

**STAKEHOLDER PERSPECTIVES ON INFORMED CONSENT AND ETHICS REVIEW
OF RESEARCH INVOLVING HUMAN SPECIMEN RESOURCE REPOSITORIES
(BIOBANKS) IN SOUTH AFRICA: A QUANTITATIVE STUDY**

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DECLARATION

I declare that this dissertation represents my own work, except for those where due acknowledgement is made, and that it has not been included in a thesis, dissertation or report submitted to this university or any other institution for a degree, diploma or other qualifications.



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ACRONYMS

DoH	Department of Health
ELSI	Ethical, Legal and Social Implications
EMA	European Medical Agency
H3Africa	Human Heredity and Health in Africa
HBM	Human Biological Materials
MoU	Memorandum of Understanding
MTA	Material Transfer Agreement
NHLS	National Health Laboratory Service
OECD	Organisation for Economic Co-operation and Development
REC	Research Ethics Committee
SOP	Standard Operating Procedures

OPERATIONAL DEFINITIONS

Human Biological Materials/ Biological Samples are defined as “samples of blood, DNA, organs and tissues commonly obtained during routine (medical) and surgical procedures, research or through direct donation by an individual” (Meslin & Quaid, 2004, p. 229).

Stakeholders: “Any identifiable group or individual who can affect the achievement of an organization’s objective or who is affected by the achievement of an organization’s objective” (Freeman & Reed, 1983, p. 91). In biobanking, stakeholders include donors (participants), investigators (researchers), research institutions, regulatory bodies, funding agencies and others (Bjugn & Casati, 2012). For this study, stakeholders include researchers, clinicians, pathologists, laboratory or repository personnel and managers, bioethicists, and research ethics committee (REC) professionals.

Human resource repositories (biobanks) are defined as “ repositories where organised collections of human biological materials, and associated data from large numbers of individuals, are collected, stored and distributed for the purpose of health research” (Dhai & Mahomed, 2013, p. 225). For the scope of this study, pathological archives and institutional professional laboratories where human biological materials (HBM) from research activities (for example, clinical trials) are stored will also be considered as biobanks. The term ‘biobank’ will be used throughout this thesis, for ease of reference, as it is a term now in common use.

ABSTRACT

On-going research has made the use of human biological materials and genetic material/data for biomedical research an area of high interest to researchers, bioethicists, philosophers, lawyers and various regulatory bodies. In this era of globalization, there are profound ethical, legal and social implications for the evolving nature of biobank research; these have to be considered during the ethics review process.

The main objective of this study was to explore stakeholders' perspectives of informed consent and ethics review of biobank research in South Africa, with the aim of obtaining information that could contribute to the harmonization of ethical guidelines of the consent process and biobank governance.

This was a descriptive cross-sectional study that employed a positivist approach involving qualitative data collection methods. The study was conducted at Stellenbosch University, the University of KwaZulu-Natal, and seven research ethics committees in the KwaZulu-Natal and Western Cape provinces in South Africa. A purposive sampling technique was used to recruit significant stakeholders in biobank research in South Africa. Data was collected using self-administered online survey instruments. Completion of the survey implied consent. Quantitative data were summarized using descriptive summary statistics. Conventional content analysis was used for data collected from open ended questions.

The response rate was low; 19 research ethics committee members and 62 researchers and other stakeholders participated in the study. All stakeholders agreed that there is need for functional regulatory frameworks to govern biobank research, particularly the strengthening of research ethics committees, to ensure comprehensive ethics review of biobank-based research. There were several areas of agreement and divergence in respondents' perspectives on the collection, storage and future use of human biological materials. There was no consensus on the issue of re-consent and the likelihood of donor identification and harm during the use of human biological materials for secondary research. Stakeholders also identified a number of challenges in the ethics review process and the sharing of human biological materials.

Generally, the attitude of research ethics committee members, researchers and other stakeholders on informed consent, ethics review of biobank research, and the export and sharing of de-identified HBM is positive and ethically informed. Stakeholders believe that there is need for robust regulatory

frameworks to govern the collection, storage, sharing and future use of HBM both within South Africa and across borders. Several recommendations are proposed that could contribute to the harmonization of ethical guidelines on the relevant consent process and biobank governance.

CHAPTER 1: INTRODUCTION AND BACKGROUND

Research is needed in Africa in order to address the numerous health challenges confronting the continent (Boatin et al., 2012; Sylla & Wild, 2012). This need for research has made the use of human biological materials (HBM) such as tissue, organs, blood and genetic material/data for biomedical research an area of high interest to researchers, bioethicists, philosophers, lawyers and various regulatory bodies (Hansson, 2009). In this era of globalization, there are profound ethical, legal and social implications (ELSI) for the evolving nature of this research. These include the use of HBM within the context of participant autonomy, informed consent, confidentiality, privacy, future use of HBM and data, ownership of HBM, return of study results, and data- and benefit-sharing (Barnes & Heffernan, 2004; Budimir et al., 2011; Cambon-Thomsen, Rial-Sebbag, & Knoppers, 2007; Hansson, 2011).

This study therefore set out to explore stakeholders' perspectives on some of these issues, particularly informed consent and ethics review of research involving human resource repositories (hereafter referred to as biobanks) in South Africa. The aim was to obtain information which could contribute towards harmonization of ethical guidelines on the consent process and biobank governance. For the scope of this study, pathological archives and institutional professional laboratories where HBM from research activities (for example, clinical trials) are stored were also considered as biobanks. The study was conducted at Stellenbosch University, the University of KwaZulu-Natal and its affiliated research institutions, and seven RECs in the KwaZulu-Natal and Western Cape provinces in South Africa. The study targeted important stakeholders in research involving the collection, storage and secondary use of HBM and associated data. Among these were research ethics committees (REC) members who review and approve the research, and clinicians, researchers, pathologists, and laboratory/biobank managers who design and/or implement the research.

Stakeholders in research involving biobanks face several challenges in ethics review and informed consent processes, especially in Africa where this is an emerging field. Though the first biobank in South Africa (Africa Centre Biobank) was established more than two decades ago, it is only in the last few years that research involving biobanks has gained prominence. The number of biobanks in South Africa is growing and so are the ethical challenges associated with biobank governance. If biobank research is to succeed in South Africa, and Africa as a whole, it has to be accepted and appreciated

by all stakeholders. Though a great deal of research has been done to document research participant perspectives on biobanking (Hansson, Dillner, Bartram, Carlson, & Helgesson, 2006; Igbe & Adebamowo, 2012; Kettis-Lindblad, Ring, Viberth, & Hansson, 2006; Moodley, Sibanda, February, & Rossouw, 2014; Tindana et al., 2012; van Schalkwyk, de Vries, & Moodley, 2012; Wendler et al., 2005), not much has been done to document other stakeholders' experiences and perspectives concerning informed consent and the ethics review process in biobank research (Cambon-Thomsen et al., 2007).

Furthermore, studies show that guidelines regulating the acquisition, storage, use and transfer of HBM in several African countries are inadequate, conflicting and, at worst, non-existent (Sathar & Dhai, 2012; Staunton & Moodley, 2013). As a prerequisite for harmonization of biobank research, the perspectives of stakeholders need be determined, with due regard to the diverse cultural differences across the African continent.

CHAPTER 2: LITERATURE REVIEW

2.1 Introduction

In this era of globalization, there have been profound ethical, legal and social implications (ELSI) of the evolving nature of biobank research on participant autonomy, informed consent, confidentiality, privacy, future use of HBM and data, ownership of HBM, return of results, data-sharing and benefit-sharing with communities (Barnes & Heffernan, 2004; Budimir et al., 2011; Cambon-Thomsen et al., 2007; Hansson, 2011). To get a better understanding of these ethical, legal and social issues, certain terms and concepts have to be clearly defined.

Biobanks are “repositories where organised collections of human biological materials, and associated data from large numbers of individuals, are collected, stored and distributed for the purpose of health research” (Dhai & Mahomed, 2013, p. 225). Biobanks range in capacity from small institutional specimen collections to sizable scale national repositories. Millions of HBMs are collected for various purposes including clinical trials, research and epidemiological studies (Eiseman & Haga, 1999). For the scope of this study, pathological archives and institutional professional laboratories, where HBM from research activities (for example, clinical trials) are stored, will also be considered as biobanks. Pathological archives are repositories of HBM collected primarily for clinical purposes such as documenting diagnosis and for future reference in diagnostic analysis of spreading cancers. They support tissue-banking, provided they meet required standards and legal requisites for use as a research resource (Bevilacqua et al., 2010). Pathological biobanks constitute important health resources for medical care and treatment for present and future patients. When linked with quality clinical data, they are highly instrumental in biomedical research on disease mechanisms and pathogenesis (Hansson, 2007).

Another source of samples is clinical biobanks that are established for both medical care and research purposes. In routine medical care, samples are taken for various tests like clinical pathology, cytology, microbiological and biochemical analyses. These samples are usually taken in order to make proper medical diagnoses. However, the surplus samples may be kept in biobanks and, under certain circumstances, may be used for research; however, the use of such samples is often ethically problematic and will be discussed in more detail later.

Biobank samples (i.e. samples specifically collected to form part of a biobank) can be used for quality development, education and research. With research, novel clinical tests, therapeutic agents and preventive measures can be developed. Therefore, the motivation for storing biological samples is

the diagnosis, care and treatment for present and future patients (Hansson, 2007). Biobank research differs from conventional research because sample collectors may be intermediaries not actively participating in the research. In biobank research, HBM can be used in a wide range of scientific areas including future research projects that cannot be specified at the time samples are collected (Dhai & Mahomed, 2013). Furthermore, research on HBM can spread over a long duration of time with one sample being used for several unrelated studies.

In summary, specimens can be deposited into a biobank via various routes, each presenting specific ethical challenges:

1. Collected specifically to develop a biobank that can be utilised for current and future research,
2. Collected initially as part of a specific research study; leftover samples stored for future use and,
3. Collected for clinical purposes and stored.

Though biobanking and related research have been around for the last two decades, this is a relatively new field in Africa. For biobank research to be successful in Africa, opinions of the different stakeholders in this field should be established and considered. Stakeholders in biobanking include researchers, scientists, experts on ethics, RECs, laboratory managers (clinical and research) and research participants. If biobanks are to realize their full potential, there is need to maintain public trust because it is from the public that potential tissue donors are derived. This can be achieved by maintaining strict policies on privacy and professional relationships with participants and, on-going education of the populace (Budimir et al., 2011; Hansson, 2011).

Many studies exploring the opinions of participants, researchers, RECs and medical workers have been done (Colledge, Persson, Elger, & Shaw, 2014; Hansson et al., 2006; Igbe & Adebamowo, 2012; Kettis-Lindblad et al., 2006; Moodley et al., 2014; Tindana et al., 2012; van Schalkwyk et al., 2012; Wendler et al., 2005). The majority of these studies were conducted to establish participants' attitudes and perspectives. Few have targeted the other stakeholders, especially those from Africa. Ethical dilemmas in scientific research involving human participants, HBMs and personal information stem from potential conflicts between the varying research interests, the privacy, personal integrity and self-determination of research participants, and the need to preserve public trust in the research (Hansson, 2011). Therefore, the study aimed to explore stakeholders' experiences and perspectives on informed consent and the ethics review process in biobank research.

This chapter will explore literature on biobanking in South Africa, and Africa as a whole; consent and withdrawal of consent; privacy and risks of biobank research; controversial issues associated with informed consent (such as ownership of samples and return of results to participants); ensuring public trust; biobank governance; cultural issues; fair benefit-sharing; and the role of RECs in biobank research.

2.2 Biobanking in South Africa

There are numerous research projects involving HBM collection, analysis, storage and secondary use in South Africa (Moodley et al., 2014). Large quantities of these biological samples have been shipped to developed countries for storage because of lack of biobanks in Africa (Staunton & Moodley, 2013). Because of the fast pace in genetic research and the need to keep track of HBM collected from varying research activities, the South African Department of Health (DoH), in collaboration with external partners, is trying to streamline biobanking activities. For example, the National Health Laboratory Service (NHLS) set up a biobank in Braamfontein in 2012. Biorepositories are not new to South Africa; the Africa Centre biobank (Africa centre Biobank) in KwaZulu-Natal has been in existence for more than two decades and has a large collection of a wide range of human biological specimens (Dhai, 2013).

African researchers are under-represented in modern genetics and genomic research. To address this issue, the National Institutes of Health and the Wellcome trust launched the Human Heredity Health (H3Africa) project ("NIH and Wellcome Trust Announce Partnership to Support Population-based Genome Studies in Africa,"). The project aims to contribute to the enhancement of local expertise in the study of genomics and environmental determinants of common diseases among the African population, and to establish networks of African investigators. Among other functions, the H3Africa project is aimed at establishing biobanks for the storage of human biosamples, medical information and making DNA available for research purposes (H3AFRICA, n.d). The H3Africa project also has a goal of encouraging and building international collaborative partnerships between institutions and researchers.

For this cross-border collaboration to be successful there is need for solid ethico-legal frameworks. Though guidelines on the management of HBM guidelines exist in several sub-Saharan countries, they often do not address the ethical challenges associated with transfer of HBM and are not well suited to managing biobanks (Andanda & Govender, 2015; Moodley et al., 2014). Therefore, for the

H3Africa project to be a success, there should be harmonization of legal and ethical guidelines on the use and export of HBM (Staunton & Moodley, 2013). Academic institutions have also recognized the importance of streamlining biobank research. For instance, the University of Witwatersrand Human and Research Ethics Committee (Medical) (2016) released a policy document regulating the transport and storage of bio-materials arising from clinical trials.

Studies done in Europe show that people have a high level of trust and are willing to participate in genetic studies aimed at advancing scientific knowledge and treatment of disease (Hansson et al., 2006; Kettis-Lindblad et al., 2006). Numerous research studies have been conducted on participants' perspectives on biobank research; however, very few of them have been done on the African continent (Igbe & Adebamowo, 2012; Moodley et al., 2014; Tindana et al., 2012; van Schalkwyk et al., 2012; Wendler et al., 2005). A study done in South Africa on sample storage and export reported that participants were apprehensive about secondary use, sharing of benefits and export of samples (Moodley et al., 2014).

If biobank research is to succeed in Africa it has to be accepted by the populace who should also be willing to participate in the furthering of scientific knowledge. Therefore, it is essential that participant perspectives, preferences, social values and cultural/religious beliefs be determined and considered. Though much research has been done to document research participant perspective on biobanking, not a great deal has been done to document the other stakeholders' experiences and perspectives concerning informed consent and the ethical review process in biobank research.

2.3 Ensuring and sustaining public trust

As a result of the numerous documented cases of 'bio-piracy', communities have lost trust in the biobank research enterprise (Budimir et al., 2011). It is imperative that public trust is maintained if biobanks are to realize their full potential. Loss of public confidence in biobank practice may negatively affect the validity of research results; for instance, when individuals start withdrawing their consent and requesting that stored samples are destroyed. In order to maintain confidence in biobanking and related research, there should be strict policies on privacy and professional patient-doctor relationships, as well as on-going education of people (Budimir et al., 2011; Hansson, 2011).

Studies show that people are generally supportive of biobanks, with those who are more educated and familiar with biobanking being more inclined to participate in research (Hoeyer, Olofsson, Mjörndal, & Lynöe, 2004; Kaufman, Murphy-Bollinger, Scott, & Hudson, 2009; Kettis-Lindblad et al.,

2006; Secko, Preto, Niemeyer, & Burgess, 2009). Studies also show that many people are willing to donate their HBM and have a high level of trust in research aimed at advancing scientific knowledge and treatment of disease (Allen & McNamara, 2011; Hansson et al., 2006; Kettis-Lindblad et al., 2006; Petersen, Desmedt, Harris, Buffa, & Kollek, 2014; Wendler et al., 2005). In reciprocity, investigators ought to be transparent and they have an obligation to inform participants that their HBM are being stored for potential future research and could also be shared with other researchers abroad (Dhai & Mahomed, 2013). This informed consent and sharing of HBM should take into consideration local culture, social beliefs and practices of the donors and their related communities, in order to promote trust and avoid potential disruption of social relationships. Thus, establishing research procedures that do not take into consideration sample donors' opinions on how their samples may be utilized in the long term may have negative effects on public trust in biomedical research (Helgesson & Johnsson, 2005).

Another point of contention that can significantly affect public confidence is the use for research without renewed consent of samples previously collected for clinical diagnostic purposes. Public surveys have shown that most people prefer broad information and consent processes, and waive the decision to provide explicit and specific informed consent to RECs (Hansson, 2011; Hoeyer et al., 2004; Kettis-Lindblad, Ring, Viberth, & Hansson, 2007; Wendler, 2006). Patients seem to favour this consent approach because it exhibits respect for the donor's contributions, allows the donor the choice of category of research to contribute samples to and also allows donors some degree of control over the use of their samples in research while avoiding the potential burden of obtaining re-consent for each new study (Foe, 2014). Therefore, there is need for transparency so as to promote public trust and the future of research with stored samples. This can be achieved through appropriate consent processes that are not only acceptable to the majority of patients but also show respect to their autonomy.

2.4 Consent in biobank research

A great deal has been written about consent in biobank research. However, there seems to be little consensus in this area (Capron et al., 2009). Obtaining donors' consent for research with HBM shows respect for their autonomy; gives them a chance to make a decision whether their samples should be used for research; permits them to decide whether the risks of research are acceptable to them; allows them to make a decision whether to contribute to the advancement of knowledge; and enables them to make transparent and informed decisions concerning sample donation for research purposes (Cervo et al., 2013; Grady et al., 2015; Pellegrini et al., 2014). Informed consent should be a

continuous information-sharing process which allows donors some degree of control over the use of their samples in research. This, to some extent, can ensure that research participants are not exploited, as stipulated in the National Health Act No. 61 (*South African National Health Act, 2003*). On the contrary, research participants and communities may not experience this continuous informed consent process once the biological specimens have been obtained (Mahomed, Behrens, Slabbert, & Sanne, 2015). This process also includes the dissemination of results to all stakeholders, participants and participating communities.

Conflicts between advancement of scientific research and trying to maximize participants' autonomous decision-making complicate the informed consent process for the use of HBM. There is no universal informed consent approach for research where there may be a plan to specifically collect specimens for storage and future research. Choice of an appropriate informed consent procedure depends on the balance between the scientific value and potential burdens of the research. It also depends on whether the research will use previously collected HBMs or plans prospective collection of new samples for use in future studies. Therefore, RECs have the key task of balancing the potential risks and benefits posed by specific protocols on a case-by-case basis during the selection of appropriate consent procedures (Hansson, 2011; Mongoven & Solomon, 2012).

Beauchamp and Childress (Beauchamp & Childress, 2009, p. 124) state that "a person gives an informed consent to an intervention if (and perhaps only if) he/she is competent to act, receives thorough disclosure, acts voluntarily and consents to the intervention". Based on the above definition, specific consent is the most ethically ideal approach; however, it imposes considerable restrictions and limitations on investigators and participants (Mello & Wolf, 2010). Assuming that participant competence is assumed or a constant, an inter-play between the other elements of informed consent have caused many ethical controversies and points of discussion in biobank research. Several types of consent for biobanking and related research have been proposed, and will be briefly discussed in the next few paragraphs.

