaar (2019) study, which covered two South African RECs, indicated that the frequency of raising issues during protocol review meetings was in the following descending order: informed consent (26%), respect for participants (19%,), scientific validity (16.7%), administrative issues (11.9%,), collaborative partnership (6.5%), editorial errors (5.5%), favourable risk/benefit ratio (5%), fair participant selection (4.3%), independent ethics review (3.5%), and social value (1.2%) (Silaigwana & Wassenaar, 2019).

Another study which reviewed minutes of REC in South Africa was by Briers and Dempers (2017). However, this specifically targeted an REC that was responsible for reviewing protocols that involved use of human remains, both fresh and preserved, covering six years ranging from 2009 to 2014. The study also assessed the REC on the criteria of review time period, acceptance rate and revisions, although the ethical issues and other queries and issues raised were classified in terms of fair participant selection, risk-benefit ratio, consent, funding, confidentiality, authorship, reimbursement of participants/patients and whether or not they were subjected to independent review. The study also had additional criteria for science-related queries which included issues broadly related to validity, methodology and statistics but which were broken down into issues related to selection criteria and title changes as part of methodology related issues; referencing and writing styles under editorial issues. Compliance-related issues were included under the legal category while lack of documentation or incompleteness of documentation were placed under administrative issues (Briers & Dempers, 2017). Although this study differed in design from those carried out by Tsoka-Gwegweni and Wassenaar (2014), Selormey (2015) and Frimpong (2016), Bengu (2018) and Silaigwana and Wassenaar (2019), the Briers and Dempers (2017) study also reviewed REC minutes and some of the criteria used were derived from the Emanuel et al. (2008) framework although the coding system was largely different from that used by the studies that were based on Emanuel al. framework. From their results, it was found that issues related to science were the most commonly raised (22.2%) followed by administrative issues (18.9%), compliance issues (10.2 %), ethical issues (7.5%) and finally, editorial issues (5.1%). Among ethical issues were informed consent (14.2%), confidentiality (6.3%), risk-benefit ratio (5.5%), validity and viability (0.8%). It was further found that methodology issues were the most commonly raised (44.1%) followed by statistics (29.9%), permissions (29.9%), interpretation of regulations (15.0%), title changes (14.2%), documentation (7.9%), writing style (6.3%), compliance with legislation (5.5%), funding (budget, resources) (3.9%), and references (3.9), while the rest scored below 10% (Briers & Dempers, 2017).

2.4 Research related to REC functioning in Uganda

The history of bioethics and RECs in Uganda has origins in the 1990s when HIV/AIDS in Uganda made headlines (Loue, Okello & Kawuma, 1996). With the alarming prevalence and

incidence rates of HIV infections and internationally acclaimed strategies to control the threat of HIV/AIDS (Kuhanen, 2009), substantial funding was made available for Uganda to engage in HIV related research and also to build capacity for research administration and management (Puderbaugh, Potash & Zeitvogel, 2016). This included building the capacity to conduct independent scientific and ethical reviews of protocols, and the first national guidelines, though not well formulated and not backed by national legislation, were published in 1997 (Loue & Okello, 2000; National Consensus Conference on Bioethics and Health Research in Uganda, 1997). Over the last several decades, several foreign funded projects have carried out capacity building training and other activities, in a bid to enhance local capacity to conduct scientific and ethical reviews of research protocols for both locally funded and international collaborative research, which has resulted in the formation and accreditation of 24 RECs (National guidelines for the conduct of research involving humans as participants (UNCST), 2007; UNCST, 2014; UNCST, 2014; UNCST, 2018; http:www.uncst.go.ug).

Locally, the relevant legal structures for overseeing research activities have been put in place and they have developed programs and the necessary guidelines for researchers and RECs to use in their activities and for conducting training (UNCST, UNHRO Act, 2009). It is envisaged that before a REC is accredited it has to have fulfilled the requirements for accreditation according to the Uganda National Council for Science and Technology (UNCST) guidelines which include: (1) being properly constituted; (2) members having acquired the appropriate training; (3) written standard operating procedures (SOPs) that are used in day-to-day proceedings; (4) properly formulated protocol and consent form templates; (5) a review fee policy and structure in place; (6) reviewer checklists; (7) schedules for meetings and reporting on protocol reviews; and (8) systems for monitoring approved studies. Each REC is also required to have a properly constituted and accredited scientific committee to handle the science in the studies (UNCST Guidelines, 2014). However, having these requirements in place is one thing and being able to do the work effectively and efficiently is another.

There have not been many studies directly targeting the operations of RECs in Uganda apart from a retrospective study by Ochieng, Ecuru, Nakwagala and Kutyabami (2013). This study was aimed at demonstrating the capacity of RECs to monitor compliance and to evaluate the effectiveness of the available monitoring tool in the setting (Ochieng et al., 2013). The study

reviewed research site-monitoring reports covering a period of four years. The framework employed during the monitoring included reviewing the regulatory documents, informed consent process, study related documentation, participants' welfare, serious adverse event management and reporting, and study-related training and working practices at the sites. The documents reviewed included approved study protocols, REC and UNCST/National Drug Authority (NDA) approvals and their validity, signed informed consent forms, case report forms, data collection forms, valid practicing licences for clinicians, study-related trainings, Good Clinical Practices (GCP)/Good Laboratory Practice (GLP), and other research ethics trainings. They also reviewed study-related training and working practices that included minutes of meetings, communication memos, communication with collaborators, availability of standard operating procedures (SOPs), material transfer agreements, delegation logs, informed consent process and documentation, protocol deviation and protocol violation reports, and any other study documents. The adequacy of study site facilities, participant welfare, serious adverse events (SAEs) management and reporting, were also assessed (Ochieng et al., 2013). Although this review gives a comprehensive picture of the activities of RECs in Uganda, including examination of meeting minutes and SOPs of RECs, their concerns were on the frequency of meetings, what was discussed in the meetings, duration of meetings and procedure explanations (Ochieng et al., 2013). The findings of this review were that there were violations of regulatory requirements for ethics approval in 25%, informed consent violation in 36%, research participant rights/welfare violations in 28% of the site monitoring reports and that 38% of the monitoring reports did not report serious adverse events to regulatory authorities. However, they did not conduct a systematic review of REC minutes to ascertain the typical issues raised by the REC members during review meetings. The model used in their assessment was different. As such, their study did not describe the ethical issues that were raised during review meetings. Therefore, undertaking a study that considers the issues raised by REC members during the REC meeting may serve to help to supplement the limited information obtained from site monitoring reports by Ochieng et al. (2013).

CHAPTER THREE

3.0 METHODOLOGY

3.1 Introduction

This study is based on the fact that Emanuel et al. (2008) framework has increasingly become acceptable to many institutions as an important working document for application during the ethics review process. Apart from the Tsoka-Gwegweni and Wassenaar (2014) pilot study in South Africa, there was paucity of data with regard to applicability of the Emanuel et al. (2008) framework to various settings and cultures in Africa. Therefore, this study was aimed at identifying the main ethical issues raised during ethics review of research proposals by RECs and assess their relative weight using the principles of ethical review of clinical research recommended by the Emanuel et al. (2008) framework.