2.4.1 Consent for HBM collected for biobank research

In the context of this study, HBM collected for biobank research includes residual samples that were initially collected as part of a specific research study, and those that are specifically collected to develop a biobank to be utilized for current and future research. Several consent models have been used in biobank research including specific consent, broad consent, general/blanket consent, tiered consent, dynamic consent, presumed consent and the incorporation of exclusion clauses in informed

consent documents. However, some authors agree that HBM could be used without consent if they fulfill the following conditions: 1) when the research is of interest; 2) when HBM are anonymized with minimal risks of violation of privacy; 3) unwarranted use of samples and personal information is minimized; and 4) approval is obtained from a REC (or any other regulatory authority) (Hansson, 2011; Hawkins, 2010; Helgesson, Dillner, Carlson, Bartram, & Hansson, 2007; Hoeyer et al., 2004).

In specific consent, participants are given 'adequate information' on the nature, purpose, methods and risk-benefit assessment before a decision to participate in the research is made. As a way of respecting their autonomy and protecting their interests, they are also given an option to withdraw their consent (Chalmers, 2011; Eriksson & Helgesson, 2005; Hansson, 2011; Helgesson & Johnsson, 2005). In biobank research, if samples are stored with consent for only one specific research project, this process has to be repeated whenever stored samples are to be used for any new research. It enables participants to decide whether or not to take part in new research in the quest to further scientific knowledge. In essence, participants retain control over their samples and medical information. This consent approach allows individuals protection of their rights and gives them the liberty to decide how their HBM should be used.

In practice, specific consent in the use of stored samples is laden with multiple challenges. The use of stored HBM poses fundamental ethical concerns in biobank research because of the challenges in obtaining re-consent for each new study on the samples. Ethically, it is desirable that the autonomy of donors be respected; however, at times it is not possible to re-contact them. Obtaining new consent for every secondary study is not practical, is expensive and in most cases impossible (Peto, Fletcher, & Gilham, 2004). Request for re-consent might not achieve the desired response rate because of refusal to give new consent; inability to locate participants; and where the participant is dead and the family is unwilling to co-operate. This affects the quality and validity of results by posing significant potential for selection bias due to drop-outs (Hansson, 2005). Caulfield, Brown, and Meslin (2007, p. 70) summarized this, saying re-consenting is "logistically impracticable, prohibitively expensive and, in the case of long-term projects where the donors have died, impossible". Therefore some decision-making should be delegated to RECs as a sign of respect for the integrity of the donor (Hansson, 2006; Hansson et al., 2006; Kettis-Lindblad et al., 2007).

Though request for re-consent is done in respect for the ethical principle of autonomy, there are instances when it may violate personal integrity (Helgesson et al., 2007). It can place a psychological burden on participants. Repeated contacts for consent can bother participants (Ram, 2008). Request

for renewal of consent may be experienced as a lack of respect by the donor because they may feel that their contribution to furthering scientific knowledge is not being appreciated (Hansson, 2007). There are several instances where participants might feel disrespected, for example: when consent is sought from relatives of a deceased donor; acting against one's deeply held social values; and if a donor feels that re-consent threatens their contribution to advancement of scientific knowledge (Helgesson et al., 2007). Potential risks and benefits of re-contacting donors should therefore be considered carefully.

In view of the intricacies of specific consent, several different approaches to informed consent have been suggested and used. These include: presumed consent with opt-out; tiered/multi-layered consent; broad consent; general consent; waived consent; and insertion of exclusion clauses in the consent form (Master & Resnik, 2013; Tasse, Budin-Ljosne, Knoppers, & Harris, 2010). In presumed consent, research participants are informed of the possibility of their samples being used for future research, if they do not have any objections. They also have an option of withdrawing from research studies (Johnsson, Hansson, Eriksson, & Helgesson, 2008; Mello & Wolf, 2010; Tasse et al., 2010). Some authors suggest that where there is no consent, it should be presumed (Johnsson et al., 2008). This approach is usually applied in the use of surplus tissues obtained in medical care. Participants have very limited say in the use of their samples and their consent is not informed because they are not provided with specific information on the nature of scientific research (Mello & Wolf, 2010). Though presumed consent maximizes the scientific utility of HBM, it is unsuited ethically for biobank research.

Tiered consent offers participants an appreciable level of control over the use of their HBM for future research. Participants are given a range of options concerning the future use of their samples and associated data. Options can include: the various potential areas of research; whether they want to be contacted again for new consent for studies unrelated to the ones they consented to; and the use of their HBM/data for commercial research (Master & Resnik, 2013; Mello & Wolf, 2010). It gives less latitude to the researcher than specific consent. This approach is mostly used in oncological research where follow-up is very important in deciphering disease mechanisms and trial of new therapeutic agents (Ram, 2008).

Though tiered consent is impressive regarding respect for autonomy, it is complex and almost impossible to implement in large public biobanks and international collaboration research (Tasse et al., 2010). On the other hand, there are arguments that the tiered approach to consent may not be

informed after all (Ram, 2008). Ram argues that consumer psychology has shown that when a person is offered many options, they get overwhelmed by the information, make random choices, at times fail to make choices and have regrets after making the decisions (Ram, 2008). In the end, this affects the quality of autonomous decision-making. Therefore, researchers should be selective when deciding whether to use this approach to consent for research. The next consent option to biobanking research to be discussed is broad consent.

Broad consent “means the donor donates materials with permission to use them for a broad range of future studies, subject only to further prior ethics review and approval” (DOH, 2015, p. 41). In broad consent, at the time of sample collection, participants consent for the use of their HBM in the current study and any future studies without the need for re-consent. The future research in most cases cannot be specified in detail because no factual information is available at that time (Steinsbekk, Myskja, & Solberg, 2013). Based on the above assertion, some authors would argue that broad consent is not binding because it is not informed.

Broad consent seems to be favoured by most researchers, compared to specific consent. It is perceived to allow donors some level of control over their samples, provide flexibility for future research projects while leaving an open avenue for sample- and data-sharing, and minimizes costs and burdens to donors and researchers (Colledge et al., 2014; Grady et al., 2015). Broad consent is also seen to promote ethical acceptability of future research with biological samples and exhibits respect for donors’ contributions. Proponents further argue that broad consent preserves participant autonomy if the following stipulations are met: personal data is protected; participants have the right to withdraw consent; and subsequent studies obtain approval from RECs (Hansson et al., 2006). Supporters of broad consent argue that if participants are properly informed of what it entails to give broad consent and they understand, then their consent is valid (Helgesson, 2012). They further assert that, if the information given to participants is sufficiently relevant to enable making a decision, then they are properly informed and can make an autonomous decision (Hansson et al., 2006). Therefore, consent forms should have a broad consent option in studies designed to use stored HBM, because this is more practical (Helgesson, 2012).

Opponents of broad consent argue that it is difficult to withdraw consent in cases where participants are included in studies of which they do not approve (Hofmann, 2008). However, lately, much discussion is taking place on the use of broad consent in genomics and biobanking (Grady et al., 2015; Ramsay, de Vries, Soodyall, Norris, & Sankoh, 2014; Rothwell et al., 2015). Broad consent is

considered ethically permissible when three conditions are met: broad consent for the initial study; REC oversight and ethical approval of any future research on the samples/data; and, wherever feasible, communication and provision of information to the donors (Grady et al., 2015).

Another consent model is general consent, also known as open, generic or blanket consent. In this model, participants give a one-time consent for the use of their HBM in all prospective research (Master & Resnik, 2013); in essence, participants have no control over the use of their HBM. Though general consent is permissible according to some international laws and ethical guidelines, researchers often have difficulties using it because RECs are reluctant to approve general consent forms (Colledge et al., 2014). That is why some researchers utilizing HBM for scientific research try to avoid the use of the term 'biobank' while describing their repositories. They do this in order to evade certain regulatory guidelines, most prominent of which are the informed consent requirements (Shaw, Elger, & Colledge, 2014). In countries like China, general consent with an opt-out option has been proposed for biobanking (Liu & Hu, 2014). Participants are given regular updates on the research that is being conducted on their samples so that they can opt out or withdraw their HBM if they want to (Liu & Hu).

During the consent process participants are provided only with information that is considered relevant because a great deal of information can just confuse them (Ram, 2008). However, there are instances where the omitted information would have significantly affected the participant's decision. The participant might then want to opt out. To avoid such scenarios, research studies should provide regular, free and easily accessible information on on-going research activities (Helgesson, 2012). Since it is almost impossible to estimate future risks, RECs should have the ability to weigh the scientific validity against risks for individual studies and avoid generalization of studies. Particular care should be exercised concerning dignity, discriminatory and stigmatization risks, to avoid a repeat of the several cases that have already been documented (Helgesson, 2012; Mello & Wolf, 2010).

Therefore, in view of the intricacies associated with the informed consent process for the future use of HBM, a broad consent option should be incorporated on the consent form in addition to specific consent. Based on the arguments of a majority of authors, large-scale population bank research can use broad consent as the only alternative as long as ethical review is done by a competent REC. The lack of consensus on the most ideal consent model for biobank research has led to innovative consent models.

As a way of improving the respect for participants' autonomy in this era of technological advancement, various consent approaches to biobank research have been proposed. One such approach is a dynamic consent model that uses information technology systems or websites to ease communication with participants (Kaye, 2011; Kaye et al., 2011). Electronically based communication (e.g. the Internet) is used to disseminate detailed information and updates concerning specific studies, thus improving on the validity of consent for secondary projects (Steinsbekk et al., 2013). Participants are requested to consent for any new studies utilizing their samples, even for trivial modifications. There is active engagement and participation, and donors have an increased control and rights over the use of their samples.

Proponents state that this strategy builds public trust, as people are more willing to enroll in research and there is improved participant retention (Kaye et al., 2012). They opine that dynamic consent could be used to curtail REC oversight for future research. This in itself undermines ethical assessment because REC oversight is not only about informed consent. Opponents of the dynamic consent strategy argue that it risks undermining the ethics review process; risks participant disenchantment as a result of unmet expectations; increases risk of therapeutic misconception; and risks not being practical in population banking and the developing world where there are perennial power outages and internet coverage is low (Steinsbekk et al., 2013).

Some authors have proposed the incorporation of exclusion clauses in the informed consent process as a way of minimizing risk, promoting accountability and establishing public trust (Master & Resnik, 2013). Exclusion clauses are written statements in the consent process that exclude the use of HBM and personal information for particular types of studies and regulate the sharing of HBM and information with certain investigators or organizations that are perceived to be untrustworthy by the public (e.g. insurance companies, government agencies and commercial entities). These clauses are aimed at preventing controversial research that could pose social risks to individuals and communities (Master & Resnik, 2013). Benefits of exclusion clauses include: participants are given more information about the various potential uses of their HBM and personal information; increased transparency and accountability by all stakeholders; and promotion of public trust by providing guarantees to participants. On the other hand, exclusion clauses are associated with some disadvantages: they can only be useful in small, disease-specific biobanks; they might inculcate unwarranted anxiety and possibly discourage potential participants from enrolling in research; it may become necessary to contact participants for new consent if there is a motivation to expand the

research to include the excluded areas; and researchers may not foresee future areas of exclusion at the time of primary consenting (Master & Resnik, 2013).

2.4.2 Consent for HBM collected for clinical purposes

There are also ethical challenges in obtaining consent for samples that are collected for diagnostic and clinical purposes, and stored in pathological archives and repositories. In some instances, these samples were collected many years ago and stored without consent (primarily in case the specimen may be required again for diagnostic clinical purposes in the future). The purpose of the storage in the first instance was in the best interest of the patient and not for research purposes. However, these archives can also be viewed as potentially valuable research repositories.

In some countries, the law requires explicit and specified consent when obtaining samples from patients in routine medical care and this poses ethical challenges when such samples are to be utilized for research. Furthermore, clinicians have complained of the long duration of routine consultations because of the requirement for a comprehensive informed consent process before obtaining clinical samples. Enough time has to be assigned for comprehension of information on the disease and its treatment, in addition to information about biobank regulations and other potential uses of the specimen (Hansson, 2007). Such explicit informed consent policies in routine medical care can be difficult to implement in countries where health workers are in short supply. This can, in the end, lead to misconduct because of failure to cope with the heavy workload while at the same time trying to obtain proper informed consent.

Hansson (2007) argues that re-consent is not essential in the use of stored HBM obtained for medical purposes because samples are taken in the patients' interest with respect to diagnosis, care and treatment. Stored HBM can be used in research without re-consent when no explicit consent was obtained at the time the sample collection as long as strict privacy and confidentiality measures are taken to protect the donors'/patients' integrity. They can also be used when the initial consent was restricted to a specific study with no other information given on its use in other studies (Helgesson et al., 2007). However, a sample should not be used in any other research if the donor objected to it in the initial consent or if the initial consent was restricted to the original research only (Helgesson et al., 2007). In this case, if these samples are to be utilized for research and re-consent is impracticable, then the responsibility is on the REC to make a considered determination on this issue.

From the above arguments it can be observed that there are many contentious ethical issues with respect to the informed consent process in the secondary use of biological samples and personal information. Each research study should be considered on its own merits as long as there is a fine balance between the fundamental principles of competence, disclosure, understanding, voluntariness and consent. It is also imperative that perspectives of all stakeholders in the biobanking research industry be explored if consensus on this issue is to be obtained.

2.4.3 Withdrawal of consent

Article 26 of the Helsinki Declaration states that “the potential [participant] must be informed of the right to refuse to participate in the study or withdraw consent to participate at any time without reprisal” (WMA, 2013). The principle of respect for persons denotes that participants should be able to sanction the destruction of their HBM and associated data upon withdrawing their consent. The World Medical Association declaration on health databases stipulates “that patients should have the right to decide that their personal health information in a database (as defined in 7.2) be deleted” (WMA, 2002, p. 3). Therefore, any continued use of participant biological samples and data would mean that they are still involved in research against their will (Harlan, 2004).

Conversely, some guidelines are ambiguous with respect to the destruction of samples and consent withdrawal. For instance, Article 9 of the United Nations Organization for Education, Science and Culture (UNESCO) International Declaration of Genetic data stipulates that consent withdrawal may not be possible when the “data are irretrievably unlinked to an identifiable person” (UNESCO, 2003). However, if the sample and data are not “irretrievably unlinked”, then the participant’s wishes should be respected.

Withdrawal of consent in biobank research is complicated because, at times, the sample and associated data might have already been supplied to a secondary researcher who was not involved in sample collection. In such instances, it is almost impossible to recall the sample and data. Best practice guidelines from the US Code of Federal Regulations recommend that the residual specimen must be withdrawn but the sample and data already distributed may not necessarily have to be recalled (ISBER, 2012; NCI, 2007).

There are several other alternatives available should participants wish to withdraw their consent. For example, the biobank can stop contacting participants for updates or re-consent but will continue accessing their medical records and utilizing the biological sample and associated data; the

biobank can stop contacting the participant and accessing their medical information but will continue utilizing the residual HBM and data; anonymization of HBM and permanent destruction of the link with any identifiers but the biobank will continue utilizing the de-identified HBM and data; and disposal of the residual HBM and cessation of use of updates or any personal medical information (McGuire & Beskow, 2010).

In the USA, use of anonymized HBM for research is not considered as involving human participants; as such, it does not require informed consent (NIH, 2008). The continued use of HBM and associated data can only be justified on the assumption that the participant would approve and the potential risks are minimal. However, such an argument is difficult to accept, especially when a participant has explicitly indicated their wish to withdraw from a study.

Withdrawal of consent in biobanking and genetic research raises a multitude of ethical challenges. Most international guidelines concur that participants have the right to withdraw their consent but are devoid of details. My view is that, for as long as the HBM and data can be linked to the participants, they should be destroyed upon withdrawal of consent unless the participants decide otherwise. In instances where the HBM and data are irreversibly anonymized, withdrawal may be impossible because of inability to identify the particular sample and data. This is in agreement with the basic ethical principle of respect for autonomy.

2.5 Risks of biobank research

When performing a risk-benefit analysis, it is always important to weigh the potential benefits expected from the research against potential risks for individuals and the wider community (Rothstein, 2005). Though physical harm is rare, possible risks may affect not only the individual but also involve the society with which participants are associated. The risks are usually social and/or dignitary. Among the social risks are stigmatization and genetic discrimination that often affect groups and can affect those participating as well as those not participating in the research. Social harm could arise when research findings indicate that certain population groups or ethnic groups are genetically predisposed to certain disease conditions (Hansson, 2011; Rothstein, 2005). There is a possibility of establishing a connection between confidential medical data and groups of people that could readily be identified after publication of research findings. Thus the Swedish law on Genetic Integrity recommends that investigators and REC ensure that information “be disguised or coded in a way that makes it impossible or very difficult to identify the group being studied” (Lag om genetisk integritet m.m. (Swedish law on Genetic Integrity), 2006, p. 417, In Hansson, 2011).

Harms to dignity “involve violations of collective rights or disrespectful treatment of the affected community” (Sharp & Foster, 2002, p. 145). Harm to dignity may not only affect the individual but also involve the entire society. For instance, the inappropriate handling of HBM in a way that is seen to desecrate the values, beliefs and cultural norms of a population group can amount to harm to dignity, not only to the individual participant but also the entire sub-population (Sharp & Foster, 2002). Existing ethical regulatory policies and guidelines emphasize immediate risks to individual participants and tend to ignore potential harms to those who are not participating directly (Emanuel, Wendler, & Grady, 2000). Hence, many ethical guidelines encourage the use of a participatory, community-based approach to research through its entire life cycle (Reid, Brief, & LeDrew, 2009). Taking into account potential harm to those not participating in research and socially discernible societies is a manifestation of respect for social and cultural diversity, and an appreciation that research results can unsettle harmony within societies. Thus, during ethics review, RECs should utilize effectively the services of community representatives when trying to weigh the risks and benefits of any given research. Attention will now be turned to the safeguarding of individual participants’ interests by protecting their personal information.

2.5.1 Privacy and confidentiality

Public willingness to take part in research is reliant on the public’s trust in biobanks. Therefore, it is paramount that participant privacy is protected at all levels of the biobank structure because a breach in privacy could significantly affect people’s readiness to participate in research (Schulte in den Baumen, Paci, & Ibarreta, 2009; Ursin, 2008). To this end, the European Medical Agency (EMA) recommended several alternatives for protecting participant data (“Data integrity: key to public health protection,” 2016). Biobanks have devised several methods of protecting personal information, for example, the use of codes. Codes are used where identities are delinked from samples/data (Witt & Witt, 2016). In single-coded samples/data, the investigator keeps the code keys. In double-coded samples/data, there is a second coding system which is kept by a third party. In coded samples/data, there is the possibility of clinical monitoring, consent withdrawal, re-contacting and return of results to donors. In anonymous and anonymized samples/data, the link with the donor is permanently destroyed.

The main objective of coding HBM and data is to safeguard the privacy of the participant; however, maintenance of absolute anonymity is almost impossible with the current advancement in genetic techniques (Witt & Witt, 2016). Though coding is the best way to safeguard personal data, it limits the scientific value of research, especially in longitudinal epidemiological studies; this is because it is

not possible to re-contact participants for consent to use stored HBM and to update healthcare information (Cambon-Thomsen, 2004; Eriksson & Helgesson, 2005; Hawkins, 2010). Participant withdrawal from research, return of results and monitoring of disease progression are all impossible. Because of the technicalities involved in the destruction of samples, withdrawal of consent, re-contacting specific participants for re-consent and the need to return results, many authors prefer coding to permanent anonymization, as the most suitable way of safeguarding privacy (Greely, 2007; Hansson, 2009).