Specifically, the study was designed to: (1) study the minutes of a selected Ugandan RECs' review meetings to identify and describe the pattern of ethical concerns and issues raised in their reviews of research proposals over the period 2012 to 2013; and (2) analyse the ethical issues and concerns using the Emanuel et al. (2008) framework, ranking them and identifying how they do or do not fit the framework. These objectives were to be achieved by providing answers to the following questions: (1) What ethical concerns does the selected REC in Uganda raise when reviewing protocols? (2) Is there a systematic prioritisation of some ethical issues over others? (3) Is there an observable pattern to the ethical concerns raised by committee members? If so, what is the pattern? (4) Are the concerns raised consistent with the framework developed by Emanuel et al. (2008)? (5) Does any feature of the Emanuel et al. (2008) framework dominate the concerns? If so, which one? (6) Are there other concerns raised by the Ugandan REC which are not compatible with the Emanuel et al. (2008) framework?

3.2 Location of the study

Data were collected during March 2018 from REC minutes of meetings from an REC selected from Uganda as one site of a joint project by the 2013 and 2015 South African Research Ethics Initiative (SARETI) Masters' students from the University of KwaZulu-Natal, South Africa. The countries and partners included: Ghana (Frimpong, Selormey), Malawi (Chilungo, Tiwonge),

Nigeria (Alimasunya) and Zimbabwe (Madanhire), Uganda (Kirimuhuzya), Cameroon (Muh Abinyui) and South Africa (Magolela, Bengu).

3.3 Data collection procedure and tool

Data for the broader study were collected from selected RECs in the partnering countries after which the results will be pooled together to investigate possible differences in review outcomes of a sample of African RECs. The present study was based on a content analysis of archived written documents, the minutes for a period of two years (2012–2013) of the meetings of one REC that was selected from the 24 RECs in Uganda. However, for this study to be able to contribute to the international group project, a standard methodology and analytic framework used by Tsoka-Gwegweni and Wassenaar (2014) was adopted across all countries. Minutes from all participating countries should ideally cover the same period. Therefore, the selected REC had to have been in existence during the time covered by the study period and to fulfil the criteria of an accredited REC. The selected REC was one that reviews biomedical science research, especially from graduate students and is based at a medical school.

For the present study site in Uganda, all the records of minutes of the review meetings carried out by the selected Ugandan REC for the years 2012 and 2013 were considered and assessed. With the REC expected to meet at least once a month, it was estimated that there would be about 24 sets of minutes to consider although a total of 28 sets were actually analysed. Considering that this was not too big a sample to handle, all the sets of the minutes were analysed in this study. However, only the minutes of full committee meetings were considered. Again, only initial reviews were considered with expedited and continuing reviews being excluded to ensure comparability with Tsoka-Gwegweni and Wassenaar (2014).

Data collection was done using a predetermined data collection sheet that was designed based on the eight principles in Emanuel et al. (2008) framework although modifications were made to accommodate some issues that could not be accommodated by the framework. From the minutes for initial reviews of protocols, for the two years, summaries of the review comments were extracted, assigned various themes and coded and ranked according to the predetermined criteria based on the principles of Emanuel et al. framework, as well as into the categories that were not falling into those based on the principles of Emanuel et al. framework. As a quality control

measure, two independent coders were involved in the coding process. There was 93.2 agreement, with the 7.8 percent disagreement being mainly on the issues that needed to be included under scientific validity or under the extra category that could not be covered by Emanuel et al. (2008) framework.

The data collected covered year and month of review as well as number of protocols per meeting, type of research participants, area of research, study design and the category of issues raised during the review meeting basing on the Emanuel et al. framework. Only the issues raised by reviewers to be responded to by the researchers were considered and any repetitions were counted once.

Non-ethical issues which could not be accommodated under the eight principles were coded as "administrative issues". These included queries on referencing styles, queries about abiding with the institutional protocol format, issues to do with grammatical and typographic errors, issues related to writing styles (page numbering styles, and paraphrasing styles), and absence or presence of supervisors' appropriately written names and titles.

3.4 Data analysis

The numerical data were captured using Microsoft Excel and simple descriptive analysis was used to determine emerging patterns and trends in terms of frequency tables and histograms, coding having been done using the eight principles of the Emanuel et al. framework and one other category included to cater for issues that did not fall under the principles included in the framework.

Since this part of a wider continental study, it is expected that data from Uganda will be pooled together the data sets from other countries (see section 2.3 above) and aggregated to generate continental trends and regional variations, if any.

3.5 Validity, reliability and rigour

According to Hammersley (1990, p. 57), validity in research is defined as "…truth: interpreted as the extent to which an account accurately represents the social phenomena to which it refers". Cook and Campbell (1979) developed a taxonomy of threats to research validity, namely: statistical conclusion validity; construct validity; external validity and internal validity. Internal

validity refers to whether the inferences made from the collected data are accurate (i.e. valid) and external validity to the ability to generalise from the results of the study to other environments and populations.

For both practical and logistical reasons, it was not possible for the researcher to incorporate all of the above strategies into this study; however, the strategies of peer review of methods (with fellow researchers doing the same topic), as well as clarifying researcher bias was taken care of in the design and conduct of this study from the outset. Furthermore, the researcher identified the specific problem of 'anecdotalism' or the inclination of some researchers to convince both themselves and their readers that the findings of their study are genuine results, based on a critical unbiased analysis of the data collected and not based on a few 'well-chosen examples' – as a potential threat to the overall validity of the study (Silverman, 2006).

Other threats to both the internal and external validity of the present study have were identified by the researcher during the design process. The researcher acknowledges Cook and Campbell's (1979) taxonomy of threats to validity and recognises that: (a) because the research was a review, carried out on specific documents kept for specific purposes with a specific group of people working in a specific environment, it is possible that the study might not return results that are high in external validity (i.e. that it might not be possible to generalise the results to other populations and/or to other environments); and (b), because the REC studied was not randomly selected, the element of randomness is not present. This may, therefore, impact upon the internal validity of the study's results. However, the fact that similar field work was used as was used by Tsoka-Gwegweni and Wassenaar (2014) and Silaigwana and Wassenaar (2019), this could be regarded as a replication of the same study in a different setting and this improves on its validity.

This is one part of an international collaborative study which was among the first attempts to describe the most frequent ethical issues raised by several African RECs and may contribute to better understanding of the ethical concerns raised by African RECs in the course of their work.

3.6 Ethical considerations

This was a retrospective chart review with no human contact but involving confidential documents, which were archived minutes of the REC that was selected in Uganda. The only ethical issues involved in this study were about confidentiality. The documents that were

accessed were highly confidential. A breach of confidentiality might damage the reputation of the REC in question and even attract some legal action if sensitive information is put into the public domain. To counter this, all identifiable information made available to the researcher for the purposes of this collaborative study, on the ethical issues raised by selected African Research Ethics Committees, including all research proposals reviewed by the said RECs as a whole or communicated to him/her or otherwise in connection with the research work, were treated with utmost confidentiality. And to make it legally binding, the researcher, together with the supervisor, signed a confidentiality agreements with the host REC under which they undertook not to disclose any identifiable information to any person, legal entity, or to the media, and also not use such information other than for the purposes of the study, as stipulated in the protocol. To strengthen the confidentiality all data collected were analysed and reported in anonymised aggregated form with no identifiers in form of name of any researchers, protocols, studies, sponsors/funders or participants and the identity of the host institution and the collaborating REC were concealed. The results of the study are to be made available to the host institution and its REC by the researcher using the methods suggested by the host REC itself. Prior to its commencement, ethics approval for the study was obtained from the University of KwaZulu-Natal Biomedical Research Ethics Committee (BREC) with approval Number BCA 342/16. In-country approval was also obtained from a REC in Uganda (approval number withheld to preserve confidentiality; available for audit purposes) as well as site permission from the selected REC.

3.7 Problems encountered

The biggest problem encountered was scepticism from the RECs towards accessing their minutes, which are confidential documents, for research purposes. The first REC that was approached actually dismissed the proposal as being “too risky” regardless of the fact that there were guarantees of confidentiality and privacy including signing of a confidentiality agreement. The one REC which accepted to provide the minutes also insisted on review of the protocol by a local REC, before the site permission could be granted and this this caused serious delay although this was eventually overcome and the study conducted, the results of which are presented in the next chapter.

CHAPTER FOUR

4.0 DATA PRESENTATION AND INTERPRETATION

4.1 Outcome of the analysis of the minutes of the selected Ugandan REC's review meetings

A total of 28 meetings took place in the two years covered by the study during which initial ethics review of 110 research protocols was done. This yielded an average number of protocols reviewed per meeting of 110/28 = 3.93, giving approximately four protocols per meeting. In 2012, there were 47 protocols considered for initial review in 17 meetings at an average of 47/17 = 2.8 giving approximately 3 protocols per meeting while the 11 meetings in 2013 carried out initial review of 63 protocols giving an average of 63/11 = 5.7 indicating an approximate average of 6 protocols per meeting, which shows an increase from the year 2012. Also, the committee was meeting at least once a month unless they had a heavy load of protocols to warrant an extra meeting in the month, which occurred in 2012, where there were 17 meetings although this was not reflected in the number of protocols reviewed. When it came to the nature of protocols reviewed, these showed wide diversity, as reflected in Table 1 but which were dominated by research on HIV followed by tuberculosis and other infectious diseases with non-communicable diseases not featuring as much (Table 1).

With regard to the type of participants, about 85 percent were adults with children taking 12 percent, pregnant women taking about 1 percent and about three percent involving animal models of disease, as depicted in Table 2. Of these, 41% were cross-sectional studies, with the same percentage using experimental or quasi-experimental study designs. Ten percent were descriptive, 7 % were on medical device development while only 4 % were clinical trials (Table 3).

Table 1: Types of research covered by the protocols (Ranked in descending frequency)

Type	Frequency	Percentage
HIV	17	15.45
Tuberculosis	15	13.63
Others	7	6.36

General Bacterial infections and antibiotic resistance	5	4.55
Nutrition/Malnutrition	4	4.55
Reproductive health	4	4.55
Cardiovascular disorders	4	4.55
Malaria	4	4.55
Diarrhoea	4	3.64
Education system evaluation and childhood learning	3	2.73
Brucellosis	3	2.73
Research ethics research (Informed consent process etc.)	3	2.73
Meningitis	3	2.73
Diabetes	3	2.73
Urinary tract infections	2	1.82
Febrile illness in children	2	1.82
General fungal infections	2	1.82
Schistosomiasis	2	1.82
Typhoid	2	1.82
Self-medication	2	1.82
Herbal medicine toxicity evaluation	1	0.91
Charcoal stove technology	1	0.91
Musculoskeletal disorders	1	0.91
Conduct of health care workers	1	0.91
HIV and Tuberculosis	1	0.91
Hernia	1	0.91
Statistical knowledge of medical students	1	0.91
Medical students' career choices	1	0.91
Alcoholism and other drug use problems	1	0.91
Pneumonia	1	0.91
Helminths	1	0.91
Erectile dysfunction	1	0.91
Ethnic genomes	1	0.91

Haemorrhagic fevers	1	0.91
Sickle-cell anaemia	1	0.91
Grant project evaluation	1	0.91
Post-traumatic stress disorder	1	0.91
Total	**110**	**100.00**

Table 2: Nature of research participants/subjects involved

Type of participants	**Frequency**	**Percentage**
Adults (male and female)	94	85.45
Children	12	10.90
Animal models	3	2.73
Pregnant mothers	1	0.91
Total	**110**	**100.00**

Table 3: Types of study designs involved

Design	**Frequency**	**Percentage**
Cross-sectional	41	32.27
Quasi experimental/experimental	41	32.27
Descriptive	10	9.09
Cohort	07	6.63
Medical device development	07	6.36
Clinical trials	04	3.63
Total	**110**	**100.00**

4.2 Results from the analysis of the ethical issues and concerns raised during the review meetings using Emanuel et al. (2008) framework

The findings from the analysis of the issues raised during the review meetings are presented in the tables and figures below. When the issues raised were analysed using the 8 principles contained in the Emanuel et al. (2008) framework, it was found that, generally, most issues could be accommodated by the Emanuel al. (2008) framework. The issues that could not fit exactly in the Emanuel et al. (2008) framework were coded as "administrative" issues.

After coding and counting of the issues raised by the REC members, it was found that a total of 2008 issues were raised in the 28 meetings that reviewed the 110 research protocols. Of these, it was found that 90.5% could be accommodated under the eight principles in Emanuel et al. (2008) framework. The most commonly raised issues were those that fell under scientific validity (60.2%); informed consent came in as second at 11.4% but interestingly, what came third were administrative issues (which are not part of the framework) 9.5%, followed by collaborative partnerships in fourth position at 5.9%; with fair participant selection coming fifth at 4.3% followed by independent review in sixth position at 4.1%; ongoing respect for participants and risk to benefit ratio came in at 7th and 8th at 2.5% and 1.2 %, respectively; and surprisingly the principle of social value came last with a 0.9% showing (Table 4). Excluding the issues that fell under 'administrative' as defined for this study, the frequency of issues followed the order of scientific validity, informed consent, collaborative partnerships, fair selection of participants, independent review, ongoing respect for participants, risk/benefit ratio and, finally, social value (Table 4 and Figure 1).

The most frequent issues that emerged under scientific validity were under appropriateness of design and methods at 45.57% of the total of all issues raised giving 75.7% of the 1208 issues raised under scientific validity. This was followed by study design feasibility at 7.92% overall (and 13.2% of the issues under scientific validity); availability of the required expertise came third at 2.24 % overall (and 3.7 % of issues raised under scientific validity); adequacy of the financial resources (budget issues) came fourth at 1.15% overall (1.9 % of issues under scientific validity); availability of a willing study population coming fifth at 1.05% overall (1.74% of scientific validity issues); availability of the required facilities was sixth at 0.85% overall (1.41% of scientific validity issues); adequacy of the time resource (appropriateness of time frame) came

seventh at 0.75% (1.24% of scientific validity issues); applicability of results was eighth at 0.60% (1.0% of scientific validity issue); with impact on provision of health care services coming last at 0.05% overall (and 0.8% of all the issues raised issues raised under scientific validity) (Table 5).