Several countries have enacted laws and formulated policies that aim to protect personal information (DHHS; Slaughter, 2013; Wolf, Patel, Williams, Austin, & Dame, 2013). In South Africa, there are several legal instruments that govern the privacy of information. First, the safeguarding of the right to privacy is recognized as a fundamental human right in the Constitution ("South African Law Reform Commission: Privacy and data protection," 2005). However, it is not an absolute right but should balance out with other rights enshrined in the Constitution. There is no law that specifically addresses the protection of the right to privacy ("South African Law Reform Commission: Privacy and data protection,"). Second, Chapter 2 Section 14 of the National Health Act provides that "[a]ll information concerning a user, including information relating to his or her health status, treatment or stay in a health establishment is confidential" (*South African National Health Act*, 2003). However, it also provides that confidential information can only be disclosed either after written consent or by "court order or any law that requires that disclosure" (*South African National Health Act*, 2003). In essence therefore, an investigator can be compelled to disclose confidential information (Harrell & Rothstein, 2016).

Third, the Protection of Personal Information Act No. 4 (POPIA) (2013) provides for the protection of the "right to privacy of all [people] in relation to the collection, storage, use and communication of their personal information by the government or another individual". The POPIA is aimed at promoting the uninhibited flow of information, considering the right to privacy against other rights, but is subject to justifiable limitations (Andanda & Govender, 2015). However, Section 32 (5) permits the processing of personal "information concerning inherited characteristics where a serious medical interest prevails or where the processing is necessary for the purpose of scientific research or statistics" (Andanda & Govender, 2015, p. 792).

From the above analysis, it is evident that there may not be an absolute protection in all circumstances of genetic information from government and other law enforcement agencies.

Maintaining adequate privacy and confidentiality is one of the core ethical challenges associated with the contentious issue of sharing of HBM and associated data.

2.5.2 Export and sharing of HBM and associated data

The issue of sharing of human biological materials and data is riddled with legal and ethical complexities. Sharing of samples and their derivatives is cost effective and allows for the maximum exploitation of biological samples. However, the export of HBM raises pertinent ownership and intellectual property rights concerns. To address these concerns in advance, sharing of HBM is generally covered by a material transfer agreement (MTA). An MTA is a legally binding contract that governs the exchange of HBM between institutions/organizations and details the rights of the provider and recipient of the materials and any derivatives. This is generally perceived as enabling the sharing of HBM while proffering protections to local institutions (Ramsay et al., 2014).

Material transfer agreements should describe the materials, purpose of transfer and usage, any restriction to use, ownership of the materials and their derivatives, period of use, any intellectual property rights, commercialization rights, the terms of any publication arising from the materials, technology transfer, responsibilities, liability and warranty, terms of amendment and termination of the MTA (UNCST, 2014).

Over the years, there has been a one-way export movement of HBM from Africa to several destinations in the Western world with minimal benefits to the local populace, researchers and institutions (Staunton & Moodley, 2016). This has impacted negatively on the growth of local capacity, infrastructure and expertise. With the fast pace of advances in genomic research, efforts should therefore be made to ensure that South African HBM and data are used locally. In instances where the expertise or infrastructure is lacking in South Africa, efforts should be made to ensure that sharing of samples and data is non-exploitative and mutually beneficial to all stakeholders. However, there are deficiencies in the South African framework concerning the use, storage and transfer of HBM (Staunton & Moodley, 2016).

The export of HBM from South Africa is governed by the National Health Act No 61 of 2003 and samples cannot be exported without a valid export permit (*South African National Health Act, 2003*). However, many researchers and institutions are flouting this legal requirement. For example, a study done at a South African institution reported that researchers and RECs did not sufficiently address inter-related ethical and regulatory issues related to HBM (Sathar, Dhali, & van der Linde, 2013). The

authors opined that HBM were being exported from South Africa minus export certificates and MTAs because 72.2% and 94.7% of reviewed protocols did not have export certificates and MTAs, respectively. In addition a majority of researchers neither requested the permission of RECs nor sought the informed consent of research participants to store HBM for future research and export (Langat, 2005; Sathar et al., 2013).

The insistence of developing countries on the inclusion of provisions for benefit-sharing and ways of handling intellectual property rights in standard MTAs has often been rebuffed by northern research partners (Zhang et al., 2010). This is further compounded by national and institutional variations in intellectual property policies on the sharing of HBM and associated data (Vaught & Lockhart, 2012). There is a need to study sources of contention to formulate a consistent framework for comprehending the sharing of benefits and constituent clauses in MTAs (Zhang et al., 2010). The World Health Organization (WHO) recommends increased participation and acknowledgement of the contribution of investigators from countries of origin in research and specimen-utilization, and fair representation in scientific publications (WHO, 2011b).

In South Africa, there seems to be a lack of national guidance on the requirement for an MTA for transfer of HBM, yet they can be a valuable tool in protecting the rights of the donor (Staunton & Moodley, 2016). The export system appears to lay more emphasis on the export certificate (to enable the tracking of the transfer of HBM) than on safeguarding the rights of donors and local institutions (Staunton & Moodley, 2016). The most recent revised edition of the Department of Health (DoH) guidelines (DOH, 2015) is silent about the export of HBM, without even the requirement for REC oversight. The result of this is the loss of REC oversight and jurisdiction over HBM once they cross borders; as a result, any guarantees that participants may have received concerning storage, future use and confidentiality can no longer be assured, and the REC has no capacity to regulate the HBM use in secondary studies that are divergent from those views (Nnamuchi, 2015; Staunton & Moodley, 2016).

Another weakness in the South African health research ethics guidelines is ambiguity concerning the requirement for donors to consent to the export of their HBM (DOH, 2015). The Organisation for Economic Co-operation and Development (OECD) guidelines on human biobanks require that all participants be informed of access to their HBM, in addition to export across borders (OECD, 2009). The guidelines recommend the approval of all future research by a REC, but the South African health research regulations are non-committal on the required consent prior to the transfer of HBM abroad

(Staunton & Moodley, 2016). Therefore, there is need to streamline the regulations and guidelines for HBM and data transfer to rid them of any existing ambiguities (Whitley, Kanellopoulou, & Kaye, 2012). It is also important to determine stakeholders' perspectives on this topic. Related to sample export and sharing is the concern of ownership; who owns the sample and associated data?

2.5.3 Ownership of biological samples and data

Human biological materials are the shared property of patients and participants, researchers, and the institution to which the investigators belong; this means that any responsibilities and benefits should ideally be shared (O'Brien, 2009). This was recognized by the World Health Organization Recommendation 19 (2003, p. 19) which states that:

Serious consideration should be given to recognising property rights for individuals in their own body samples and genetic information derived from those samples. In all circumstances, the provision of research materials, including DNA samples, should be on the undertaking that some kind of benefit will ultimately be returned, either to the individual from whom the materials were taken or to the general class of person to which that individual belongs.

These tissues are often collected and stored for use in the future, awaiting the advancement of novel methods or for additional investigations of interest. One may ask whether "investigators have an ethical obligation to patients beyond the time at which they donate their HBMs" (Knoppers, Joly, Simard, & Durocher, 2006, p. 1170), "even though the courts have decided that the patient relinquishes their rights to the HBMs once they are donated" (Barnes & Heffernan, 2004; Kaiser, 2006). Therefore, any responsibilities and benefits should be shared (O'Brien, 2009).

Over the years, several instances of biobank governance misconduct by researchers from developed countries have been highlighted in the literature. The main point of contention in these disputes is the question of who has the entitlement to control the use and sharing of HBM and their derivatives (Vaught & Lockhart, 2012). There have been accusations of contravention of national guidelines (Mudur, 2002), cultural indifference (Mello & Wolf, 2010), fraud and theft of intellectual property (Andanda, 2008), exploitation of participants (Emerson, Singer, & Upshur, 2011), inequitable benefit-sharing (Zhang et al., 2010), exclusion of local investigators from publication authorship (Emanuel, Wendler, Killen, & Grady, 2004), loss of revenue to uncontrolled export of HBM (Upshur, Lavery, & Tindana, 2007) and allegations of viewing African institutions and their investigators as sample-collecting centres and collection technicians respectively (Ndebele, 2007).

Large quantities of HBM have been shipped from low-resource to developed countries for storage because of lack of biobanks in Africa (Staunton & Moodley, 2013). The fate of these HBM is unknown because regulatory authorities/bodies from most resource-limited countries have no mechanisms for monitoring HBM once they cross their borders (Andanda et al., 2011; Brown, 1998). Therefore, there is a need to keep track of HBM collected from varying research activities. Several other disputes over ownership of HBM have been documented in the literature, for example, the Catalonia case between Dr William Catalonia and Washington University ("Who owns your body? ,"), the case of Greenberg versus the Miami Children's Hospital Research Institute (United States District Court, 2003), the Havasupai cases (Mello & Wolf, 2010), and many more.

Studies show that people are willing to donate their HBM and have a high level of trust in research aimed at advancing scientific knowledge and treatment of disease (Hansson et al., 2006; Kettis-Lindblad et al., 2006). In reciprocity, investigators ought to be transparent and have an obligation to inform participants that their HBM are being kept for future research which may involve trans-border transfer (Dhai & Mahomed, 2013; Tindana, Molyneux, Bull, & Parker, 2014).

A study carried out to determine research participants' perspectives on sample export and sharing in South Africa reported that, while researchers considered the provision of biological samples as a donation, participants believed that they still had ownership rights (Moodley et al., 2014). In the same study, almost half of the respondents were in favour of benefit-sharing and expressed the wish to be re-contacted for consent for any secondary use of their samples for research. Most potential sample donors expect to have a say in the utilization of their biological samples and associated information (Chen et al., 2005; Trinidad et al., 2010).

Many patients are uncomfortable with researchers accessing their health records without specific consent. They feel respected if they are notified whenever their samples are used. Others would not mind a surrogate decision-maker like a REC to decide on their behalf (Hoeyer et al., 2004). Informed consent may be needed for a study as well as for biobanking of specimens because some participants may object to their HBM being stored indefinitely and for unspecified research purposes. Instead of focusing on the notion of ownership, some authors have proposed the custodian model that focuses on the nature of the duty to the research participant (NCI, 2011; Yassin et al., 2010). The National Cancer Institute best practices define custodianship as the "caretaking responsibility for biospecimens that extends from collection through research use" (NCI, 2011, p. 31). In this model "the custodian is the trusted intermediary and caretaker of biospecimens and

associated data, and the custodian's caretaking responsibilities should align with applicable ethical and policy standards" (NCI, 2011, p. 31). In this case, biobanks are just custodians of the HBM and data in their possession. Custodians of these resources should establish "a governance plan consisting of the set of authorities, processes, and procedures guiding key operational decisions made within the resource" (NCI, 2011, p. 31). They should also exhibit their answerability in order to foster public trust by accepting certain custodial obligations. Closely related to ownership are the concepts of fair benefit-sharing, stewardship and governance.

2.5.4 Fair benefit and stewardship

Agomoni Ganguli-Mitra (Ganguli-Mitra, 2008, p. 218) posed the following questions regarding benefit-sharing in biobank research: 'When does the obligation to share benefits exactly arise?'; 'Who should be the beneficiaries of a benefit-sharing arrangement?'; 'What does a fair benefit constitute?'; and 'How should benefits be shared without making them undue inducement?'

Though research participants are often willing to donate samples, many object to the use of their samples in commercial ventures while others indicate that they would at least wish to share in any profits accrued from their samples (Moodley et al., 2014; van Schalkwyk et al., 2012).

O'Brien (O'Brien, 2009, p. 195) asks: "Who controls the specimens, the biobank, the intellectual property, and the data, and who gets access to use them and under what conditions?" In response to the several court cases on the ownership of HBM, Dressler (2007, In O'Brien, 2009) suggested four guiding principles on the ownership and custodianship of HBM repositories: 1) encouragement of openness of scientific inquiry so as to maximize the full potential of HBM use and sharing in promoting health; 2) ensuring the privacy of participants and including provisions for the unforeseen use of HBM in informed consent; 3) respect for investigators' intellectual input in the development of biorepositories; and 4) protection of ownership information and addressing the concerns of funding agencies during specimen-sharing.

The World Health Organization (2003) consultations on the impact of genetic research on humans and patients observed that, though Intellectual property is an essential incentive to research, developing countries were at a disadvantage. They proposed what they thought were suitable forms of benefit-sharing. They proposed local community involvement, nurturing of local research and human resources, in addition to contributing to general medical care and keeping participants informed on the progress of the research. Researchers and policy makers opine that intellectual

property rights for research on exported HBM should be shared with local scientists and communities (Zhang et al., 2010). Local principal investigators would also like to be consulted whenever any samples exported from their repositories are used for new research (Zhang et al., 2010).

Biobanks should have management and operational frameworks. In order to obtain valid analytical results, the collection, processing and storage, quality assurance and control, and distribution of HBM and associated information should follow standardized methods (Vaught & Lockhart, 2012). Several institutions and organizations have developed and published best practice guidelines for proper handling of HBM, as well as ethical and regulatory practices (Eiseman & Haga, 1999). They have also developed universal standard operating procedures (SOP), compatible informatics systems and harmonized informed consent and material transfer procedures to co-ordinate their HBM collection (Vaught, Kelly, & Hewitt, 2009).

There is a need to harmonize regulations applying to biobank access and utilization. These regulations should unequivocally encompass HBMs, medical information and genetic data accumulated in the various biobanks around the world. These regulations should be lawfully binding and applicable in the participating countries as when the Nuremberg Code and Helsinki Declaration were enacted (O'Brien, 2009). According to O'Brien (2009, p. 205), "[t]he role, responsibilities, and benefits to the principal investigators of the study, to the custodian/steward of the specimens, and to their institution should be clearly defined".

Consensus on the ownership of HBMs and their associated data, and the sharing of proceeds therefrom seems to be a long way off. I propose that a stewardship model of biobank governance be adopted because governance decisions are made with regard to participants' autonomy because the decision-makers act as stewards and not owners of the HBMs (Dressler, 2007).

2.6 Governance of biobanks

Some aspects of biobank governance have already been discussed in the preceding sections; however, some issues require more in-depth consideration. Biobank governance requires developing trust, acceptance and meticulous political negotiation (Gottweis & Zatloukal, 2007). Biobanks are governed by national legislation and guidelines. Unlike most countries in sub-Saharan Africa, South Africa has gone a long way towards streamlining legal and ethical regulations to govern the utilization of human tissue samples. At the national level, the governance of biobanks is provided for

in the National Health Act No. 61 of 2003. The DoH also gives a relatively comprehensive set of guidelines that address the following: a wide range of biological tissues, their associated information and methods of acquisition; autonomy; responsibility of institutions; consent requirements; waiver of consent requirements; confidentiality; and human tissue repositories (DOH, 2015). Research ethics committees are delegated the function of overseeing the operation of biorepositories and their data management centres. The supervisory roles include (but are not limited to): review and approval of protocols; ensuring adequate protection (privacy and confidentiality) of participants; and review and approval of HBM acquisition and distribution.

The H3Africa project plans to develop repositories for human tissues in several African countries with the aim of fostering scientific research collaborations across borders. Studies have shown that this might not be easy to achieve since there is discord in the ethico-legal frameworks concerning the acquisition, storage, transport and sharing of human biological materials and associated data (Staunton & Moodley, 2013). There is no standard guidance on the re-use of biological specimens in sub-Saharan Africa. Regulations on export of biological tissues are silent on the issue of consent prior to removal of the sample. They require signing of an MTA and approval from the REC (Cambon-Thomsen et al., 2007). To mitigate this, the developed world has established institutions like Biobank and Biomolecular Resources Research Infrastructure- European Research Infrastructure Commission (BBMRI-ERIC), a 54-member consortium with more than 225 associated organisations (largely biobanks) from over 30 countries.

In summary, biobank governance is complex with regard to ethical and legal requirements. As an emerging field in Africa, there is a need to harmonize biobanking regulations across borders. These regulations and guidelines need to be entrenched in national legislation with special consideration given to potential socio-cultural challenges. It is imperative that the cultural and social beliefs and practices of the potential study population be considered as a way of developing trust (Budimir et al., 2011).

2.7 Community engagement and cultural issues

So as to protect the autonomy of human participants, any cultural attributes that may influence their decision-making during the informed consent process must be taken into consideration (Halkoaho, Pietilä, Ebbesen, Karki, & Kangasniemi, 2015). Culture is multifaceted and can be influenced by national, ethnic, religious, regional and generational aspects; this creates cultural disparities. Investigators must recognize and respect cultural aspects that influence participant

decision-making capabilities so as to obtain proper informed consent (Halkoaho et al., 2015). The WHO also emphasizes the significance of population- and community-based concerns in the ethics review process (WHO, 2011a).

Research results can cause disruption of social relationships between communities. Respect for the various social and cultural traditions within and between communities should therefore be considered, right from the inception of the research, to avert social harms (Sharp & Foster, 2002). There is a need for culturally sensitive recruitment and study designs (Denny, Silaigwana, Wassenaar, Bull, & Parker, 2015). The research team should have respect for cultural disparities and human dignity, as a way of creating a basis for confidential and appreciative treatment of participants. Social groups are often wary of the potential stigma and polarization associated with susceptibility for certain diseases. Historically, lack of respect for cultural traditions and beliefs has instigated discord and dissonance in society. An example of this was the harm to dignity against the Havasupai Indian community in USA where blood samples initially taken for the investigation of diabetes mellitus and mental health problems were used for genetic tests to which the community had not consented (Mello & Wolf, 2010).

In the context of cultural issues in biobanking, two terms which are often used interchangeably need be defined: community and ethno-cultural community. Community is used “to describe a wide variety of human associations: ethnic, cultural, political, religious, geographical, municipal, professional, artistic, sexual, and even disease communities” (Weijer, 1999, p. 501). An ethno-cultural community is defined as “a community or a group defined by the shared characteristics unique to, and recognized by, that group” (Canada Reserve "Canada reserve agency. Policy Statement: Applicants Assisting Ethnocultural Communities. Reference Number CPS-023," 2005). This definition also encompasses “characteristics such as cultural traditions, ancestry, language, national identity, country of origin and/or physical traits” (Godard, Ozdemir, Fortin, & Égalité, 2010, p. 469).

It is a requirement by funding agencies that individual participants and social groups are protected (National institute of Health, 2002). Therefore, it is crucial to appreciate the perceptions, beliefs and values of ethno-cultural communities in establishing robust public partnerships (Godard et al., 2010). International guidelines stipulate that individual consent cannot be substituted by group consent. However, consultations with cultural authorities can be done for additional consent in consideration of stigmatization and discrimination risks (Forsberg, Hansson, & Evers, 2013).

Studies have highlighted the importance of including ethno-cultural community leaders in the success and sustainability of biobanks (Godard et al., 2010). Emphasis is further put on the importance of educating community leaders on some of the pertinent issues with regard to biobanking, to avoid misconceptions. Studies on the perceptions of community leaders show that they support genetic research as long as it is for the good of their communities. However, they insist on ethical and legal guidelines of biobank governance; restriction on the use of results for commercial gain; openness; privacy and confidentiality; and justification for use of genetic information (Godard et al., 2010). Though controversial, some community leaders were of the view that population databases could be used in forensic investigations to apprehend criminals (Godard et al., 2010). It is therefore prudent that community members are provided with understandable information on the nature, objectives and connotations of biobanks in order to promote public trust (Godard et al., 2010).

Cultural issues should always be borne in mind right from the start when establishing human tissue repositories. Socio-cultural and institutional factors continuously influence the way sample donors perceive themselves and view biobank research (Petersen et al., 2014). Thus, researchers and REC professionals should always bear in mind cultural idiosyncrasies that might potentially lead to harm if not addressed adequately. Ethical challenges involving minors as research participants in biobank research will be discussed next.