When it came to informed consent, the most frequently raised issues out of the 228 raised under informed consent, were on the context of the consent process (26.32%), followed by presentation and accuracy of information (22.37%); appropriate disclosure documents and process (18.86%); recruitment and incentives applicability to local context (15.35%); respect for autonomy (7.89%); legally authorised representatives and issues of assent (5.7); and lastly, gate-keepers' permission (1.75%) (Table 5).

Of the 118 queries under collaborative partnerships, issues to do with responsibility sharing (collaboration) was the most frequently mentioned (77.97%); respect for local context/environment (15.25%); community representatives (4.24%); while fair research benefits for community and sharing research products had the least consideration (1.69%) (Table 5).

Under the principle of fair participant selection, issues about suitable study population were the most frequently raised (86.21%); risk minimisation and vulnerability issues covered 5.75% each, with benefits to participants being considered the least at 2.30% (Table 5).

In the case of the principle of independent review, the most frequently raised issues fell under regulatory compliance (81.13%) followed by minimisation and reconciliation of multiple reviews (10.84%); and REC members' conflict of interest at 4.82%, and transparent review at 1.20% (Table 5). Issues to do with material transfer agreements (MTAs) were included under regulatory compliance since this is emphasised in the Uganda National Council for Science and Technology Guidelines for the Protection of human research participants (UNCST, 2014) (Figures 2 & 3 and Table 5). Although the issues of material transfer agreements (MTAs) were included under regulatory compliance, they could as well have fitted under fair research benefits for the community or sharing of products and under collaborative partnerships. However, the complexity surrounding MTAs placed them in overlapping codes and the compromise was to include them under one of the items that fell under independent review.

With regard to the principle of ongoing respect for participants, issues to do with monitoring health and well-being, were the most frequently raised (42.00%), followed by confidentiality and privacy (21.00%); post-research obligations (18.00%) and voluntariness (14.00%) while there was no issue raised about research results dissemination.

In the case of favourable risk-benefit ratio, the most frequently raised issues were about risk identification and minimisation (72.00%); type, probability and magnitude of benefits came second (24.00%), while the least considered were issues about comparison of benefits and risks (4.00%) (Table 5).

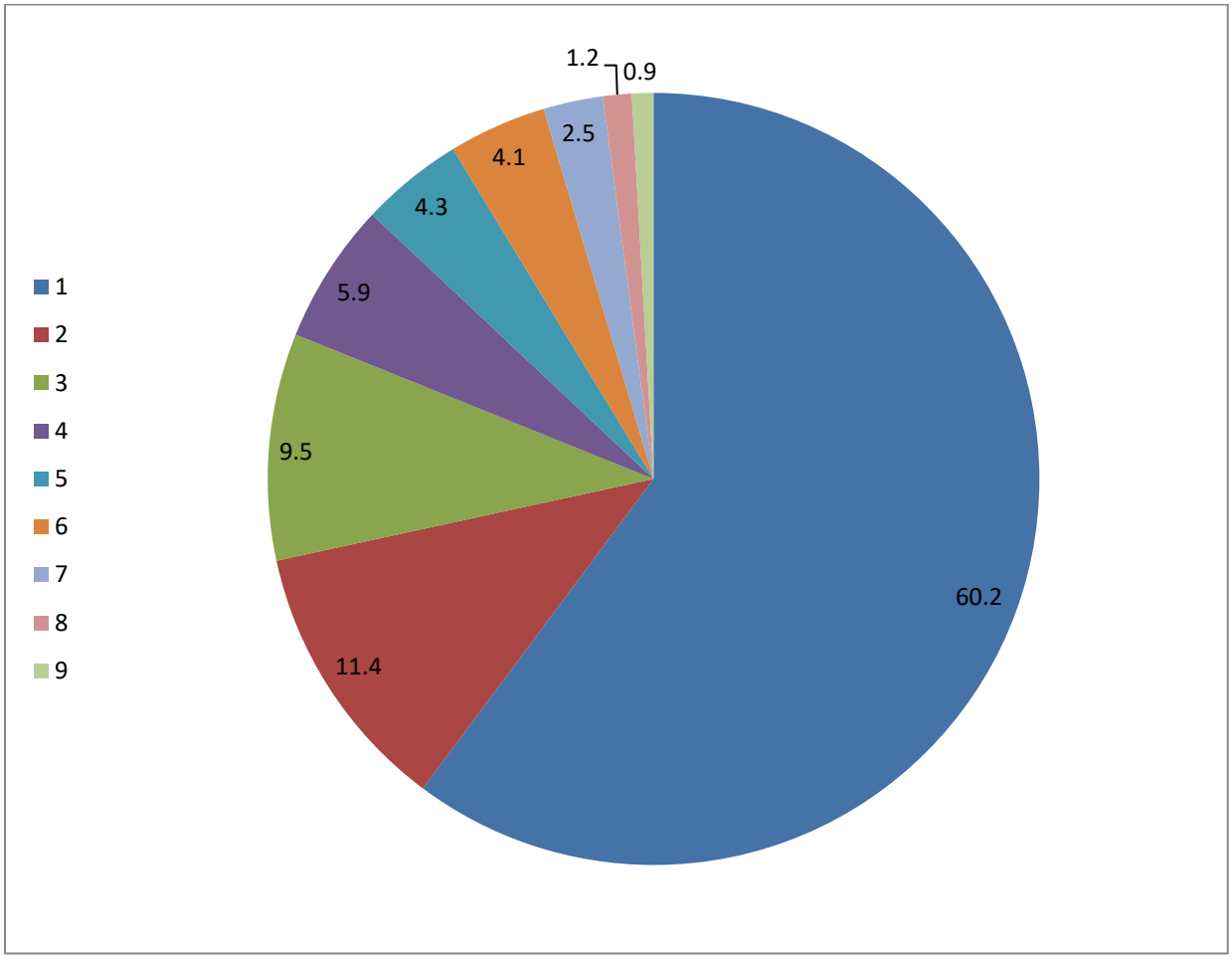
When it came to the 19 issues raised under social value, the most frequently considered were those related to research benefits (68.2%). Impact on health systems came second (31.58%), while issues to do with research beneficiaries and benefit enhancement were not raised at all (Table 5).

Of the issues that could not be coded with the Emanuel et al. (2008) framework principles, the most frequently raised issues were queries about abiding with the institutional protocol format and with grammar and typographic errors, each of which covered 32.11%. Issues related to writing styles such as page numbering styles and paraphrasing styles, among other issues (26.32%), queries on referencing styles (21.05%), with issues to do with absence or presence of supervisors or supervisors' appropriately written names and titles coming last (9.47%) (Table 5).

Table 4: Results of analysis of issues raised during review meetings against the 8 principles of Emanuel, Wendler and Grady's (2008) framework

Principle	Frequency of mention	Percentage (%)
Scientific validity	1208	60.2
Informed consent	228	11.4
Administrative issues	190	9.5
Collaborative partnerships	118	5.9
Fair participant selection	87	4.3
Independent review	83	4.1
Respect for participants	50	2.5

Risk to benefit ratio	25	1.2
Social value	19	0.9
Total	**2008**	**100**



KEY: 1. Scientific validity **2.** Informed consent **3.** Administrative issues **4.** Collaborative partnerships **5.** Fair participant selection **6.** Independent review **7.** Respect for participants **8.** Risk to benefit ratio **9.** Social value

Figure 1: Results of Analysis of issues raised during review meetings against the 8 principles of Emanuel, Wendler, and Grady's (2008) framework presented in percentages

Table 5: Coding of issues raised during review meeting under the 8 principles and benchmarks of Emanuel et al. (2008)

Benchmark (Principle)	# issues raised	% under each
1: Scientific validity	**1208**	**60.16**
Appropriate design and methods	915	75.7
Study design feasibility	159	13.2
Availability of the required expertise	45	3.7
Adequacy of the financial resources (Budget issues)	23	1.90
Availability of a willing study population	21	1.74
Availability of the required facilities	17	1.41
Adequacy of the time resource	15	1.24
Applicability of results	12	1.0
Impact on provision of health care services	01	0.8
2: Informed consent	**228**	**11.35**
Context of consent process	60	26.32
Presentation and accuracy of information	51	22.37
Appropriate disclosure documents and process	43	18.86
Recruitment and incentives applicability to local context	35	15.35
Respect for autonomy	18	7.89
Legally authorised representatives and issues of assent	13	5.70
Gate-keepers' permission	04	1.75
3: Collaborative partnerships	**118**	**5.88**
Responsibility sharing (collaboration)	92	77.97
Respect for local context/environment	18	15.25
Community Representatives	05	4.24
Fair research benefits for community	02	1.69
Sharing research products	02	1.69
4: Fair participant selection	**87**	**4.33**
Suitable study population	75	86.21
Risk minimisation	05	5.75

Vulnerability	05	5.75
Benefits to participants	02	2.30
5: Independent review	**83**	**4.13**
Regulatory compliance	69	83.13
Minimisation and reconciliation of multiple reviews	09	10.84
REC members conflict of interest	04	4.82
Transparent review	01	1.20
6: Respect for participants	**50**	**2.49**
Monitoring health and well being	21	42.00
Confidentiality and privacy	13	26.00
Post-research obligations	09	18.00
Voluntariness	07	14.00
Research results dissemination	00	0.00
7: Favourable risk to benefit ratio	**25**	**1.25**
Risk identification and minimisation	18	72.00
Type, probability and magnitude of benefits	06	24.00
Comparison of benefits and risks	01	4.00
8: Social value	**19**	**0.95**
Research benefits	13	68.42
Impact on health systems	06	31.58
Enhancing benefits	00	0.00
Research Beneficiaries	00	0.00
Issues not covered by Emanuel at al.'s (2008) framework		
1. Administrative issues	**190**	**9.46**
Queries about abiding with the institutional protocol format	61	32.11
Issues with grammar and typographic errors	61	32.11
Issues related to writing styles	50	26.32
Queries on referencing styles	40	21.05
Supervisors' appropriately written names and titles	18	9.47
Total	**2008**	**100.00**

4.3 Summary of the main findings

Over 90% of queries raised during the review meetings could be accommodated into the eight principles and benchmarks in the Emanuel et al. (2008) framework with a few, mainly administrative issues being raised that fell out of the benchmarks. Findings, in descending order, were as follows:

1. Scientific validity (60.2%)
2. Informed consent (11.4%)
3. Administrative issues (which are not part of the framework) (9.5%)
4. Collaborative partnerships (5.9%)
5. Fair participant selection (4.3%)
6. Independent review (4.1%)
7. Ongoing respect for participants (2.5%)
8. Risk to benefit ratio (1.2%)
9. Social value (0.9%)

CHAPTER FIVE

5.0 DISCUSSION, CONCLUSIONS, STUDY LIMITATIONS AND RECOMMENDATIONS

5.1 Discussion

5.1.1 Pattern of ethical concerns and issues raised in the reviews of research proposals

Issues of scientific validity were the most frequently mentioned followed by informed consent, and administrative (non-ethical) issues (which also covered mentoring issues and supervision of academic research protocols), fair participant selection, independent review, respect for participants, risk/benefit ratio considerations and finally issues related to social value (Table 4 and Figure 1). Although over 90% of the issues raised could be accommodated into the eight principles and benchmarks in the Emanuel et al. framework a deeper consideration of the issues indicates that administrative issues, which may be regarded as non-ethical issues took substantial amount of discussion time during research protocol review meetings.

5.1.2 Analysis of the concerns raised by the selected using Emanuel et al. (2008) framework

Emanuel et al. (2008) propose that the 8 principles of collaborative partnership, social/clinical value, scientific validity, fair selection of participants, favourable risk/benefit ratio, informed consent, independent review, and on-going respect for participants and study communities, should be used together and in no particular order. However, analysis of the results from the study indicates that the issues raised followed a descending order of: scientific validity, informed consent, collaborative partnerships, independent review, fair participant selection, on-going respect for participants and communities, risk/benefit ratio and the least mentioned being the social value (Figure 1). The interesting thing is that some issues, which for the purpose of this study, have been coded under “administrative issues”, which do not feature under Emanuel et al. (2008) framework, featured more prominently coming after scientific validity and informed consent.

5.1.3 Implications and reasons for the observed trends

The issue which came out strongly, was the fact that review largely concentrated on scientific validity, possibly at the expense of other ethical issues. The combined consideration of science-related issues contributed more than half of the total queries (60.16 %), with informed consent coming a distant second, contributing only 11.35%. This in disagreement with the studies by Cleaton-Jones (2010) in South Africa, Tsoka-Gwegweni and Wassenaar (2014) in South Africa, and Selormey (2015) in Ghana, which found that informed consent issues were the most frequently mentioned, but with varying percentages. However the results of the present study are in strong agreement with the study carried out by Frimpong (2016) on the REC in Ghana, which found that the most commonly raised queries were those related to scientific validity (51.3%) followed by issues related to informed consent (20.6%). This study is also partly in agreement with the Briers and Dempers (2017) study in South Africa, which also indicated a strong showing of issues related to science and scientific validity, although the study had a different methodology and design. Also, and unlike the findings by Tsoka-Gwegweni and Wassenaar (2014), and other related studies mentioned above, feasibility issues in terms of availability of willing population, availability of sufficient intellectual capacity to conduct the study, adequacy of funding and time resources (budget issues), availability of laboratory and other facilities as well as equipment, showed strongly under scientific validity. Budget issues and queries about sources of funding and guaranteeing source of funding, and appropriateness of time-frame were raised frequently. This went to the extent of recommending specific co-investigators to ensure collective qualification of research teams as well as demanding that principal investigators (PIs) seek assistance from people with the necessary expertise such as statisticians, microbiologists and radiologists, in addition to insisting on the Curriculum Vitae of supervisors and those of PIs, where academic research was involved. This trend can be taken as a strength in that these factors contribute strongly to ensuring scientific validity of a study although they do not normally feature as part of the body of the research protocols.