2.8 Inclusion of minors as research participants

The Health Professionals Council of South Africa (HPCSA) guidelines for good practice in the health care professions set the age limit for legal competence for medical treatment at 12 years, whereas the legal age limit for giving informed consent for research is 18 years. This is particularly important in medical care when, for example, pathological specimens which are initially not meant for research are obtained (HPSCA, n.d). Children present the most vulnerable group because they have limited capacity to comprehend the ethical and other issues associated with biobanking (Budimir et al., 2011; Strode, Slack, & Essack, 2010). Though many authors are supportive of the idea of including children in biobank research, many biobanks are hesitant to include them because of ethical complexities. Some authors have even suggested banning of the sharing of children's data until they reach the legal age to give specific consent (Gurwitz, Fortier, Lunshof, & Knoppers, 2009). However, others argue that such proposals may lead to failure of medical research on children to develop.

Professionals do appreciate the utility of pediatric samples for research and recommend ongoing provision of sufficient information to parents and children about the storage and intended use of HBM and associated data, in addition to the consequences to the parent and child (Dove, Avard, Black, & Knoppers, 2013; Gurwitz et al., 2009). This is important because research suggests that parents do not always understand all of these aspects during the informed consent process (Klima et al., 2013). Experts assert that in addition to parental consent, children should be given the right to assent as they grow older and are able to understand the implications of storage of their HBM for future studies (Hens, Snoeck, Nys, Cassiman, & Dierickx, 2010).

The provision of assent is recognised in the United Nations Convention on the Rights of the Child (UN, 1998). The use of proxy decision-makers in research involving minors is well recognised. However, policy makers and RECs should encourage minors to make their own decisions, especially as they become of age and develop the ability to understand the implications of the research. Whenever possible, consent from children should be obtained, in addition to parental consent (Davidson & O'Brien, 2009). This should be done in concert with RECs so as to protect children's interests (Davidson & O'Brien, 2009; Merlo, Knudsen, Matusiewicz, Niebroj, & Vahakangas, 2007).

Several authors have argued that minor participants must have the choice of whether to re-consent or withdraw earlier parental consent, on attainment of the age of majority (Brisson, Matsui, Rieder, & Fraser, 2012; Hens, Cassiman, Nys, & Dierickx, 2011; Hens et al., 2010; Kranendonk, Ploem, & Hennekam, 2015). This is on the premise that the original proxy consent provided by the parent was made in the best interest of the child, while consent allows the adult child to express his/her own wishes and autonomy (Alderson, Sutcliffe, & Curtis, 2006; Hens, Levesque, & Dierickx, 2011). Re-contacting mature children is an essential requirement for regulations on biobanking in children (Kranendonk et al., 2015) but the exact age for this requirement under South African law and ethical guidelines is obscure.

2.9 Returning the results to participants

Return of research results and incidental findings has far-reaching ethical and social implications. The American College of Medical Genetics recommends that patients be informed of highly actionable incidental findings because of the potential benefit, irrespective of patient preferences (Green et al., 2013). Researchers have a moral duty to notify participants of any significant findings of interest (Bredenoord, Onland-Moret, & Van Delden, 2011). However, ethically "participants have the right to know and the right not to know the results of research" (Budimir et al., 2011, p. 268).

This has generated much debate in the literature, with several authors in favour and others against it (Lemke, Bick, Dimmock, Simpson, & Veith, 2013).

This issue is equally contentious in pediatric research, especially with regard to incidental findings of genomic and genetic tests (Dressler et al., 2012; McGuire & Beskow, 2010; Wright, Koornhof, Adeyemo, & Tiffin, 2013; Yu, Crouch, Jamal, Tabor, & Bamshad, 2013). However, the American Academy of Pediatrics (AAPA) encourages parents or guardians to inform children about genetic testing and also advises them to respect any requests from mature adolescents regarding result disclosure (AAPA, 2013). It also encourages the return of results as stated in this excerpt: "... results from genetic testing of a child may have implications for the parents and other family members. Healthcare providers have an obligation to inform parents and the child, when appropriate, about these potential implications" (AAPA, 2013).

The main purpose of biobank research is to increase knowledge rather than provide clinical care, just as standard operating procedures in research laboratories may not necessarily be applicable in clinical laboratories (Clayton, 2012). Therefore, returning findings before validation of their clinical significance can potentially cause harm to participants, especially when misinterpreted (Clayton, 2012; Clayton & McGuire, 2012). Indeed, "[t]his is particularly true if no relevant treatment or prevention modality to combat the investigated risk is yet available" (Helgesson et al., 2007, p. 974). If the research is expected to generate clinically relevant findings, close collaboration with clinical departments must be carried out right from the start to enable proper disease management (Hansson, 2011). Therefore, some authors are in favour of returning results to individual participants, especially if they are of very high clinical importance and there is an effective remedy that could to a large extent improve health or save life. This should be done properly and professionally (Budimir et al., 2011). In practice, the governing policies of the majority of biobanks are inclined towards not returning results, although several authors agree that this is not always ethical (Bovenberg, Meulenkamp, Smets, & Gevers, 2009; Greely, 2007). However, researchers have a duty to publish all pertinent findings for the betterment of society (Budimir et al., 2011).

Hanson (2008, p. 218) suggested six conditions to be taken into account when communicating "genetic information that had not been asked for by individual participants". These conditions include one or more of the following:

- (1) that the information is reliable according to medical science or tested experience, (2) that the information is linked to a reasonably certain risk of illness, (3) that the illness is of a

reasonably serious kind or is at least nontrivial, (4) that the genetic component has high penetrance, (5) that there is an effective prevention or treatment, (6) that personal support and regular check-ups are offered.

The issue of return of results should be clearly addressed during the informed consent process and participants should be given all the available options so that they are in position to make an informed decision on this issue. In the case of researchers intending not to return results (including incidental findings), such researchers have the responsibility of explaining this to participants. Lastly, the role of RECs in biobanking will be discussed.

2.10 The role of research ethics committees

Research ethics committees (RECs) play a vital role in protecting the rights and welfare of donors with respect to the usage of their HBM in undefined future research studies. Ethico-legal frameworks delegate the function of overseeing the acquisition, storage and usage of HBM for research to RECs. Thus, all scientific research utilizing human samples should be ethically reviewed and approved by RECs (CIOMS, 2009; DOH, 2015; WMA, 2013). The OECD guidelines on human biobanks recommend the approval of all future research by a REC (OECD, 2009). However, RECs in sub-Saharan Africa have several challenges hampering their effective functioning including lack of membership diversity, insufficient training of members, insufficient capability to review and monitor studies, lack of resources and lack of national ethics guidelines (De Vries et al., 2015; Milford, Wassenaar, & Slack, 2006; Nyika, Kilama, Chilengi, et al., 2009; Nyika, Kilama, Tangwa, Chilengi, & Tindana, 2009; Ochieng, Ecuru, Nakwagala, & Kutwabami, 2013; Rodriguez, Hanna, & Federman, 2003; Silaigwana & Wassenaar, 2015).

To preserve public trust, RECs should evaluate the risk-benefit relationship for donors for every new study on the samples. RECs should review the information security measures, coding measures and other potential risks that could emanate from changes in research administration. For each individual study, the REC should decide whether informed consent should be obtained (Beauchamp & Childress, 2009). The roles of RECs in risk-benefit analysis, waiver of consent, and informed consent have already been discussed in the preceding sections. In this section, emphasis will be put on a few pertinent issues.

Research ethics committees function under ethical and legal structures entrenched in national statutes, which require that participants are protected from harm and that their samples are used

appropriately (Winickoff & Winickoff, 2003). Researchers and REC professionals have always had divergent views on re-consent and potential harm resulting from re-identification of genetic data (Edwards et al., 2012). Informed consent for research evolved from consent for medical care and some stakeholders find problems distinguishing the two. Therapeutic and research ethics differ; therefore, RECs should, according to Hansson (2011), refrain from the intuitive response of applying ethical principles that evolved from the doctor-patient relationship to research ethics. For this reason, many biobanking initiatives have established separate RECs in their governance structure. However, some authors have expressed their scepticism about this issue because the mandate of these RECs is ambiguous, with members often elected by biobank-affiliated interest groups, which, in the process, creates additional unnecessarily costly bureaucratic hurdles (Hansson, 2011).

Informed consent forms are becoming increasingly long, complicated and harder to understand. They have become more intimidating and perhaps impede rather than improve understanding (Emanuel, Grady, & Menikoff, 2008). Because of this, stakeholders have advocated for more simplified consent forms (NCI, 1998, 2008). Furthermore, participants, researchers and REC professionals have differing perspectives with regard to the informed consent process (Beskow, Friedman, Hardy, Lin, & Weinfurt, 2010).

Studies on the attitudes of researchers on the informed consent process have drawn mixed reactions. Whereas some researchers are highly critical of the ethical review process, others are appreciative especially with regard to the protection of human participants (Whitney et al., 2008). However, research ethics review systems have been criticized for delaying the implementation of research and deterring the emergence of young researchers in human research (Burman, Reves, Cohn, & Schooley, 2001; Elwyn, Seagrove, Thorne, & Cheung, 2005; Green, Lowery, Kowalski, & Wyszewianski, 2006).

Research ethics review systems have also been blamed for: use of lengthy consent forms that are unsuitable and difficult to understand; dwelling on minute details; and protection of institutions rather than research participants. Multicentre and biorepository research have been identified as one of the most affected by inconsistencies in the REC system (Whitney et al., 2008). Though investigators often criticize the REC system, distinctions should be made between faulty implementation of procedures by local RECs and problems integral to the REC system or the guiding regulations themselves (Whitney et al., 2008).

Research ethics committee members have also been accused of depending on their instincts rather than careful scrutiny of situations in making decisions (Rid, Emanuel, & Wendler, 2010). Other RECs depend on non-scientific (community) members for information on public attitudes, customs, cultures and inclination (Rid et al., 2010). They also tend to over-rate the potential of psychological and emotional harm (Fendrich, Lippert, & Johnson, 2007). To mitigate discrepancies in decision-making by RECs, Anderson and Dubois (2012) suggested the use of evidence-based research ethics review (EBRER).

From the above discussion, it is noted that consensus on a wide range of ethical issues concerning research utilizing HBM is far from being realized. At the centre of it all is the requisite respect of participants' right to self-determination and protection from any unforeseen harm. Research ethics committees are mandated to ensure that participants' rights are upheld and participants are afforded adequate protection in the use of their tissues for research. Therefore, this study was aimed at exploring stakeholders' experiences and perspectives on informed consent and ethics review of research involving human biobanks in SA, with the goal of obtaining information that could contribute to the harmonization of ethical guidelines on the consent process and biobank governance.

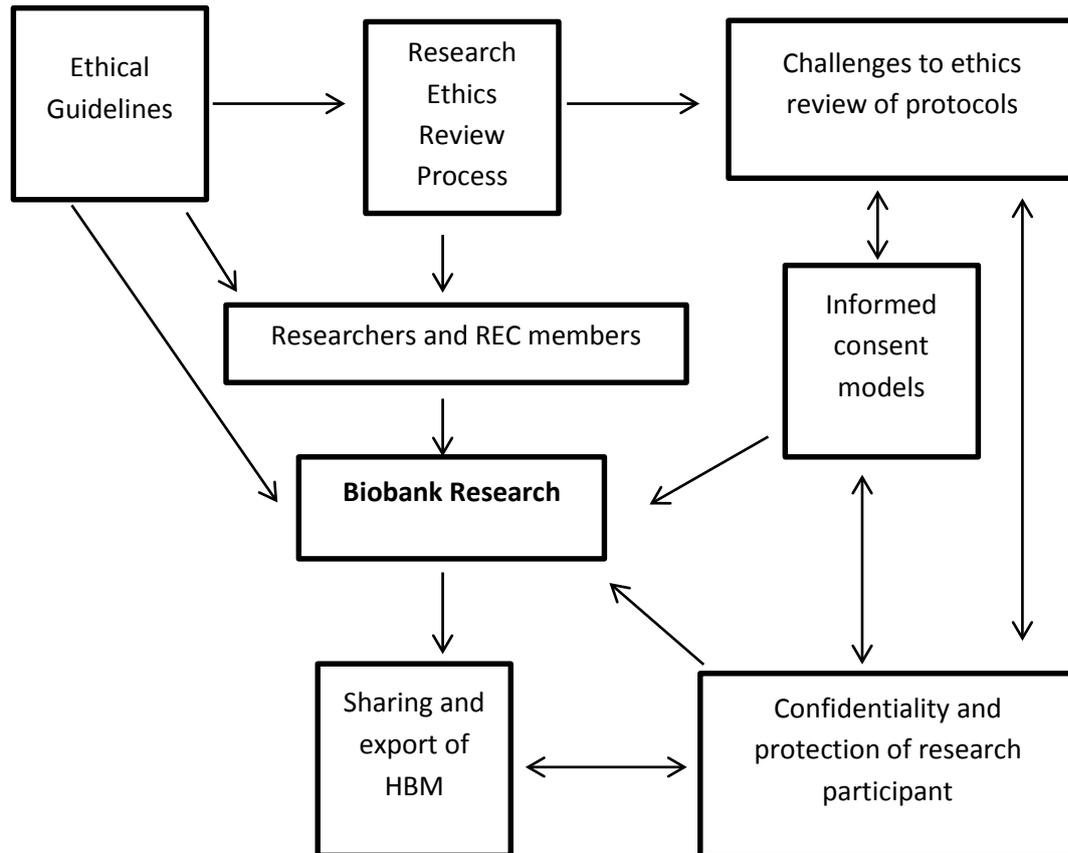
2.11 Rationale of the study

Over the years, several allegations of breach of biobank governance norms and standards by researchers from developed countries have been highlighted in the literature (Emanuel et al., 2004; Emerson et al., 2011; Mello & Wolf, 2010; Mudur, 2002; Ndebele, 2007; Upshur et al., 2007; Zhang et al., 2010). In addition, large quantities of HBM whose fate is unknown have been shipped from low-resource to developed countries (Staunton & Moodley, 2013). This has partially been attributed to weak regulatory systems (Whitney et al., 2008). Research ethics committees are guided by national and international ethical and regulatory frameworks with regard to the acquisition, storage and use of HBM for research purposes. However, not all RECs are fully informed about these regulatory requirements (Sathar & Dhali, 2012). Research ethics committee systems have been criticized for delaying the implementation of research (Burman et al., 2001; Elwyn et al., 2005; Green et al., 2006). They have also been blamed for: use of lengthy consent forms that are unsuitable and difficult to understand; dwelling on minute details; and, protection of institutions rather than research participants. Previous studies in South Africa have reported non-adherence of researchers and sponsors from developed countries to ethical guidelines with regard to the acquisition and use of HBM in international collaborative research (Sathar et al., 2013). To the best knowledge of the

author, no empirical study has been conducted in South Africa to determine the opinions and perspectives of REC members, bioethicists, researchers and scientists on the ethical issues in research involving human specimen resource repositories in this country. Therefore, as a prelude to streamlining biobank activities in the country, there is need to obtain the views and perspectives of stakeholders in the biobanking industry.

2.11.1 Conceptual framework

Figure 1: Conceptual framework



Biobank research must go through an ethics review process to ensure that it complies with regulatory standards. Ethics review of research aims at ensuring that the rights, safety and welfare of research participants are protected; and this can be achieved through appropriate informed consent processes and the protection of research participants' confidentiality. Several consent models have been proposed and are currently being used in biobanks research however some of them are not well suited for this type of research (Chalmers, 2011; Colledge et al., 2014; Eriksson & Helgesson, 2005; Hansson, 2011; Helgesson & Johnsson, 2005; Master & Resnik, 2013; Mello & Wolf, 2010; Tasse et al., 2010). Biobank research involves the sharing of HBM and associated data hence, the need for harmonization of ethical guidelines and regulatory processes within countries and across borders to ensure that they are robust, comprehensive and facilitate international

collaborative research. For this to be achieved there should be meaningful engagement of all key stakeholders (researchers and REC members) in the research industry to ensure that they clearly understand and appreciate the ethical issues associated with the collection, storage and future use of HBM. In this era of technological advancement coupled with the rapid evolution of biobanking and related research, there is need for dynamic and innovative informed consent approaches if the rights, safety, and welfare of research participants are to be adequately protected. At the same time, there is also need for regular review of ethical guidelines and regulatory processes to ensure that they evolve in tandem with technological advancement and innovative research methods and practices. This study therefore aimed to determine the perspectives of stakeholders on informed consent and the ethics review of biobank research to obtain information that could contribute to streamlining biobank research.

2.11.2 General objective

The general objective of this study was to explore stakeholders' perspectives on informed consent and ethics review of biobank research in South Africa with the aim of obtaining information that could contribute to the harmonization of ethical guidelines on the consent process and biobank governance.

2.11.3 Specific objectives

The specific objectives of the study were:

1. To establish stakeholders' attitudes towards the ethics review process in research involving the future use of HBM and associated data.
2. To determine stakeholders' perspectives on informed consent and the protection of participants in research involving biobanks.
3. To identify obstacles in the ethics review process that affect research involving biobanks.

CHAPTER 3: METHODOLOGY

3.1 Research design and methodological/theoretical approach

This was a pilot survey study that was designed to investigate the applicability of two survey instruments that were developed to explore general views of researchers and REC members on informed consent and ethics review of biobank research. The study employed a positivist approach that used quantitative data collection methods. Positivism as a research approach is grounded on the ontological principle and doctrine “that truth and reality is free and independent of the viewer and observer”(Aliyu, Bello, Kasim, & Martin, 2014, p. 81). The positivist paradigm emphasizes that “genuine, real and factual happenings could be studied and observed scientifically and empirically and could as well be elucidated by way of lucid and rational investigation and analysis”(Aliyu et al., 2014, p. 83). This approach involved quantitative research methods that focused on facts and enabled the objective collection and interpretation of data with observable and quantifiable research findings. It also allowed the determination of the validity, reliability and generalizability of research findings. Opponents of positivism assert that it lacks the unique ability to interpret personal experiences. Thus, “[i]t regards human behaviour as passive, essentially determined and controlled, thereby ignoring intention, individualism and freedom” (Cohen, Manion, & Morrison, 2007, p. 18). Therefore, as a way of enhancing the depth of the data to be collected, both open and closed ended questions were used.

3.2 Study sites and population

The study was carried out at Stellenbosch University, the University of KwaZulu-Natal and affiliated research institutions such as the Centre for the Aids Programme of Research in South Africa (CAPRISA), the Africa Centre for Health and Population Studies and the KwaZulu-Natal Research Institute for Tuberculosis and HIV (K-RITH), as well as six RECs. Several RECs in the KwaZulu-Natal and Western Cape provinces were approached for permission to include their members in the study but only the following responded positively: Stellenbosch University Health Research Ethics Committees (SU-HREC), University of Kwazulu-Natal Biomedical Research Ethics Committee (BREC), SA Medical Research Council Ethics Committee, Hospice Palliative Care Association of South Africa Research Ethics Committee, Human Sciences Research Council Research Ethics Committee and uMgungundlovu Health Ethics Review Committee. Respondents included clinicians, researchers, bio-ethicists, pathologists, laboratory or biobank managers and REC professionals.

3.3 Sample size estimation

Since there had been no previous web-based research in this area in South Africa, the calculation for the sample size was based on the assumption that 50% of respondents would be well conversant with ethical issues in biobank research. With an estimated population of 2,000 researchers and REC members participating in biobank research, and a design effect of 1.2, the target population was estimated to be 387 for a power of 0.95; this was done using the Open Source Statistics for Public Health (OpenEpi, n.d.) online sample size estimator. Assuming a non-response rate of 20%, the final sample size was estimated at 465 participants.

3.4 Method of data collection

Both positivist and phenomenological approaches to data collection were employed. Data was collected using online self-administered questionnaires with both closed-ended and open-ended questions. Self-administered online questionnaires were chosen because they are convenient, cost-effective, less time consuming and reduce interviewer bias (Schonlau, Ronald Jr, & Elliott, 2002).