Although the present study had informed consent coming at relatively low percentage (11.4%, ranked second), it does not give a clear indication that the weight the RECs in South Africa or Ghana give to informed consent contrasted sharply with the practice in Uganda. Where informed consent was given priority, scientific validity was given almost the same weight as informed

consent. For example, the study on a South African social science REC by Bengu (2018) had informed consent at 31% and scientific validity at 21% while the Silaigwana and Wassenaar (2019) study, had informed consent at 26% and scientific validity at 16.7%, whereas the number of queries concerning scientific validity and informed consent in the Ugandan REC varied widely. Since the research protocols reviewed by the Ugandan REC were only health related but with very few clinical trials involved, a different picture might be got if a REC in a different setting is considered. However, the study by Bengu (2018) which was on a social science REC, tends to indicate that the issues raised during ethics review of social science research protocols might not be entirely different.

Furthermore, the strong showing of science related issues in the Ugandan REC, may be partly explained by the fact that the REC was doubling as a higher degrees committee, where scientific rigour is highly emphasised, almost overriding the other ethical issues. It was not clear, from the review minutes analysed, whether there was a scientific committee that vetted the protocols before they were submitted to the REC for ethics review. However, this trend also tends to emphasise the fact that if the research has no scientific validity it cannot be ethical.

In agreement with the Tsoka-Gwegweni and Wassenaar (2014) study findings, there was prominent featuring of issues about Material Transfer Agreements (MTAs) especially in collaborative research. This could be partly attributed to the fact that there is strong emphasis on MTAs and elaborate description in Uganda's Guidelines for Protection of Humans as Research Participants (UNCST, 2014). However, this could also be partly due to the fact that the bulk of health research in Uganda is foreign-funded and frequently involves transfer of samples to collaborating countries because of limited local capacity.

The fact that issues related to social value did not feature strongly, tends to agree with the findings of Tsoka-Gwegweni and Wassenaar (2014) and the Selormey (2015) and Frimpong (2016) studies although this should be a cause of concern. Research that is geared towards improving the welfare of the communities from which the participants are drawn, should take precedence. This can be promoted if the emphasis is put on research that is relevant to the needs and aspirations of the communities. However, this principle is undermined by the fact that some countries do not have research agendas (Uganda inclusive) which should be driving the research enterprise. A country like, Uganda, where there is no harmonised research agenda and where

research funding from the national budget has not yet reached a priority stage, might not be able to enforce a drive towards research that is tailored towards its societal needs. However, this may not be entirely true since the four studies in consideration covered Uganda, South Africa and Ghana, which are different levels of development and which may be contributing to research differently. There is, therefore need to interrogate this issue further to find the real factors that could be contributing to this. It is also possible that during the training of members of RECs the principle of social/clinical/scientific value is not emphasised, hence the dismal showing among the queries raised during ethical reviews of research protocols.

The next consideration is about what the present study coded as "administrative issues". These took the form of queries regarding, e.g., the size of protocol in terms of page numbering, paraphrasing styles, typographical and grammatical errors such as issues of abbreviations, referencing styles, among others. They also included RECs suggesting supervisors, or proposing removal of supervisors or insisting on addresses and affiliations of supervisors and PIs to be included on the protocol, and demanding that presentations be made in the presence of supervisors (postponing review due to absence of supervisors of students). This can be construed as an indication of merger of ethical review and scientific and academic reviews. Mentoring issues and queries about whether the research was for academic qualification or not also featured frequently. There were also queries related to journals where the researcher was to publish the findings. This could be partly explained by the fact that this REC also functioned as a higher degrees research and research ethics committee. Declaring the affiliations of PIs and supervisors may have ethical connotations since they may help in identifying situations with potential conflict of interest or interest of commitment, which are major factors under ensuring objective review by REC members. However, this has some degree of agreement with some of the above studies, considering the fact that 20% of the queries raised by the REC studied by Selormey, (2015) could not be catered for using the Emanuel et al. framework while Frimpong (2016) found that 2.3% of the queries raised could not be accommodated under the Emanuel et al. (2008) benchmarks. A summary of the integrated results from the Silaigwana and Wassenaar (2019) study found that administrative issues accounted for 11.9% of queries. Furthermore, there was repeated insistence on the name of the REC being mentioned in the proposal as well as the REC contacts and the name of REC chairperson appearing on the protocol and informed consent form for contact purposes by participants.

These may be looked at as not being part of what would require serious attention during protocol review, which is expected to determine the scientific validity and ethical correctness of the proposal. The study by Selormey (2015) also reported that there were many issues raised during the review meetings that had to do with administration, typographic and grammatical errors (Selormey, 2015). The Briers and Dempers (2017) study also found that administrative issues were the most commonly raised, after the science-related issues and they also mention a relatively strong showing of editorial and documentation issues, which also tends to agree with findings of Cleaton-Jones (2010), who also reported queries about typing errors and incompleteness of application forms contributing largely among the issues raised.

Nevertheless, the findings of the present study showed strong compatibility with the benchmarks of the Emanuel et al. (2008) framework considering that over 90% of the queries raised were accommodated under the framework in spite of the fact that the national guidelines and other international documents on which ethical reviews are based are not necessarily tailored for conformity with the Emanuel et al. (2008) framework.

5.1.4 Strengths and weaknesses of the Emanuel et al. (2008) framework

Despite some of the minor inconsistencies cited in the discussion above, this study has further revealed that the Emanuel et al. (2008) ethics benchmarks are largely useful in evaluating the research protocol review process. The level of agreement between the framework and the findings of this study and other studies already undertaken, tends to support the assertion that the framework is comprehensive enough to serve as a tool for application in variable settings and contexts (Bengu, 2018; Frimpong, 2016; Selormey, 2015; Silaigwana & Wassenaar, 2019; Tsoka-Gwegweni & Wassenaar, 2014). It could be argued that the framework has been demonstrated to be suitable for both scientific and ethical review of protocols, which is in line with the two cardinal principles of review, namely ‘scientific validity’ and ‘ethical correctness’ of research, which this study brought out clearly, considering that scientific validity and informed consent issues were dominant (Table 5). Even with the variations recorded among the various studies, it was clear that there was a high degree of agreement with the framework, in spite of the fact that the Uganda National Guidelines for Protection of Humans as Research Participants (UNCST, 2014), which are the basis for protocol reviews in Uganda are not expressly aligned to Emanuel et al. framework.