3.4.1 Survey instrument

The survey instruments were developed from several studies in the literature that reported on the perspectives of researchers and REC professionals (Edwards et al., 2011; Edwards et al., 2012; Hens et al., 2010; Lemke et al., 2010). Two different survey instruments were used; one for researchers (Appendix I) and another for REC members (Appendix II). These instruments comprised different types of response categories that varied based on the questions and included: either yes/no/uncertain options, Likert scales (e.g. 5-point scales rating agreement or likelihood of the statement with a sixth 'Don't know' option), categorical responses and open-ended questions. Open-ended questions facilitated in-depth probing for further information. Data scales (Likert, 1932) were used to determine attitudes and perspectives, whereas the open-ended questions were used to acquire more in-depth information about challenges in ethics review and sample/data sharing.

The REC members' survey instrument had a total of 26 items, including a subset of demographic questions, whereas the researcher instrument had 37 items. The REC members' survey instrument covered four general topic areas: demographic information (6 questions), REC application and review process (8 questions), informed consent (7 questions) and human participant protection (5 questions). The researchers' survey instrument covered five general topic areas: demographic information (9 questions), REC review process (1 question), informed consent (both for adults and minors < 18 years) (14 questions) and human participant protection (7 questions). It also included

two open-ended questions, one on opinion on the export and sharing of human biological specimens and associated data and the other on challenges in research ethics review. All survey questions were pretested and adjusted accordingly to ensure that all questions were clear and understandable.

3.5 Study procedure

The study employed a purposive sampling technique. Selection criteria included either or both of the following: 1) active participation in research biomedical research and/or health care and 2) involvement in the ethical review and regulation of research. The survey was distributed to researchers from the University of KwaZulu-Natal (UKZN) and affiliated research institutions such as CAPRISA, K-RITH and the Africa Centre for Population Health, and Stellenbosch University (SU). The survey was also distributed to members of selected RECs using two electronic survey programs (LimeSurvey and SurveyMonkey®).

After obtaining full approval from UKZN BREC and SU-HREC, official permission was obtained from UKZN and SU administrations to include their staff in this study. Permission was also obtained from UKZN-affiliated research institutions and REC secretariats. At UKZN, the names and email contacts of potential respondents were obtained from the respective official institutional websites and a list of 410 members was generated. Invitation emails were sent to all members on the list. At Stellenbosch University no list was generated; instead, the link to the surveys was included in a weekly e-mail newsletter, *Impromptu*, that is distributed to all staff members every Monday, and this was done consecutively for one month.

For RECs, administrators/coordinators were requested to distribute to members the link to the survey. An invitation email was sent to all potential respondents requesting them to participate in an anonymous online survey. Included in the mail was a brief introduction of the investigators, the sponsor (SARETI), a summary of the purpose of the study, links to the informed consent form and the survey, and a description of the confidentiality policy. Survey instruments were initially distributed by a UKZN server using LimeSurvey software; however, later on, distribution was done using the SurveyMonkey® online program after experiencing technical problems with LimeSurvey. Completion of the survey implied consent. Responses were anonymous and de-linked from email addresses; each respondent was automatically assigned a special code by the software. On average, five reminders were sent.

3.6 Validity, reliability and rigour

The rigour of a positivist approach lies in the ability for objective collection and interpretation of data, with observable and quantifiable research findings.

The survey instrument provided adequate coverage of the topic of study based on what was obtained from the review of literature. Internal consistency and reliability were ensured by item analysis of the questionnaire during pre-testing. The 'final copy' of the questionnaires was piloted on six respondents. The survey instrument was sent by email and questions and comments (if any) were requested. On receiving back the completed questionnaires, all comments were addressed to clean and improve the questionnaire. The adjusted instrument was then tested on 'new respondents'. This procedure was repeated until there were no more questions or comments. Questions were scrutinized and amended until the researcher was satisfied that they were accurate and covered the scope of the study. Data entry and analysis were done using computer software to ensure accuracy of study results. The use of a purposive sampling technique in addition to a low response rate may affect the validity and generalizability of research findings to the broader communities of biomedical research, other genetic researchers, and REC professionals.

The use of open ended questions did not provide respondents with the opportunity to give an in-depth account of their perspectives. However, direct quotes have been included in the result section to give a true account of respondents' responses and assure credibility and conformability of study findings.

3.7 Data analysis

For quantitative data, data spreadsheets were downloaded from LimeSurvey and SurveyMonkey® and exported to STATA 13 (StataCorp LP, Texas, USA) where, after checking for duplicate entries, a preliminary analysis of each variable was made to identify additional range and omission errors. Descriptive summary statistics were used to summarize the data. For each Likert scale, five categories were collapsed into three, combining 'strongly agree/somewhat agree/Very likely/somewhat likely'; 'neutral and don't know'; and strongly disagree/somewhat disagree/very unlikely/somewhat unlikely'. This was done to facilitate analysis and interpretation. Ordinal logistic regression analysis was used to assess differences in opinions between respondents who had ever participated in biobank-related research and those who had not. A p-value of <0.05 was considered significant.

Conventional content analysis (Hsieh & Shannon, 2005) was used for the data collected using open ended questions. This entailed first identifying significant statements or quotes that provided understanding of participants' opinions on the export and sharing of HBM and associated data, and perceived challenges to informed consent and ethics review (Creswell, 2007). Since data can elicit varying interpretations of participants' experiences, it is imperative that "clusters of meaning from significant statements" be developed into themes (Creswell, 2007, p. 61). These themes were then used to construct "descriptions of what the participant experienced, or textural descriptions, and descriptions describing the context or settings that influenced the experience, or structural descriptions" (Creswell, 2007, p. 61). "Amalgamation of the textural and structural definitions gives an integrated descriptive account" (Campbell, *Introductory Methods to Qualitative Research: Course Notes* n.d., p. 6). Data from both groups was analysed separately.

3.8 Ethical considerations

The study was conducted in accordance with three basic ethical principles described in the Belmont Report, namely respect for persons, beneficence and justice ("The Belmont report: Ethical principles and guidelines for the protection of human subjects of research," 1978). The study was also conducted according to the ethical principles that were proposed by Emanuel *et al.* (2004).

Social value: Biobanking and genomic research are increasingly being conducted in South Africa; therefore, it is imperative that views and opinions of scientists and bioethicists be investigated. This study aimed to expose knowledge gaps and varying points of view that might help improve the ethical review process of research involving the collection, storage and future use of human biological materials.

Scientific validity: This was a cross-sectional study that employed an online survey tool with both closed- and open-ended questions. This allowed for collection of detailed data from a wide range of respondents in the most cost-effective way.

Fair participant selection: The study included all stakeholders involved in research that involves the collection, storage and future use of human biological materials, except research participants. Research participants were not included because their perspectives (in South Africa) have been explored in recent research; this Master's project was limited in scope due to both time and funding constraints.

Independent review: Ethical approval was obtained from the University of KwaZulu-Natal (UKZN) Biomedical Research Ethics Committee (BREC REF: BE412/14, Appendix III) and the Stellenbosch University Health Research Ethics Committee (S15/04/076, Appendix IV). Official permission was obtained from UKZN and SU administrations to include their staff in this study. Permission was also obtained from UKZN-affiliated research institutions and REC secretariats. Informed consent forms were sent to all participants and consent was implied on completion of the survey.

Informed consent: Participants were provided with a link to the informed consent form (Appendix V). Consent was implied on completion of the questionnaire. Responses were anonymous and de-linked from email addresses; each respondent was automatically assigned a special code by the software programs used. Survey data is securely kept in a password-protected computer file and will be kept for a period of at least five years. Data accruing from the study is only available to the research team.

Favourable risk-benefit ratio: This was a minimal risk study. Participants did not stand to benefit directly from the study but there is potential that the information gained will contribute to knowledge in this field.

Respect for participants: Participation was voluntary and respondents were free to unconditionally withdraw from the study.

3.9 Results dissemination

Research results will be available in the UKZN library. Findings will be communicated back to all respondents as well as the general public through peer-reviewed publications, presentations at conferences, workshops and invited lectures. Only pseudonyms will be used in all disseminated information. The researcher declares no competing interests.

3.10 Assumptions

It was assumed that the sample was representative of South African stakeholders who utilize HBM for research. It was also assumed that the questionnaire had validity and that respondents would answer the survey truthfully.

CHAPTER 4: RESULTS

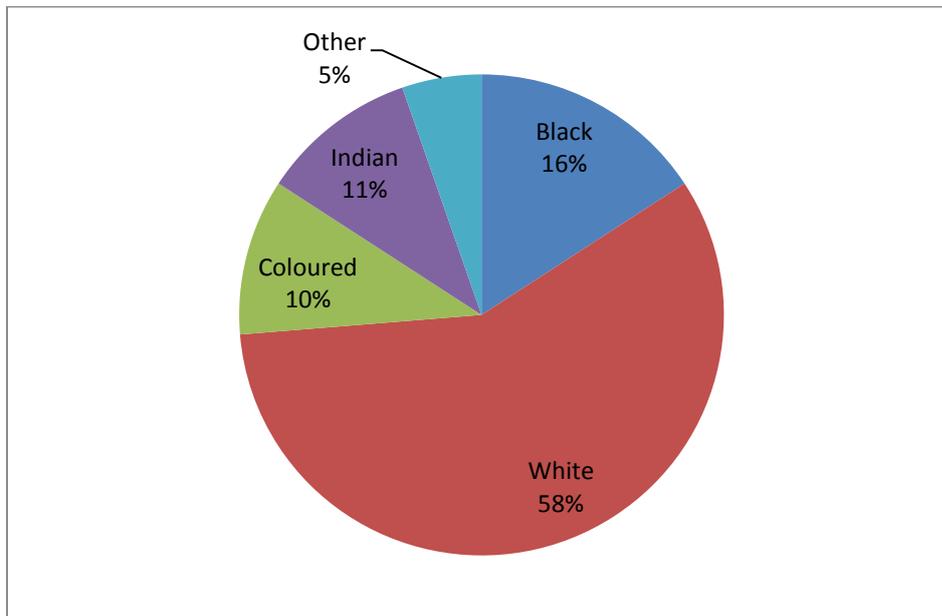
4.1 Introduction

This study enrolled REC members and researchers/scientists from universities and affiliated research institutions. The overall response rate could not be computed because of the different strategies that were employed to distribute the survey link. These included placing the survey link in a university newsletter, the generation of staff lists from institutional websites, and requesting REC administrators to internally distribute the link to members. Therefore, the total number of individuals to whom an invitation to participate in the survey was sent is unknown.

4.2 Research ethics committee members

Nineteen members from six different RECs completed the survey, a majority of which were male (13/19; 68.4%). Most respondents were white (11/19; 57.9%), and 10/19 (52.5%) had a PhD as their highest attained qualification (Figure 1 and Table 1).

Figure 2: REC members' race distribution



Only one REC vice-chairperson responded; the remainder were REC members. The majority of respondents (12/19; 63.2%) had served on RECs for more than five years and 13 (68.4%) had participated in the review or coordination of research that involves the collection, storage and future use of HBM. Table 1 shows the demographic characteristics of the REC members.

Table 1: REC members' demographic characteristics

	Freq (%) N=19
Gender	
Male	13 (68.4)
Female	6 (31.6)
Highest degree attained	
PhD	10 (52.5)
Masters/Fellowships	7 (36.8)
Bachelors	2 (10.5)
Role on REC	
Chair/vice-chair	1 (5.3)
Member	16 (84.2)
Legal member	2 (10.5)
Years served as REC member	
< 1 year	0
1- 2 years	5 (26.3)
3- 4 years	2 (10.5)
>5 years	12 (63.2)

4.2.1 REC members' perspectives on REC application and review process of biobank research

Questions in this section of the survey inquired about specific aspects of the REC application process. Respondents were asked whether their respective RECs give investigators any specific guidance when preparing applications involving the collection, storage and future use of HBM, compared to other types of research. A majority of respondents (12/19; 63.2%) indicated that their REC gives specific ethical guidance to researchers on how to prepare new applications in human research that involve the collection, storage and future use of HBM. The majority reported that their RECs give specific ethical guidance with regard to writing informed consent documents (100%); designing procedures for recruiting sample donors (84.2%); developing a research study design (64.8%); and developing a repository for human biological materials and associated data (73.7%)(Table 2).

To learn more about REC members' exchanges with researchers, respondents were asked to identify the issues that require 'considerable discussion' between researchers and their REC in the review of applications involving the future use of HBM. Considerable discussion was defined as "more than two or three back-and-forth rounds and/or more than a one-hour conversation". A sizable majority indicated that procedures for protecting participants' personal information or samples caused considerable discussion, followed by informed consent process and documentation; re-consent for use of sample/data for a new study or change in purpose; re-use of stored samples for future

studies; export of samples abroad; plans, or lack of plans, to deal with community harms or benefits; and scientific aspects of the study (Table 2).

Table 2: REC members’ opinions on the REC application and review process*

Question	Freq (%) (N=19)
“Do you feel that specific ethical guidance is needed for research that involves the collection, storage and future use of human biological specimens?”	
Writing a consent form/information sheet	19 (100)
Designing procedures for recruiting sample donors	16 (84.2)
Developing a research study design	13 (64.8)
Developing a repository for human biological materials and associated data	14 (73.7)
“Which of the following issues (if any) have required considerable discussion between researchers and REC in the review of research involving the future use of biospecimens? By ‘considerable discussion’ we mean more than 2 or 3 back-and-forth rounds and/or more than a 1-hour conversation”.	
Informed consent process or documentation	12 (63.2)
Procedures for protecting personal information and samples	15 (78.9)
Scientific aspects of the study of the study	6 (31.6)
Re-consent for use of sample/ data for a new study or change in purpose	12 (63.2)
Re-use of stored samples for future studies	12 (63.2)
Plans or lack of plans to deal with community harm or benefits	7 (36.8)
Shipping of samples abroad	8 (41.2)
None of the above	1 (5.3)

*Adapted from Lemke et al. (2010)

For applications requiring full committee review, only 5/19 (26.3%) of REC members agreed that more time is taken by their REC when reviewing biobank related research compared to other types of research; the rest either disagreed or were not sure (Table 3).

4.2.2 REC member’s perspectives on the informed consent process and the protection of participants in biobank research

Respondents were further asked to indicate their level of agreement with regard to informed consent concerns that are often raised in the conduct of research that involves the collection and storage of human biological specimens for future research. Only 47.3% agreed that the use of broad consent was acceptable. Seventeen respondents (89.5%) agreed that studies involving the storage of HBM for future research require separate informed consent forms for the current study and subsequent new studies using the stored sample.

Table 3: REC members' opinions on the informed consent process*

Question	Strongly agree	Somewhat agree	Neutral	Somewhat disagree	Strongly disagree	Don't know
(N=19)	Freq (%)	Freq (%)	Freq (%)	Freq (%)	Freq (%)	Freq (%)
"For applications requiring full committee review, my REC takes more time to review biobank research compared with other types of research."	3 (15.8)	2 (10.5)	5 (26.3)	5 (26.3)	3 (15.8)	1(5.3)
"The use of a broad consent form that anticipates future research studies (for example, to establish a repository, genetic research, study additional diseases) is acceptable to my REC."	2 (10.5)	7 (36.8)	2 (10.5)	2 (10.5)	3 (15.8)	3 (15.8)
"Studies that involve the storage of human biological materials for future research require separate informed consent forms for the current study and another one for each new study using the stored sample."	14 (73.7)	3 (15.8)	0	1 (5.3)	1 (5.3)	0
"I believe it is ethically necessary to obtain re-consent from research participants if":						
"The researcher wants to investigate a different, but related, condition or clinical manifestation."	8 (42.1)	5 (26.3)	2 (10.5)	3 (15.8)	1 (5.26)	0
"The researcher wants to investigate an unrelated condition or clinical manifestation."	13 (68.4)	4 (21.1)	0	1 (5.3)	1 (5.3)	0
"The researcher wants to add genetic measures to a study that did not originally include them."	12 (63.2)	3 (15.8)	2 (10.5)	2 (10.5)	0	0
"The researcher wants to share the participant's de-identified sample or data (without a linkage file) with an investigator at another institution."	7 (36.8)	8 (42.1)	1 (5.3)	2 (10.5)	1 (5.3)	0
"The original consent was given by a minor subject's parents and the subject is now old enough to decide for him or herself."	12 (63.1)	5 (26.3)	0	1 (5.3)	0	1 (5.3)
Fresh ethical approval is necessary for the re-use of stored samples						13 (68.4)

*Adapted from Lemke et al. (2010)

Respondents were probed on their beliefs about researcher-REC agreement on a number of important issues. Most REC members were in agreement that it is ethically necessary to obtain re-consent for research participants if: “the researcher wants to investigate a different, but related, condition or clinical manifestation” (68.4%); “the researcher wants to investigate an unrelated condition or clinical manifestation” (89.5%); “the researcher wants to add genetic measures to a study that did not originally include them” (79%); “the researcher wants to share the participant’s de-identified sample or data (without a linkage file) with an investigator at another institution” (78.9%); and “the original consent was given by a minor subject’s parents and the subject is now old enough to decide for him- or herself” (89.4%)(Table 3).

Most respondents (68.4%) felt that fresh ethical approval was necessary for the re-use of stored samples. There were several areas of agreement regarding the ethical necessity to obtain re-consent in biobank research, as shown in Table 3.

4.2.3 Confidentiality and the protection of human participants with respect to de-identified/anonymized samples for REC members

Questions in this section of the survey asked respondents about the protection of human participants in research involving the use of their biological samples. A strong majority of respondents (79%) agreed that storage of biological specimens and data for future genetic studies is acceptable as long as they are de-identified or anonymized. A majority of respondents (73.7%) were also in agreement that improper handling of research results can cause harm to the community to which a sample donor belongs.

Views differed with regard to the risk of research participants being personally identified and the possibility of harm in a study involving the use of coded HBM or data. “Coded” was used to refer to anonymized HBM where personal identifiers are permanently destroyed or de-identified HBM/data in which the original investigator maintains a linkage file (with study numbers and personal identifiers) separately from the specimens/samples/data, with the linkage file not being available to other investigators (Lemke et al., 2010). When asked to indicate the likelihood of identification, 42.1% indicated that identification was likely, whereas 47.4% believed this would be unlikely. Over half of respondents (57.9%) agreed that there was a likelihood of harm resulting from such identification, while 26.4% believed that harm would be unlikely and 15.7% were either neutral or did not know. Most respondents disagreed on the likelihood of government agencies or another law

enforcement agency compelling investigators to disclose information about genetic research participants; 47.3% believed this was unlikely, whereas 31.6% felt this was likely (Table 4).

Table 4: REC members’ opinions on HBM identifiability and possible harm*

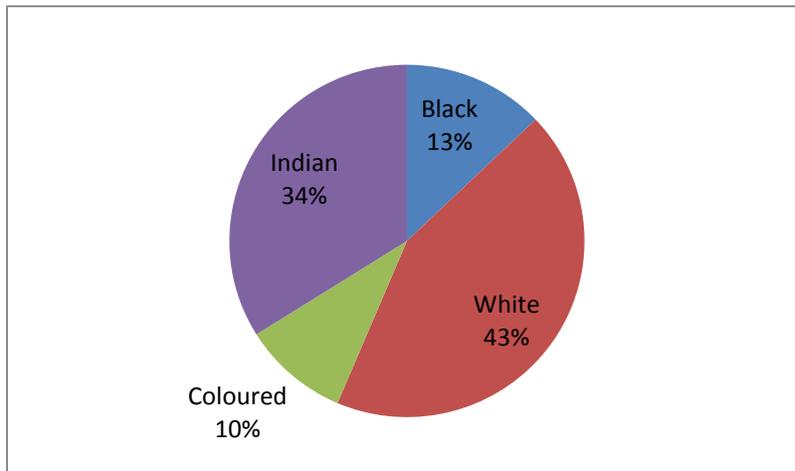
Question (N=19)	Strongly agree	Somewhat agree	Neutral	Somewhat disagree	Strongly disagree	Don't know
	Freq (%)	Freq (%)	Freq (%)	Freq (%)	Freq (%)	Freq (%)
“The storage of human biological specimens and data for future genetic research is acceptable as long as they are anonymized.”	4 (21.1)	11 (57.9)	1 (5.3)	1 (5.3)	1 (5.3)	1 (5.3)
“Improper handling of research results can cause harm to the community from which a sample donor belongs.”	6 (31.6)	8 (42.1)	2 (10.5)	0	1 (5.3)	2 (10.5)
	Very likely	Somewhat likely	Neutral	Somewhat unlikely	Very unlikely	Don't know
	Freq (%)	Freq (%)	Freq (%)	Freq (%)	Freq (%)	Freq (%)
“How likely is it that a research participant would be personally identified in a study involving coded data?”	5 (26.3)	3 (15.8)	1 (5.3)	4 (21.1)	5 (26.3)	1 (5.3)
“How likely is it that a research participant would be harmed as a result of identification from coded data?”	3 (15.8)	8 (42.1)	2 (10.5)	4 (21.1)	1 (5.3)	1 (5.3)
“How likely is it that a government agency or other law enforcement agency might compel investigators to disclose information about genetic research participants?”	2 (10.5)	4 (21.1)	2 (10.5)	4 (21.1)	5 (26.3)	2 (10.5)

*Adapted from Lemke et al. (2010) and Edward et al. (2012)

4.3 Researchers and other stakeholders

Sixty-two researchers and other stakeholders completed the survey; of these, 33/62 (53.2%) were female and 29/62 (46.8%) male. Most respondents were white (27/62; 43.5%), followed by Indians (21/62; 33.9%), as shown in Figure 2. The majority had a Master’s degree/Fellowship (31/62; 50%) or PhD (19/62; 30.6%) as their highest attained degree. Some respondents were affiliated to more than one institution; most were affiliated to a university 46/62 (74.2%), hospital/health facility (17/62; 27.4%) or research institution (14/62; 22.6%). The most frequent work activities were research (24/62; 38.7%) and clinical work (22/62; 35.5%).

Figure 3: Researchers and other stakeholders' race distribution



More than half of respondents (36/62; 58.1%) had participated in research involving the collection, storage and future use of human biological materials. Most of those who had participated in such research were researchers (24/62; 38.7%), principal investigators (15/62; 24.2%) or clinicians (8/62; 12.9%), and most had been involved in this type of research for more than three years (Table 5). Only 9/62 (14.5%) of respondents had served on a REC. Participant demographic characteristics are summarized in Table 5.

4.3.1 Researchers' and other stakeholder's opinions on the informed consent process and the protection of participants in biobank research

4.3.1.1 Opinions on the informed consent process for adult participants

Respondents were asked their level of agreement on a Likert scale with regard to informed consent issues that are often raised in conduct of research that involves the collection and storage of human biological specimens for future research. Table 6 summarizes the responses. Thirty-eight respondents (61.3%) agreed that studies involving the storage of HBM for future research require separate informed consent forms for the current study and subsequent new studies using the stored sample. There was no significant difference in opinion between respondents who had ever participated in biobank related research and those who had not (OR: 0.90; CI: 0.63-1.29; $p=0.57$).

Table 5: Researchers' demographic characteristics

	Freq (%) (N=62)
Gender	
Male	29 (46.8)
Female	33 (53.2)
Highest degree attained	
PhD	19 (30.6)
Masters/Fellowships	31 (50.0)
Bachelors/MBChB, LLB	12 (19.4)
Institution of affiliation	
University	46 (74.2)
Research institution	14 (22.6)
Hospital/Health facility	17 (27.4)
Public Health	5 (8.1)
Repository/Biobank	1 (1.6)
Non-governmental organization	1 (1.6)
Most frequent work activity	
Research	24 (38.7)
Clinical	22 (35.5)
Academic/Lecturing	9 (14.5)
Administration	7 (11.3)
Role in research involving the collection, storage and future use of human biological materials	
Principal Investigator	15 (24.0)
Co-Principal Investigator	6 (9.7)
Researcher	24 (38.7)
Clinician	8 (12.9)
Laboratory/Repository personnel/Pathologist	3 (4.8)
Study co-ordinator	2 (3.2)
Not applicable	8 (12.9)
Duration of involvement in research involving the collection, storage and future use of human biological materials	
Never been involved	28 (45.2)
> 1 year	4 (6.5)
1-2 years	6 (9.7)
3-5 years	13 (21)
6-9 years	5 (4.8)
> 10 years	8 (12.9)

When asked for their opinion on the type of consent that is applicable to biobank research, 41/62 (66.1%) of respondents were in agreement that broad consent is permissible for research that

anticipates future (unknown) research studies. There was no significant difference in opinion between respondents who had ever participated in biobank-related research and those who had not (OR: 0.86; CI: 0.62-1.12; p=0.38). With regard to general consent, 38/62 (61.3%) opined that it should only be acceptable when samples are anonymous.

Table 6: Researchers and other stakeholders’ opinions on the informed consent applicable to biobank research*

Question (N=19)	Strongly agree Freq (%)	Somewhat agree Freq (%)	Neutral Freq (%)	Somewhat disagree Freq (%)	Strongly disagree Freq (%)	Don’t know Freq (%)
“Studies that involve the storage of human biological materials for future research require separate informed consent forms for the current study and another one for each new study using the stored sample.”	22 (35.5)	16 (25.8)	6 (9.7)	13 (21)	4 (6.5)	1 (1.6)
“Opinion on the type of consent applicable to research involving the collection, storage and future use of human biological materials”						
“The use of a broad consent for research that anticipates future (unknown) research studies is acceptable.”	15 (24.2)	26 (41.9)	3 (4.8)	3 (4.8)	14 (22.6)	1 (1.6)
“A general consent should only be accepted when samples are anonymous.”	24 (38.7)	14 (22.6)	8 (12.9)	7 (11.3)	7 (11.3)	2 (3.2)
“A research participant has the right to establish limits regarding the research that can be done using his or her tissue.”	42 (67.7)	13 (21)	2 (3.2)	3 (4.8)	1 (1.6)	1 (1.6)
“The limits should apply even after the tissue sample has been completely made anonymous.”	25 (40.3)	20 (32.3)	6 (9.7)	6 (9.7)	5 (6.5)	1 (1.6)

*Adapted from Lemke et al. (2010)

For this study, general consent was defined as the consent given by participants at the time of sample collection for the use of their samples in any and all future studies, with no restrictions on the purpose of the research. Broad consent was defined as the consent given by participants at the time of sample collection for the use of their samples in the current study and a wide range of future research studies based on a broad category and whose specifics are unknown. A majority (55/62;

88.7%) of respondents were of the opinion that research participants have the right to establish limits regarding the research that can be done using their tissues, while 45/62 (72.6%) agreed that the limits should apply even after tissue samples have been completely made anonymous. When asked whether it is ethically necessary to obtain re-consent from research participants, respondents had varying views, as shown in Table 7.

Table 7: Opinions on re-consent of research participant and consent/assent of minors in research*

Question (N=19)	Strongly agree Freq (%)	Somewhat agree Freq (%)	Neutral Freq (%)	Somewhat disagree Freq (%)	Strongly disagree Freq (%)	Don't know Freq (%)
Opinions on re-consent of research participants						
"I believe it is ethically necessary to obtain re-consent from research participants if:"						
"The researcher wants to investigate a different, but related, condition or clinical manifestation."	10 (16.1)	10 (16.1)	6 (9.7)	25 (40.3)	11 (17.7)	0
"The researcher wants to investigate an unrelated condition or clinical manifestation."	22 (35.5)	18 (29)	4 (6.5)	13 (21)	5 (8.1)	0
"The researcher wants to add genetic measures to a study that did not originally include them."	30 (48.4)	12 (19.4)	1 (1.6)	13 (21.3)	5 (8.2)	0
"The researcher wants to share the participant's de-identified sample or data (without a linkage file) with an investigator at another institution."	23 (37.1)	8 (12.9)	4 (6.5)	19 (30.7)	8 (12.9)	0
Consent and assent for minors (<18 years)#						
"Parental consent is sufficient for storage of biological samples for genetic research of any child who cannot assent (give permission) because he/she cannot understand the nature of research."	24 (38.7)	28 (45.2)	4 (6.5)	5 (8.1)	1 (1.6)	0
"Once a child can understand the implications of biological sample storage and genetic research, he/she must be allowed to assent (give permission)."	37 (59.7)	20 (32.3)	2 (3.2)	1 (1.6)	2 (3.2)	0
"A child should have the right to withdraw their biospecimen/data from a repository when he/she is 18 years old."	47 (75.8)	10 (16.1)	0	5 (8.1)	0	0

*Adapted from Lemke et al. (2010), # Adapted from Hens *et al.*, 2010

Thirty six respondents (58%) were in disagreement that it is necessary to obtain re-consent if the researcher wants to investigate a different but related, condition or clinical manifestation. Forty respondents (64.5%) agreed that it is necessary to obtain re-consent if the researcher wants to investigate an unrelated condition or clinical manifestation, while 42/62 (67.7%) respondents agreed that it was necessary if the researcher wants to add genetic measures to a study that did not originally include them. Respondents were evenly split with respect to whether it is necessary to obtain re-consent if the researcher wants to share the participant's de-identified sample or data (without a linkage file) with an investigator at another institution (Table 6). A slight majority (51/62; 82.3%) indicated that REC approval would suffice in cases where re-consent of participants is not possible.

4.3.1.2 Opinions on informed consent and assent from minors (< 18 years)

Respondents were asked to rate their level of agreement on a Likert scale with regard to informed consent and assent for minor participants (Table 7). A large majority of respondents (83.9%) believed that parental consent is sufficient for storage of biological samples for genetic research of any child who cannot assent because he/she cannot understand the nature of research. However, an overwhelming majority (57/62; 92%) opined that children should be given the opportunity to assent once they are in position to understand the implications of HBM storage and genetic research. The same majority (57/62; 92%) also thought that young participants should be given the right to withdraw their biological specimens/data when they reach the age of 18 years.

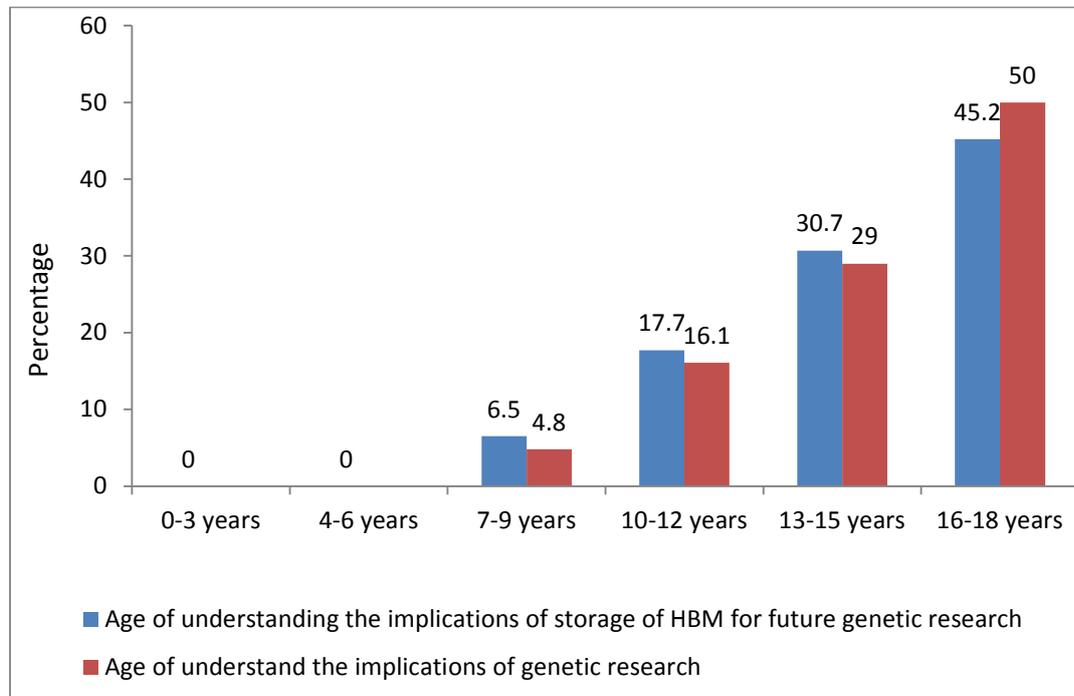
The age at which respondents thought children are able to understand the implications of storage of biological samples and of genetic research was also investigated (Figure 3). Slightly less than half (28/62; 45.2%) of respondents thought that this age is 16-18 years for storage of biological samples for future genetic research and 31/62 (50%) for understanding the implications of genetic research.

4.3.2 Confidentiality and the protection of human participants with respect to de-identified (anonymized) samples for researchers and other stakeholders

Questions in this section of the survey asked respondents about the protection of human participants in research involving the use of their biological samples. A small majority (33/62; 52.2%) were of the view that a participant who donates blood for scientific research remains in control of his/her sample. A majority of respondents (42/62; 67.8%) agreed that the use of coded HBM constitutes human participant research (when the researcher does not have access to the link between identifiers and biological samples). A large majority of respondents (79%) agreed that

storage of biological specimens and data for future genetic studies is acceptable as long as they are anonymized. They were also in strong agreement that improper handling of research results can cause harm to the community from which a sample donor belongs (90.3%).

Figure 4: Respondents’ opinion on the age of understanding the implications of storage of HBM and genetic research



Views differed with respect to the risk of research participants being personally identified and the possibility of harm in a study involving the use of coded HBM or data. “Coded” was used to refer to de-identified/anonymized HBM or data in which the original investigator maintains a linkage file (with study numbers and personal identifiers) separately from the specimens/samples/data with the linkage file not being available to other investigators (Lemke et al., 2010). When asked to indicate the likelihood of identification on a Likert scale, 47/62 (75.8%) opined that personal identification is unlikely. About 19/62 (30.6%) of respondents thought that there was a likelihood of harm resulting from such identification whereas 38/62 (61.3%) thought that harm would be unlikely. The majority of respondents disagreed on the likelihood of government agencies or other law enforcement agency compelling investigators to disclose information about genetic research participants. Most respondents (30/62, 48.4%) believed this was unlikely whereas 23/62(37.1%) felt this was likely. These results are summarized in Tables 8 and 9.

Table 8: Researchers and other stakeholders' views on the use of human biological samples*

Questions (N=62)	Strongly agree Freq (%)	Somewhat agree Freq (%)	Neutral Freq (%)	Somewhat disagree Freq (%)	Strongly disagree Freq (%)	Don't know Freq (%)
"The storage of human biological specimens and data for future genetic research is acceptable as long as they are anonymized."	25 (40.3)	24 (38.7)	1 (1.6)	6 (9.7)	5 (8.1)	1 (1.6)
"A participant who donates blood for scientific research remains in control over his/her blood."	10 (16.1)	23 (37.1)	6 (9.7)	15 (24.2)	8 (12.9)	0
"Use of coded human tissue specimens constitutes human subject research (Assume researchers do not have access to the link between the original and coded data)."	23 (37.1)	19 (30.7)	10 (16.1)	6 (9.7)	2 (3.2)	2 (3.2)
"Improper handling of research results can cause harm to the community from which a sample donor belongs."	34 (54.8)	22 (35.5)	1 (1.6)	4 (6.5)	1 (1.6)	0

*Adapted from Lemke et al. (2010)

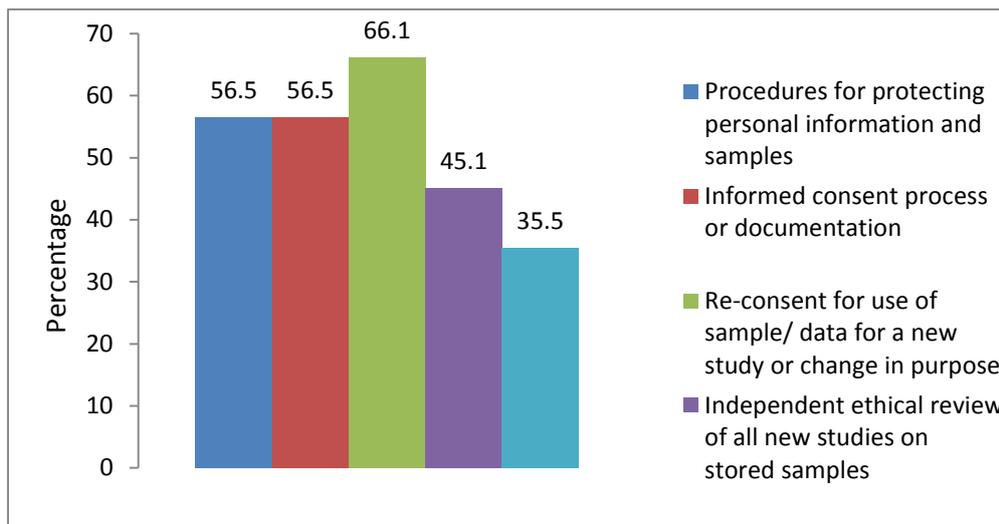
To learn more about researchers' exchanges with RECs, respondents were asked to identify the issues that necessitate 'considerable discussion' between researchers and their REC in the review of applications involving the future use of HBM (Figure 4). Considerable discussion was defined as "more than two or three back-and-forth rounds and/or more than a one-hour conversation". A majority (41/62; 66.1%) indicated that issues concerning re-consent for use of sample/data for a new study or change in purpose cause considerable discussion followed by procedures for protecting participants' personal information or samples (56.5%); informed consent process and documentation (38/62; 56.5%); independent ethical review of all studies on stored samples (28/62; 45.1%); and plans, or lack of plans, to deal with community harms or benefits (22/62; 35.5%).

Table 9: Researchers' and other stakeholders' opinions on identifiability and possible harm*

Question	Very likely	Somewhat likely	Neutral	Somewhat unlikely	Very unlikely	Don't know
(N=62)	Freq (%)	Freq (%)	Freq (%)	Freq (%)	Freq (%)	Freq (%)
"How likely is it that a research participant would be personally identified in a study involving coded data?"	0	10 (16.1)	3 (4.8)	14 (22.6)	33 (53.2)	2 (3.2)
"How likely is it that a research participant would be harmed as a result of identification from coded data?"	2 (3.2)	17 (27.4)	3 (4.8)	17 (27.4)	21 (33.9)	2 (3.2)
"How likely is it that a government agency or other law enforcement agency might compel investigators to disclose information about genetic research participants?"	5 (8.1)	18 (29)	6 (9.7)	15 (24.2)	15 (24.2)	3 (4.8)

*Adapted from Edward et al. (2012)

Figure 4: Issues that require considerable discussion during REC review of research



4.4 Perspectives on the ethics review process, informed consent and the protection of human participants during the sharing of HBM in biobank research

In this section, the data collected from open-ended questions on researchers and other stakeholders' perspectives on the export and sharing of biological specimens and associated data is presented.

4.4.1 Attitudes on ethics review and regulation of biobank research

Most respondents argued that there is need for "strong systems [and] protocols" to regulate the export and sharing of HBM and associated data in order to "ensure that the communities are not

unduly disadvantaged/stigmatized". There must be "... proper ethical guidelines and practices" that ensure that research participants consent to sample- and data-sharing. Research ethics committee members were of the view that the storage and future use of biological samples "needs to be strictly monitored by research committees" to ensure that they are not used "...for purposes not originally consented to".