However, several weaknesses of the Emanuel et al. (2008) framework can also be cited. One major weakness is that it does have a mechanism one can use to prioritise or grade the bench marks, other than stating that all the benchmarks have to be considered together. It does not give any guidance as to which of the benchmarks, if any, could be regarded as core, so that if they are not given serious consideration, the REC performance is given a low score. On the other hand, protocols reviewed may not have warranted comments on the low ranking elements of the framework.

Furthermore, there was a strong showing in this study, and the others cited, of issues related to feasibility that are not mentioned directly by the Emanuel el al. framework. Since feasibility of a study contributes to its validity, this study coded such issues under scientific validity. The feasibility issues related to availability of willing population, availability of sufficient intellectual capacity to conduct the study, adequacy of funding and time resources (budget issues), availability of laboratory and other facilities as well as equipment are important issues that cannot be ignored. Budget issues and queries about sources of funding and guaranteeing sources of funding were raised many times as well as issues related to appropriateness of time-frame together with ensuring that there is collective qualification of research team, including seeking people with the necessary expertise such as statisticians, microbiologists and radiologists, in addition to provision of curriculum vitae of supervisors and principal investigators. This is in agreement with the concerns raised by the Tsoka-Gwegweni and Wassenaar (2014) study especially with regard to evaluation of competencies of the study team as a means of ensuring collective qualification as well as issues to do with funding.

Other issues that could not be coded basing on Emanuel et al. benchmarks but which are vital in the research enterprise include issues related to transfer of samples between countries and matters related to bio-banking or use of stored samples. There might have been strong consideration of such issues in this study because the Uganda National Guidelines for the Conduct of Research Involving Humans as Participants (UNCST, 2014) include details regarding Material Transfer Agreements (MTAs). But although this falls in line with other international guidelines like the Declaration of Helsinki (World Medical Association, 2013), Guideline 11 of CIOMS (2016), as well as the South African Guidelines (Department of Health, 2015), the Emanuel et al. (2008) framework does not explicitly require this.

5.2 Conclusions

This was the first known study to evaluate the ethics review outcomes of a Ugandan REC by analysing its minutes using the benchmarks of Emanuel et al. (2008).

As set out in section 1.4, this study set out to answer the following questions:
(1)What ethical concerns did the selected REC in Uganda raise when reviewing protocols?
(2) Is there a systematic prioritisation of some ethical issues over others?
(3) Is there an observable pattern to the ethical concerns raised by the REC? If so, what is the pattern?
(4) Are the concerns raised consistent with the framework developed by Emanuel et al. (2008)?
(5) Does any feature of the Emanuel et al. (2008) framework dominate the concerns? If so, which one?
(6) Are there other concerns raised by the REC that are not compatible with the framework discussed by Emanuel et al. (2008)?

With regard to the first question, it is clear from the results that this question was answered by the study which identified the full range of Emanuel et al.'s (2008) eight categories of ethical issues arising in the sampled REC minutes.

With regard to the second question, the sampled minutes were clearly dominated by queries about Scientific Validity, which far exceeded the next category - Informed Consent, followed then by a non-ethical category - Administrative Issues.

With regard to question 3, it can clearly be discerned from the results that an observable pattern of ethical concerns emerged from the analysis of the minutes (see Table 4).

In addition, over 90% of the ethical issues raised by the REC could be accommodated by the Emanuel et al. (2008) framework, with the remaining 10% of (non-ethical) issues coded as 'administrative' rather than ethical, thus answering question 4.

With regard to question 5, the data show that the dominant ethical issue raised was Scientific Validity.

The answer to question 6 is that the data show that the Emanuel framework accommodated 90% of the issues raised but did not allow for administrative issues which accounted for about 10% of the queries raised by the REC.

The general picture that comes from the results is that the framework provides a useful tool that can be used to categorise most issues and concerns raised during research ethics protocol review meetings of a REC in Uganda. The results also demonstrate that it is possible to use this framework to carry out comparative studies to evaluate the performance of RECs in the country, which now number 24 but are at different stages in terms of experience and expertise (http:www.uncst.go.ug).

5.3 Study limitations

The first limitation of this study is that it focused on only one REC out of the 24 accredited RECs in Uganda. Therefore, it is difficult to generalise the findings to other RECs in Uganda. Beyond description, it is not easy to make comparisons at national level since this research work has not previously been carried out in Uganda, leave alone the information bias involved since the study was retrospective. The work was done on the assumption that the minutes are a true reflection of the meetings. It is possible that some issues may have been debated but not included in the minutes. Only after a more representative sample of RECs in Uganda has been studied can a clearer picture emerge. RECs in Uganda are mainly based at academic and research institutions although several them are also Hospital-based and some social science RECs have also been established. Of the academic-institution based RECs, the majority are at health related institutions with a very small number being social science based. Since the present REC study was biomedical science-based and also served as a higher degrees committee, there are bound to be variations in terms of the nature and level of expertise available and definitely the nature of issues raised when different RECs are considered.

Furthermore, the study excluded expedited reviews which are normally done by the REC chairs or small designated sub-committees. Continuing reviews and meetings convened to review

protocol changes were also not considered. Positive attributes of protocols are usually not emphasised during review meetings. There is always a tendency to emphasise what has not been done right at the expense of what has been done correctly and this introduces information bias. In other words, some of the lower ranked elements of the Emanuel et al. (2008) framework shown in Table 5 might be ranked low because investigators/PIs dealt with them well in their applications and they did not warrant comment by the REC – this limitation is also acknowledged by Silaigwana and Wassenaar (2019).

Another limitation is that it was not possible to establish the relationship between frequency of mention and importance attributed to each of the issues raised since the framework used does not provide a scoring mechanism. The fact that administrative issues could have a frequency that ranked third after scientific validity and informed consent, tends to indicate that sometimes trivial issues could take precedence over more serious ethical issues. Further, this descriptive study does not attempt to determine the relationship between the findings and the training or composition of the members of the REC nor with the provisions of local ethics guidance.

Finally, the standard operating procedures and training of REC members in Uganda were based on the national guidelines, which, in turn, were based on international guidelines including the USA Code of Federal relations, WHO Guidelines, CIOMS, Declaration of Helsinki, as well as ICH-GCP, but there is no mention of Emanuel et al. (2008) in these guidelines. On the other hand, as mentioned earlier (Chapter 2), the Emanuel et al. framework was based on analysis of the essential features of the major international research ethics guidance documents, suggesting compatibility with Ugandan guidance and review practice as suggested by the present data. However, there was no attempt to control for this and, therefore, it cannot be discerned from this study as to what the impact on the outcome would be if we were to control for this factor.

5.4 Recommendations

Despite study limitations, carrying out comparative studies in the same country can generate useful validating data. This study provides baseline data for further comparative studies towards identifying and comparing the typical outcomes of the review processes in terms of the ethical issues raised by this REC, to date an unexplored process. It is recommended that similar studies should be conducted on RECs from different settings in Uganda, including RECs in hospital

settings, research institutions and those from social science backgrounds, in addition to those from academic health institutions. This will help to generate a more comprehensive picture that could be used to determine the extent to which Emanuel et al. framework is applicable in the Ugandan setting and Africa more broadly.