In biomedical research, much emphasis is placed on the protection of the rights and welfare of participants while the position of researchers is neglected. Researchers and other stakeholders felt that they too, particularly the ones who obtain the samples, should be protected from being exploited by funders, as was stated in this quote by respondent 32: "biological specimens may be shared provided very strict guidelines on the use of these with protection of the material itself and protection of the original researcher".

On the other hand, some respondents were of the view that there is a need for fewer restrictions on the sharing of HBM, particularly in the fast-evolving field of genetics research. This was clearly stated by respondent 36 in the following quotation: "In today's globalized society - rapid improvement in scientific research and increased information - there should be less [sic] restrictions on export and sharing of biological specimens, provided regulatory frameworks exist and are applied strictly".

Guidelines differ substantially regarding biobanking and the transfer of HBM, and often conflict across borders. This was alluded to by respondent 36 who highlighted the need for harmonized regulatory frameworks across countries, saying: "Careful evaluation of the studies is mandatory for the protection of the researcher and for good research in general, provided adequate regulatory frameworks are in existent [sic] across all countries and are applied uniformly. We should not hamper scientific endeavour".

4.4.2 Perspectives on informed consent

Informed consent is an ethical and legal requirement for all research involving human participants. Conflicts between advancement of scientific research and trying to maximize participants' autonomous decision-making complicate the informed consent process for the use of HBM. Almost all respondents were in agreement that informed consent is mandatory for all research and a majority had no objection to sample- and/or data-sharing and export as long as "... samples/data are anonymized" and "... proper protocols are followed in handling these specimens". They noted that it

is the responsibility of the researchers to ensure that participants receive all relevant information as was clearly stated by respondent 14 in this quotation:

Regarding the use of [the] same tissue for future projects, I think it is the responsibility of the researcher to make the participant aware of any future research that may be done on their specimen, so that the person can make the decision early on whether they agree to it or not.

Most respondents stressed the importance of informing participants about the possibility of storage, future use and export of their samples during the informed consent process and said that these aspects should be clearly indicated on the informed consent form. Concerning genetic research, respondents were of the view that research participants should be informed in advance if any such tests are to be conducted on their samples in the future: “Genetics research needs to be clearly stated in the consent form of participants ...”

One of the principal elements of informed consent is comprehension. It is therefore essential that participants understand the information that has been given to them before making a decision whether or not to participate in a study. Respondent 2 said: “There should be informed consent comprehension tests for participants undergoing informed consent for specimen storage, especially for non-study related research (current study), as participants may agree on something they do not know”.

There were divergent views with regard to the need to re-contact participants in case of export of samples and associated data. Some researchers felt that it was necessary to re-consent participants for “... consent to additional studies being performed on his/her specimen” while others felt that “the original consent form should inform research participants of this possibility and that no additional consent will be taken should this eventually occur”. But, respondent 10: “Any additional study wishing access to [stored samples or data] must apply through the original REC committee”.

4.4.3 Perspectives on confidentiality and the protection of human participants with respect to de-identified (anonymized) samples

The ethical principle of beneficence requires the maximization of benefits and minimization of risks for research participants. The potential harms associated with research utilizing HBM stem from the possible misappropriation of information, which could culminate in discrimination, stigmatization, psychological harm, and disruption to families and communities. Hence, the degree to which

biological samples and data can be linked to specific individuals is cardinal in risk assessment. Protecting the privacy of individuals who donate HBM for research and maintaining the confidentiality of associated health and research data are vital in protecting individuals from harm and maintaining trust. Almost all respondents were unanimous with regard to the need to protect the identity of the sample donor during storage and sharing of HBM and associated data for research. Respondent 7 said: “I think all data must be anonymous and safeguards [should be put] in place to prevent linking of genetic to other administrative data”.

Some respondents opined that participant protections should also be considered when developing research designs. This was clearly expressed by a Respondent 34 on the export and sharing of samples and associated data: “Anonymization of data to preclude identification or stigmatization of participants based on results [can be] resolved by anonymization of specimens, de-identification of participants and blinding between researcher and research technician conducting the core laboratory analysis of specimens”.

Respondents complained that RECs set very stringent rules with regard to the sharing of HBM and associated data. They were of the view that sharing of HBM and data is necessary to produce high quality research, “... as long as a reasonable set of rules are [is] followed - mainly around anonymizing samples” (respondent 29). Respondent 10 even suggested that “[p]erhaps it is the exceptions that should be punished (i.e. when people break the rules) rather than RECs limiting the potential to carry out good science”.

The tracking and monitoring of HBM is very difficult once they cross borders, and providers tend to lose control on their use. Some respondents opined that these resources are better destroyed rather than risk being misused. Respondent 62 said: “If used for anything other than requested, then the providers have the right to ask [the] user to destroy the specimen and show evidence of destruction”.

4.4.4 Challenges to ethics review of protocols

Only 5/62 (8.2%) researchers reported ever having had challenges in ethical review of their research studies. Respondents expressed their dissatisfaction with the ethics review process with regard to assessing the scientific validity of their studies. They expressed concerns about the issue of REC members reviewing protocols for which they lacked the technical competence. They were also critical of the stringent regulations imposed by RECs that can significantly affect the integrity of the

research, with resultant potential harm to research participants. This challenge can be summarized in this quote by respondent 22, who said the problem lies: “... mainly with the REC challenging the need to do studies they often don't have a good handle on in the first place. Also trying to impose rules that could potentially harm the integrity of the research without really adding any further protection of human subjects”.

They also cited the emphasis RECs put on the storage of biological samples and the issue of research participant confidentiality. During the review process, there is considerable discussion on these issues, primarily to ensure adequate protection of participants. Research ethics committees have to ensure that participants give informed consent for the storage and future use of their samples.

Another respondent expressed concern over the time and cost incurred during the submission and review processes. Of particular concern was the high cost of translating research-related and informed consent documents into local languages as respondent 58 stated, this is “... time consuming and costly; more funding should be available to assist with translation of consent documents as this is extremely expensive”.

Another challenge was the need to obtain re-consents when new procedures that were not in the original protocol are added. This is summarized in this example given by respondent 16: “Investigators failed to get consent for use of stored samples when a new test was added. Need to repeat consent process”.

4.4.5 Other issues that emerged on HBM and data sharing

The ability to share HBM and data is crucial for the growth of biobanking and health research in general. Overall, the majority of researchers had a positive attitude towards the export and sharing of unlinked HBM and/or data although they thought this was a very “contentious” and “controversial” issue. They felt that the sharing of samples and associated data was imperative to the research industry and is important in advancing the scientific knowledge necessary to address the ever-increasing health challenges. A 13 said: “... if the export is justifiable from a scientific point of view - e.g. analyses done elsewhere will contribute substantial knowledge and benefit society - then it is acceptable”.

Respondents opined that it is through sharing information and collaboration that a holistic view of problems and answers can be achieved, particularly for genetic diseases. Genetic epidemiological studies are expensive and require large numbers of sample donors that often require multi-centre

collaboration and the sharing of samples. This observation was made in the following two quotations:

The reality of modern genetic research is that very large study numbers are needed and this invariably means multi-centre collaboration with export of samples to sites where laboratory expertise exists. This is not, in my opinion, ethically unsound as the study is more robust and thereby the ethical dilemma of involving subjects in under-powered studies is averted.
(Clinician)

I think that we should share samples with other researcher instead of getting new samples for individual projects.

The sharing of anonymized HBM/data was also perceived as being of paramount importance in the establishing of databases or registries that can easily be accessed by other researchers, particularly for rare disease conditions. It also allows for the full exploitation of valuable biological samples. Much as most respondents viewed sample- and data-sharing as beneficial to the research industry, they also had several reservations with regard to sample/data ownership and benefit-sharing. Some respondents felt that “[i]ssues of intellectual property need to be negotiated between research institutions” before any samples are exported. Respondent 23 felt that sharing was acceptable “... as long as an MTA [Material Transfer Agreement] and MoU [Memorandum of Understanding] is set up between the provider and the user and it is clear for what purposes the biospecimen and data is used for”.

With regard to ownership, respondent 59 felt that “... ownership of data should be retained by South African researchers”. On the other hand, some respondents were not bothered with “... whether the research is conducted locally or abroad” as long as it is “very carefully controlled and monitored”.

Both researchers and the sample donor community should benefit from research, as was clearly stated by respondent 59 in this quote on the acceptability of sample and data export: “... that [the] original community benefits and not just European or American centres benefiting from research, it is acceptable”. For transparency and avoidance of exploitation, a senior researcher suggested that “disclosure of potential economic benefits, perhaps a right to share in the benefits of research either at individual or community level” should be made.

Respondents expressed their wariness about the exploitation of vulnerable communities. A co-principal investigator thought that sharing of specimens is permissible “provided that it is not used to derive commercial benefits at the expense of the study participants”. Respondents, including one clinician, suggested that strict regulations should be instituted to reduce the “potential for commercialization of research and exploitation of vulnerable populations”.

In contrast, some respondents thought the export of HBM and sharing of data was very controversial and expressed their disapproval of this activity. Over the years, the unidirectional export movement of HBM out of South Africa to several countries in the Western world has negatively impacted on the growth of local capacity, infrastructure and expertise. Therefore, some respondents were totally against the export of samples from the country of collection but were comfortable with the sharing of data attained from sample analysis. One of the reasons given was the lack of capacity to track and monitor samples once they cross borders, as observed respondent 48: “I am not in favour of this as one never knows how the other research entity will deal with specimen analysis and results”.

Respondent 49 was apprehensive because of the possibility of the host community not benefiting enough; instead it would just “... advance the research of non-locals who claim to have advanced technology”. Another reason cited against sample export is the need to strengthen local research capacity, as was ably stated by respondent 40:

I think it is an important principle to capacitate the local scientific community to the extent possible when performing scientific investigations based in a community. Therefore, I am opposed to ‘helicopter science’ or export of samples for scientific investigations that can be performed locally. That said, scientific progress should not be impeded by burdening local laboratories with work that could be done elsewhere if it is of low priority for the local laboratory. Therefore, I think that decisions about export of samples should be made in conjunction with the ... [Research Ethics Committee], PIs and local medical and scientific stakeholders, with consideration given to the importance of building scientific capacity within the communities being investigated.

Researchers and other stakeholders clearly had varying perspectives on the sharing and export of HBM; they agreed that sharing of these resources was important for science, as long as the safety and rights of research participants and researchers are protected. They also emphasized the need for local capacity and infrastructural development.

4.5 Conclusion

Overall, the attitude of REC members, researchers and other stakeholders on informed consent and ethical review of biobank research was positive and ethically informed. However, there were several areas of agreement and disagreement. Stakeholders concurred that issues concerning informed consent documentation, sample de-identification and re-consent for the use of samples/data or change in purpose required thorough discussions during ethics review meetings. All stakeholders contended that there is a need for efficient regulatory frameworks to govern the collection, storage, sharing and future use of HBM. There was no consensus on the issue of re-consent and the likelihood of donor identification and harm during the use of HBM for secondary research. Stakeholders also identified a number of challenges in the ethics review process and sharing of HBM.

CHAPTER 5: DISCUSSION

5.1 Introduction

This study set out to explore REC members, researchers and other stakeholders' perspectives on informed consent and ethics review of research involving human specimen resource repositories/biobanks in South Africa. Although the REC members' response rate was rather low, a majority of those who responded were fairly experienced, with a REC experience of more than five years. Therefore, their contribution to this study was insightful and significant. Overall, REC members, researchers and other stakeholders had positive attitudes and were ethically informed about informed consent and ethical review of biobank research. They contended that there is a need for efficient regulatory frameworks to govern the collection, storage, sharing and future use of HBM. They recommended the strengthening of RECs to ensure comprehensive ethics review of biobank research.

Most REC members indicated that their RECs give investigators useful ethical guidance during the application process although several key areas where investigators need ethical guidance were also identified. Both groups (REC members and researchers) concurred that issues concerning informed consent documentation, sample de-identification and re-consent for the secondary use of HBM/data or change in purpose required thorough discussions during ethics review meetings. Some researchers and other stakeholders expressed their dissatisfaction with the ethics review process with regard to assessment of the scientific validity of their studies. They queried the technical competence of REC members in reviewing biobank research protocols.

Areas of agreement by researchers included the ethical necessity of obtaining informed consent; the applicability of broad consent for biobank research; the obligatory requirement for fresh ethical approval for the re-use of HBM; the need to protect donors and communities through proper handling of biobank research; donors' right to establish limits to the usage of their HBM; giving children the opportunity to assent once they are mature enough to comprehend the implications of HBM storage and genetic research; and, the ethical necessity to obtain re-consent and the right to withdraw consent by children on attainment of majority age.

Areas of disagreement with regard to the usage of HBM for future research included: the circumstances under which re-consent should be obtained; the likelihood of donor identification and harm that could result from such identification; and the likelihood of government or other law

enforcement agencies compelling investigators to divulge data about genetic research participants. The identified challenges to biobank research included the emphasis placed on sample storage and participant confidentiality; loss of control on the use of exported samples due to the absence of mechanisms to track and monitor them; the lack of harmonized standards for sharing samples across national borders; and the high cost of translating informed consent and other research related documents.

Regarding other issues that emerged, the majority of researchers and other stakeholders had a positive attitude towards the export and sharing of unlinked HBM as long as proper procedures are followed in their handling. Researchers felt that the sharing of HBM and associated data is imperative to the research industry and is important in advancing the scientific knowledge necessary to address the ever-increasing health challenges. However, a minority thought this was very controversial and expressed their disapproval of the transfer of samples across borders.

5.2 REC application and ethics review process

Because of the history of exploitation in Africa, it is imperative that stringent measures for regulating research are put in place at the outset to ensure that the errors of the past do not recur or at the least are minimized. This is important, particularly when dealing with biobanking and related research, because this field of research is evolving quickly and, as discussed previously, encompasses several ethical challenges. South African ethical guidelines give RECs the responsibility of approving ethically and scientifically sound research proposals, and, in certain circumstances, they can rely on pre-scientific review by specialists in the respective field of research to ensure that the study is scientifically valid. These guidelines also recommend that “RECs should have comprehensive SOP to guide review of research that proposes use of human data or biological materials” and “be meticulous in their deliberations” with respect to research that proposes to utilize HBM and/or associated data (DOH, 2015, p. 41). Therefore, the onus is on RECs to ensure that protocols are scientifically sound and the conduct of research is ethical.

About 68% of REC members had participated in the review or coordination of biobank research and 63.2% had experience of more than five years in this area. The current study did not explicitly ascertain whether the different stakeholders had an understanding of biobank research, but assumed that REC members would have an understanding of this concept. A study on the perspectives of REC leaders in the USA revealed several areas of contention in the ethical review of biobank research (Rothwell et al., 2015). The authors also noted that some stakeholders in the

research community do not clearly understand biobanking and the secondary use of residual samples.

Most REC members (63%) in this study indicated that their RECs give investigators useful ethical guidance during the application process for review of biobank research. This figure is relatively low when compared to 93% that was reported by Lemke et al. (2010), in their survey among professionals involved in human subject protection. This may indicate that some REC members have limited experience in reviewing these protocols or are not completely comfortable with the review of biobank research. However, due to the limitation of the REC sample size, this is difficult to interpret. De Vries et al. comment that RECs often have varying levels of expertise and experience with respect to the ethical review of biobank-related protocols and thus there is an on-going need for training of REC members in particular aspects of biobanking and genetic research (De Vries et al., 2015).

Only 26% of REC members agreed that more time is taken by their REC when reviewing biobank-related research compared to other types of research. A similar study conducted among professionals involved in human subject protection in the USA reported an agreement of 46% (Lemke et al., 2010). A higher level of agreement would be expected because biobank research has multiple ethical, legal and social implications and, for this reason, RECs ought to devote enough time to reviewing such protocols. This can also be inferred from the South African ethics guidelines which call for meticulous deliberations and ensuring the integrity and comprehensiveness of the informed consent process (DOH, 2015).

Only 68.4% of REC members felt that fresh ethical approval is necessary for the re-use of stored samples. This was rather surprising because international and South African ethics guidelines clearly stipulate that every new study utilizing stored HBM and related data must undergo ethical review and approval (CIOMS, 2009; DOH, 2015; WMA, 2013). This therefore exposes a gap in knowledge on ethical guidelines that needs to be bridged through on-going professional education.

Research ethics committee members identified several key areas where they felt investigators needed ethical guidance during the REC application process: the preparing of informed consent documents; recruitment procedures for sample donors; and developing repositories for HBM and associated data. These are the same key areas that were reported as requiring considerable discussion during ethics review of biobank-related research proposals. Therefore, to avoid

unwarranted back-and-forth consultations, ensure that investigators write quality protocols, and ease the review process, RECs ought to ensure that researchers have access to relevant ethical guidance right from the point of protocol design. This is particularly important for researchers who might not be well grounded in research ethics.

There were some areas of agreement between REC members, researchers and other stakeholders regarding issues that usually require considerable discussion during the ethical review process of biobank research. All groups concurred that issues concerning informed consent documentation, sample de-identification and re-consent for the use of HBM and associated data or change in purpose required thorough discussions. It is very important that there are no ambiguities in the informed consent documents at the time of sample collection. Any confusion and uncertainties in the consent process can culminate in decisions barring the use of certain specimens for secondary research, with detrimental effects on science and public benefit from research (Grady et al., 2015).

Surprisingly, only 36% of researchers and other stakeholders, and 37% of REC members, felt that having provisions for dealing with community harms or benefits requires considerable discussion. This seems to reiterate Emanuel, Wendler, and Grady's observation that existing ethical regulatory policies and guidelines emphasize immediate risks to the individual and tend to ignore potential harms to those not participating in research (Emanuel et al., 2000). Researchers must recognize and appreciate that the risks of biobank-related research can affect the general community and should therefore ensure that measures are put in place to protect the community. In addition, research ethics committees must critically evaluate biobank studies for the likelihood of psychological, social or physical risks to individual participants, groups or the community (Emanuel, Crouch, Arras, Moreno, & Grady, 2003). The perceived lack of emphasis in this study on community risk-benefit assessment during the ethics review discussions calls for enhanced continuing review and monitoring of approved research. Post-approval monitoring is a necessary quality assurance process aimed at reviewing the progress of research studies to ensure that the information attained during the course of conducting the study does not significantly alter the original benefit-risk assessment (Rodriguez et al., 2003). Research ethics committees are expected to conduct active monitoring of approved research through field visits and on-site inspections; however, this is a challenge in resource-limited settings (Ochieng et al., 2013). Motivation for on-site monitoring by RECs is low because most members are volunteers with other more demanding primary responsibilities, while RECs have a heavy workload yet they seldom have adequate permanent staff (Nyika, Kilama, Chilengi, et al., 2009).

Many RECs also lack the capacity to actively monitor ongoing research and this compels them to work on the basis of trust where investigators are expected to follow stipulated ethical and legal guidelines when conducting research (Andanda et al., 2011); however, this trust could be abused. Another important impediment to on-site monitoring are the insufficient regulatory guidance and procedures on how it should be conducted (Brown, 1998). Research ethics committees should therefore continuously guide investigators through the ethical application and review process, and strengthen post-approval monitoring of research to ensure that researchers comply with regulatory standards.

5.3 Perspectives on the informed consent process and the protection of participants in biobank research

5.3.1 Opinions on informed consent for adult participants

Obtaining the opinions of researchers and other stakeholders is important because they are intimately involved in the collection and usage of HBM and health information in biobank research. Scientists manage biobanks and are the end-users of HBM and thus are important resources, with vital information on biobank functioning. They play a vital role in the informed consent process and offer an invaluable and necessary viewpoint that should help to inform policy around informed consent (Master, Campo-Engelstein, & Caulfield, 2015).