Furthermore, assigning scores to different benchmarks could help in mitigating the problem of failure to establish an appropriate relationship between frequency of mention and importance of issues raised during review meetings. There is also need to review the Emanuel et al. framework so that the items that appear under more than one principle or those which could be placed under more than one principle, could be assigned to one specific principle. Additional studies could attempt to relate these findings to the composition and training of REC members, and to concordance (or not) with local ethics guidance.

5.4.1 Best practices

A literature search revealed that there was relatively limited research on research ethics review in Africa and that the record for Uganda is sparse. Because of increased research funds being expended in Uganda, especially through projects sponsored by NIH and Welcome Trust, many RECs have been established and accredited. There is, therefore need to conduct research on the performance of these RECs, which will in turn help to standardise their practices. Also, such studies would help to inform discussions about recent trends towards establishment of regional ethics review bodies that could be used in situations of emergencies.

5.4.2 Research agenda

This study was undertaken along with similar studies in South Africa, Ghana, Nigeria, Malawi and Cameroon. It is envisaged that future analysis of combined results using Emanuel et al. (2008), will generate a relatively clearer picture of ethics review outcomes for several African countries, although there will still be the limitation of picking only one or perhaps two RECs from each country. This needs to be followed by more comparative research in the sample countries as well as those that were not considered in the initial studies. Future studies might also try to determine associations between these patterns and the composition of the REC, the training of members, the nature of the protocols reviewed and the concordance (or not) with local research ethics guidance.

5.4.3 Implications for training researchers and REC members

The findings of this study could help to inform stakeholders as to which ethical issues are relatively frequently and infrequently emphasised by RECs. It also underlines the basic utility of the Emanuel framework for analysing REC review outcomes. Anomalies (e.g. administrative issues) could help shape the future of ethics review or inform the framers of the Emanuel et al. (2000, 2004, 2008) benchmarks to make the necessary modifications.

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APPENDICES

Appendix 1: UKZN BREC Class Ethics Approval

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

07 February 2018

Mr Claude Kirimuhhuzya (Student No 215078171) (Uganda)
c/o Prof D Wassenaar
Discipline of Psychology
School of Applied Human Sciences
wassenaar@ukzn.ac.za

CLASS APPROVAL

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

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

The conditions have been met and the study is given **full ethics approval with effect from the date of the original full approval by UKZN HSSREC (*HSS/1450/014CA*). Your response dated 05 February 2018 submitting site permission from Makerere University in response to BREC letter dated 13 September 2016 has been noted by BREC.**

This approval is valid for one year from **07 September 2017.** To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

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

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

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

The sub-committee's decision will be **RATIFIED** by a full Committ**ee** at its meeting taking place on **13 March 2018.**

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

Yours sincerely

Professor V Rambiritch
Deputy Chair: Biomedical Research Ethics Committee

cc: **Mr Claude Kirimuhhuzya**
postgraduate officer: khanyilet@ukzn.ac.za

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

Appendix 2: REC Ethics Approval in Uganda

MAKERERE UNIVERSITY

P.O. Box 7072 Kampala, Uganda
E-mail: biomedicalresearch62@gmail.com

Fax: 256 414 532204

COLLEGE OF HEALTH SCIENCES
SCHOOL OF BIOMEDICAL SCIENCES
HIGHER DEGREES RESEARCH AND ETHICS COMMITTEE

31st March 2017

SBS-HDREC – 433

To Mr. Kirimuhuzya Claude
Principal Investigator
University of KwaZulu Natal

Category of review
[X] Initial review
[ ] Continuing review
[ ] Amendment
[ ] Termination of study
[ ] SAEs

Decision of the School of Biomedical Sciences Higher Degrees Research and Ethics Committee (SBS-HDREC) at its 66th REC meeting held on 9th March 2017.

In the matter concerning the review of a research proposal entitled, **"An evaluation of the ethical concerns of research ethics committees in Uganda using the principles and benchmarks proposed by Emmanuel et al.(2004; revised 2008)." SBS-HDREC - 433**

The investigators have met all the requirements as stated by **SBS-HDREC** and therefore, the protocol is **APPROVED.**

The approval granted includes all materials submitted by the investigators for **SBS-HDREC** review unless otherwise stated; and is valid until **8th March 2018**.

Please note that the annual report and the request for renewal where applicable, should be submitted six weeks before expiry date of approval.

Any problems of a serious nature related to the execution of the research protocol should be promptly reported to the **SBS-HDREC**, and any changes to the research protocol should not be implemented without approval from **SBS-HDREC**, except when necessary to eliminate apparent immediate hazards to the research participant(s)

You are required to register the research protocol with the Uganda National Council for Science and Technology **(UNCST)** for final clearance to undertake the study in Uganda.

MAKERERE UNIVERSITY SCHOOL OF BIOMEDICAL SCIENCES APPROVED VALID UNTIL 08 MAR 2018 HIGHER DEGREES COMMITTEE P.O. BOX 7072, KAMPALA

Signed.....
Dr. Erisa Mwaka
Chairperson, School of Biomedical Sciences Higher Degrees Research and Ethics Committee.

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Appendix 3: Site Clearance Letter
(Withheld for confidentiality reasons)

Appendix 4: Data Collection Tool (coded)

Emanuel, Wendler, and Grady's (2008) principles and benchmarks **Benchmark:**	**Number**	**% rank**
Principle 1: Collaborative partnerships		
Community representatives		
Responsibility sharing (collaboration)		
Respect for local context (environment)		
Fair research benefits for community		
Sharing research products		
Principle 2: Social value		
Research beneficiaries		
Research benefits		
Enhancing benefits		
Impact on health systems		
Principle 3: Scientific validity		
Appropriate design and methods		
Applicability of results		
Impact on provision of health care services		
Study design feasibility		
Availability of the required expertise		
Adequacy of the financial resources (Budget issues)		
Availability of a willing study population		
Availability of the required facilities		
Adequacy of the time resource		
Principle 4: Fair participant selection		
Suitable study population		
Risk minimisation		
Benefits to participants		
Vulnerability		
Principle 5: Favourable risk benefit ration		
Risk identification and minimisation		
Type, probability and magnitude of benefits		
Comparison of benefits and risks		
Principle 6: Independent review		
Regulatory compliance		
REC members conflict of interest		
Transparent review		
Minimisation and reconciliation of multiple reviews		
Principle 7: Informed consent		
Recruitment and incentives applicability to local context		
Appropriate disclosure documents and process		
Presentation and accuracy of information		
Legally authorised representatives and issues of assent		
Gate-keepers' permission		

Context of consent process		
Respect for autonomy		
Principle 8: Respect for participants		
Monitoring health and well being		
Confidentiality and privacy		
Voluntariness		
Research results dissemination		
Post-research obligations		
Issues not covered by Emanuel at al. (2008) framework		
1. Administrative issues		
Queries about abiding with the institutional protocol format		
Issues with grammar and typographic errors		
Issues related to writing styles		
Queries on referencing styles		
Supervisors' appropriately written names and titles		
Total		