Research ethics committee members, researchers and other stakeholders were unanimous in agreement on the ethical necessity of obtaining informed consent for biobank research. About 61% of researchers and other stakeholders and 89.5% of REC members agreed that studies involving the storage of HBM for future research require an informed consent form for the current study and another separate one for each subsequent new study using the stored sample. This is tantamount to re-contacting and obtaining re-consent for every new proposed study on the biological samples. There was disagreement among researchers and other stakeholders on the necessity to obtain re-consent if an investigator wants to research a different, but related, ailment or clinical manifestation; 32% believed that it is necessary while 68% were either unsure or did not agree. The majority of REC members (68%) also believed that re-consent is necessary in this instance.

Making such judgements about re-consent usually depends on the type of consent the original sample donor gave at the time of collection. If the donor gives specific consent, then any subsequent studies on the samples will require re-consent; however, this is very restrictive and can be an obstacle to scientific advancement. Much as specific consent is the best option with regard to

respecting research participants' right to self-determination, obtaining new consent for every use of stored samples is not practical, is exorbitantly expensive, and in most cases impossible (Peto et al., 2004).

One viable consent option for biobank research that is recommended by South African ethics guidelines is broad consent (DOH, 2015). An overwhelming majority (86.1%) of researchers and other stakeholders agreed that broad consent was applicable for biobank research. Globally, consensus is growing on the use of broad consent in biobank research (Denny et al., 2015; Garrett, Dohan, & Koenig, 2015; Grady et al., 2015; Master, Nelson, Murdoch, & Caulfield, 2012; Rothwell et al., 2015) because it allows donors a degree of control over the use of their HBM in research whilst avoiding the potential burden of obtaining re-consent for each new study. Broad consent also provides for: participant consent for certain types of future research (Helgesson, 2012; Steinsbekk et al., 2013; Steinsbekk & Solberg, 2011); review of all new studies utilizing HBM and/or data by an independent REC; an ongoing consent process with the possibility of consent withdrawal at any time; the opportunity to re-consent if anything changes in the framework (Steinsbekk et al., 2013); and allows the donor the choice of category of research to which to contribute samples (e.g. oncology research, malaria research) (Foe, 2014).

Researchers also opined that it is necessary to obtain re-consent if the proposed new study falls outside the scope of the initial consent or intends to add genetic measures. Such opinions have also been reported by other studies among researchers and REC professionals (Goldenberg et al., 2015; Lemke et al., 2010). Section 32 of the Declaration of Helsinki (WMA, 2013) delegates to RECs the responsibility of determining whether donors should be re-contacted and re-consented for secondary uses of their HBM; however, should obtaining re-consent be untenable, then the responsibility remains on the REC to make a considered determination on this issue. Research ethics committees provide adequate oversight to ensure that the purposes of secondary use of the HBM are not at variance with donors' values (Grady et al., 2015; Hansson, 2006; Hansson et al., 2006; Kettis-Lindblad et al., 2007). Where feasible, donors should be periodically informed about ongoing research activities including stressing to them their right to withdraw their identifiable sample from research should the need arise.

Opinions were also obtained on the applicability of general consent for the use of anonymous samples. About 61% of researchers and other stakeholders agreed that it is applicable; however, this type of consent is not recommended by the SA ethics guidelines because it is not easy to implement

and contravenes important ethical principles, particularly that of respect for autonomy (DOH, 2015). Several other studies among scientists have also documented that scientists prefer general consent (Colledge et al., 2014; Master et al., 2015). They justified their preference by noting the importance of scientific advancement and the practical difficulties of obtaining re-consent. However, there is a possibility that some researchers and other stakeholders, and REC members, do not distinguish general from broad consent, as was reported by De Vries et al. (2015) in the proceedings of a workshop with members from 40 RECs from across Africa.

Another issue that was raised is the importance of ensuring that participants understand the information provided before making an informed decision. This is particularly difficult for illiterate and semi-literate participants (Nnamuchi, 2015), thus the need for translation of informed consent forms and other research related document into local languages. However, researchers and other stakeholders in this study expressed their concern over the high cost of this translation. There are also debates on how to measure participants' comprehension of informed consent (Cervo et al., 2013; Pellegrini et al., 2014). This therefore is a potential field of research that ought to be explored, including ways of making the translation of research related documents less costly in South Africa.

5.3.2 Opinions on informed consent and assent for minors (< 18 years)

The vast majority of respondents (REC members, researchers and other stakeholders) in this study believed that parental consent is adequate for the storage of HBM for genetic research of any child who cannot assent because of inability to comprehend the nature of research. The need for parental consent and assent for minors is a legal requirement in South Africa and is consistent with ethics literature (Hens, Cassiman, et al., 2011; Master et al., 2015; Petersen et al., 2014). In South Africa, the age limit for legal competence for medical treatment is set at 12 years and that for giving informed consent for research at 18 years ("South African Child Act 38 of 2005,").

Authors have advocated for the inclusion of minors in research; however, there is a potential challenge to this in South Africa. Chapter 9 of the National Health Act No. 61 (*South African National Health Act, 2003*) has a problematic and potentially restrictive clause that mandates the Minister of Health to give consent for any non-therapeutic research involving minors. Furthermore, Section 71(3)(b)(i) indicates that ministerial consent can be denied where "the object of the research or experimentation can also be achieved if it is conducted on an adult" (*South African National Health Act, 2003*). Such ambiguous legislation has the potential for curtailing research involving minors, yet

such studies are crucial in the elucidation of disease and the development of appropriate therapeutic agents (Strode et al., 2010).

During the review of a protocol seeking to utilize stored samples, it is imperative that the original consent form used at the time of sample acquisition is scrutinized to ascertain whether the donor consented to secondary use. Pediatric biobank experts recommend ongoing provision of sufficient information to parents and children about the storage and intention to use their biological samples and derivatives in addition to the potential consequences to the parent and child (Dove et al., 2013; Gurwitz et al., 2009). This is important because research suggests that parents do not always understand during the informed consent process (Klima et al., 2013). They tend to over-rate individual benefits and under-rate the risks related to their children's involvement in research (Klima et al., 2013).

Researchers and other stakeholders, and REC members, were unanimous in agreement that it is ethically necessary to obtain re-consent from children on attainment of majority age. An overwhelming majority were of the view that parental consent is sufficient for children who are not competent enough to comprehend the nature of research. They also opined that children should be provided the chance to assent once they are in a position to appreciate the implications of HBM storage and genetic research. However, there were varying opinions between researchers and other stakeholders on the age they considered children able to appreciate the implications of storage of HBM and of genetic research. The majority indicated a relatively high 16-18 years age bracket for this ability. These results are comparable to those reported by Hens et al. (2010) in their study among genetic professionals in Belgium.

Much as parents give consent for their children to participate in biobank research, they (the children) have the right to voice their own views and should be accorded the chance to develop their own autonomy as they mature in age. There is no consensus among experts on children's rights on attaining a certain age (Kranendonk et al., 2015). Just like in this study, several authors have argued that minor participants must have the choice whether to re-consent or withdraw earlier parental consent on attainment of the age of majority (Brisson et al., 2012; Hens, Cassiman, et al., 2011; Kranendonk et al., 2015). This is on the premise that the original proxy consent provided by the parent was made in the best interest of the child while re-consent allows the adult child to express his/her own wishes and autonomy (Hens, Levesque, et al., 2011). Re-contacting mature children is an essential requirement for regulations on biobanking in children (Kranendonk et al., 2015) but the

exact age for this requirement should primarily be debated at national level. South African law and ethical guidelines are not clear on this issue, and this should be a focus of research and national debate. In the event that re-contacting is impracticable, a REC should be in position to give guidance based on national and/or institutional guidelines governing research on human participants.

Studies have shown that children are capable of participating in making decisions even at a very young age (Alderson et al., 2006). However, for genetic testing, others have reported difficulties, even for teenagers, with understanding the full extent and implications of genetic information (Boddington & Gregory, 2008). This may be the reason why the majority of respondents in this study thought that children start understanding the implications of genetic research after reaching 16 years of age. The issue of assent in biobank research should therefore be handled on a case-by-case basis, depending on maturity and social context.

All researchers and other stakeholders in this study were in agreement with regard to children having the right to withdraw their biological samples and/or data when they attain 18 years of age. This is not surprising because, at that age, they are deemed capable of making independent decisions and this provision is recognised in the United Nations Convention on the Rights of the Child (UN, 1998). However, in instances where the HBM and data are irreversibly anonymized, withdrawal may be impossible because of the inability to identify the particular sample and data.

Children are in a vulnerable position in biobank research because of the information that can potentially be obtained from HBM (Gurwitz et al., 2009; Hens, Nys, Cassiman, & Dierickx, 2011). Consent procedures should therefore be explicit to ensure that their safety, rights and welfare are protected.

5.4 Attitudes on ethics review and regulation of biobank research

Researchers and other stakeholders expressed the need to strengthen RECs to ensure comprehensive ethics review of biobank research. Research ethics committee oversight for the future use of stored samples helps to guarantee the ethical adequacy and scientific value of the research. Oversight adds further protections, since at the time of initial consent, future uses are unknown, cannot be predicted or explained, and participants consent to delegate research institutions and biobanks to make acceptable decisions about secondary research on their behalf (Mongoven & Solomon, 2012).

The ability to share samples and data is vital for the rapid growth of biobanking. Researchers and other stakeholders held a wide range of attitudes and views on the export and sharing of HBM. Overall, the majority of researchers and other stakeholders had a positive attitude towards the export and sharing of unlinked HBM, as long as proper procedures are followed in their handling. Stringent regulatory measures should be put in place to ensure that these samples are not misused. This is very important particularly when dealing with the transfer and sharing of HBM across borders.

Much as some respondents concurred that the export of HBM requires added protections, others raised concerns about the stringent conditions set by RECs. They were of the view that fewer restrictions should be put on the sharing and export of samples since these negatively affect scientific advancement. Some authors feel that RECs have over-demanding requirements and impose excessive limitations on biobanking and sample-sharing (Colledge et al., 2014). On the contrary, 50% of REC members and 79% of researchers and other stakeholders indicated that *more* restrictions should be put in place before sharing of HBM and associated data. They indicated that researchers should obtain re-consent if they wish to share the de-identified HBM or data (without a linkage file) with other researchers.

A greater majority were also of the opinion that donors have the right to set limits pertaining to the research that can be conducted using their tissues and that those limits should apply even when the samples have been made completely anonymous. Such attitudes are not surprising because, over the years, there has been a unidirectional export movement of HBM out of Africa to several destinations in the Western world with minimal benefits to the local populace, investigators and institutions (Staunton & Moodley, 2016). This has negatively impacted on the growth of local capacity, infrastructure and expertise. A study done at a South African institution reported that researchers and RECs did not tackle sufficiently inter-related ethical and regulatory issues related to HBM (Sathar et al., 2013). Therefore, research regulatory authorities should become more vigilant and ensure that biobank research in SA is adequately monitored.

Another reason cited was the loss of control on the use of exported samples once they cross borders. This issue has also been raised by local researchers from other sub-Saharan countries (Tindana et al., 2014). Enormous quantities of HBM whose fate is unknown, have been exported from low-resource to developed countries (Staunton & Moodley, 2013). This loss of control is partially attributable to the lack of effective mechanisms for tracking and monitoring HBM once they

cross their borders. To curb this, some RECs in South Africa are devising innovative ways of ensuring that all secondary analyses on samples are approved by the REC of record (*Biomedical Research Ethics Committee (BREC): Standard operating procedures, 2010*).

The above perspectives particularly with regard to the monitoring and tracking of exported samples should be seriously considered and incorporated in both national and international guidelines. This will facilitate international collaborative research, ensure that HBM are not abused and also reduce on the exploitation of disadvantaged researchers in low resource settings.

5.4.1 Perspectives on regulatory frameworks

The conduct of research is governed and guided by national legislation and guidelines; however, some researchers and other stakeholders noted that there are inconsistencies in these ethico-legal frameworks that might leave a window of opportunity for some unscrupulous researchers to exploit (Tindana et al., 2014). Some researchers and other stakeholders also noted the lack of harmonized standards for sharing samples across national borders (Whitley et al., 2012). Additionally, ethical guidelines governing biobanking are evolving and occasionally contradictory (Colledge et al., 2014). For instance, South African laws have no provisions for the governance and regulation of biobanks; neither do they have provisions for material transfer agreements (MTA) (Mahomed et al., 2015).

To address these challenges, the University of Witwatersrand (Wits) established a biobank ethics committee (BEC) in 2013 to specifically handle biobanking and related research. This BEC has developed principles, policy and guidelines governing the review and approval of applications seeking to establish biobanks, the review of all research using HBM and associated data from these biobanks, as well as a comprehensive MTA document for the transfer of HBM (Mahomed et al., 2015). Notably, these guidelines were approved for inclusion into the national Department of Health research ethics guidelines. Transfer of HBM between institutions within South Africa can also be a challenge. Whereas more emphasis is put on cross-border transfer of samples, variations across RECs within the country in terms of policies and processes concerning human participant protection for biobank research can also affect cross-institutional collaborative research. Therefore, there is a need to harmonize ethico-legal frameworks between institutions within the country and with other nations.

5.5 Confidentiality and the protection of human participants with respect to de-identified/anonymized samples

The main ethical emphasis of biobank research is centred on balancing the quest for scientific knowledge against the protection of individual participants and communities. There were varying views with regard to the use of de-identified HBM being considered to be 'human participant research'. About 68% of researchers and other stakeholders agreed that this research is human participant research while 32% disagreed. This is a cause for concern because, according to Section 1.1.7 of the South African ethics guidelines, such research does indeed constitute human participant research; therefore, such studies need to be reviewed and approved by RECs (DOH, 2015). However, in the USA, according to the Common Rule, research on de-identified/anonymized biological samples or data is not considered human participant research (provided the investigator has no access to the key to the code that could link specimens to identifiers) and can thus be exempted from ethical review (45CFR46; Harrell & Rothstein, 2016; Witt & Witt, 2016). Despite this policy, in the USA, biobank protocols are subjected to REC review, irrespective of identifiability (Harrell & Rothstein, 2016). In collaborative research, a protocol is reviewed both by a REC in the host country and by a local REC in the host country. These contradictory guidelines cause much confusion during the ethics review process (Rothwell et al., 2015) and this reinforces the debate for joint review of protocols and the need for harmonization of ethical guidelines.

Researchers and other stakeholders, and REC members, were in agreement that storage of HBM and data for future genetic studies is acceptable as long as they are anonymized. Researchers in this study had divergent views on the likelihood of donor identification and the harm that can result from such identification. The coding of samples and data is aimed at safeguarding the privacy of the participant; however, in the genomics era, maintenance of absolute anonymity is almost impossible (Witt & Witt, 2016). It is therefore not surprising that researchers had these varying opinions on this topic.

There were divergent views between researchers and other stakeholders, and REC members, regarding the likelihood of government or other security agencies compelling investigators to divulge information about research participants. Thirty-two percent of REC members believed that this is likely, compared to 58% of researchers and other stakeholders. South African ethico-legal frameworks on biobanking are incoherent, vague and in need of urgent attention (Andanda & Govender, 2015) and they do not give adequate protection in the field of genomics ("South African Law Reform Commission: Privacy and data protection," 2005).

There are several legal instruments that govern the privacy of information in South Africa ("Protection of Personal Information Act, Republic of South Africa ", 2013; *South African National Health Act*, 2003). However, they contain contradictory clauses that do not offer absolute protection to private information from government and law enforcement agencies. For comparison, the privacy and confidentiality of genetic information in the USA are also not absolute. Firstly, in the USA information is protected by privacy laws although some of them might not be applicable to biobanking. For biobanks, the USA constitution only protects those persons who have HBM or data held by government biobanks/investigators on the government payroll. However, the US Supreme Court does not acknowledge the "constitutional right to informational privacy, including in the context of health information" (Harrell & Rothstein, 2016, p. 114). Secondly, the Health Insurance Portability and Accountability Act (HIPAA) of 1996 was enacted to protect the privacy and security of individually identifiable health information held by covered entities ("generally, health care clearinghouses, employer sponsored health plans, health insurers, and medical service providers that engage in certain transactions") and their business associates (DHHS). Thirdly, the Genetic Information Non-discrimination Act was enacted to protect people from genetic discrimination at work and in health insurance (Slaughter, 2013). Fourthly, there are several other measures that have been put in place to safeguard private information, for example, the issuance of Confidentiality Certificates by the Department of Health and Human Services that protects information from law enforcement and bars the release of data whose disclosure could potentially harm an individual (Wolf et al., 2013). Although a Confidentiality Certificate is permanent, it can be waived or revoked by the researcher. The above list is not exhaustive, but it can be noted that there are several laws that are ambiguous, contradictory and confusing. From the above analysis, it is evident that there may not be an absolute protection of genetic information from government and other law enforcement agencies in all circumstances.

5.6 Challenges in ethical review of biobank research

Only 8% of researchers and other stakeholders reported ever having had challenges in their research ethics review. Most of the challenges have already been discussed in the preceding sections of this chapter. However, researchers and other stakeholders also expressed their discontent with the ethics review process with regard to assessment of the scientific validity of their studies. They queried the technical competence of REC members in reviewing biobank research protocols. This might partly be attributed to the lack of diversity and inadequate training of REC members (Milford et al., 2006; Nyika, Kilama, Chilengi, et al., 2009; Nyika, Kilama, Tangwa, et al., 2009; Silaigwana &

Wassenaar, 2015). A study conducted with 31 RECs across sub-Saharan Africa (excluding South Africa) reported that 38% of respondents had not received any form of research ethics training and 92% expressed the need have training in scientific research designs, risk-benefit determination and monitoring of research (Nyika, Kilama, Chilengi, et al., 2009). During the ethics review process, RECs have the option of co-opting individuals with the necessary technical expertise and experience to review protocols they feel are beyond their technical competence. There should also be continuing professional development activities for REC member to ensure that they keep abreast with current advances in research and their associated ethical, legal and social implication.

5.7 Other issues that emerged on HBM and data-sharing

The majority of researchers and other stakeholders felt that the sharing of samples and associated data was imperative to the research industry and is important in advancing the scientific knowledge necessary to address the ever-increasing global health challenges. They opined that sharing of samples and data is cost effective and allows for the full exploitation of valuable biological samples. In fact, the USA National Institutes of Health, a major funder of biomedical research in SA requires that all genomic data be shared and made easily accessible to other researchers (NIH).

On the other hand, some researchers and other stakeholders thought the export of HBM and associated data was very controversial and expressed their disapproval of the transfer of samples across borders. They were wary of the exploitation of vulnerable communities and the possibility of local researchers and communities not benefitting from exported samples. Instead, they suggested that all necessary tests be conducted in South Africa to enhance local research capacity, but if this was not possible, then samples be destroyed. The genesis of these attitudes probably originates from the several instances of biobank governance misconduct by researchers from developed countries that have been highlighted in literature (Andanda, 2008; Emanuel et al., 2004; Emerson et al., 2011; Mello & Wolf, 2010; Mudur, 2002; Upshur et al., 2007; Zhang et al., 2010), particularly allegations of viewing African institutions and their investigators as sample-collecting centres and collection technicians respectively (Ndebele, 2007). In fact, two researchers expressed the need to protect the “original researcher” who obtains the sample. As a sign of transparency and respect, the “original researchers” should not be treated as ‘dignified sample collectors’. They should have access to the exported samples as and when they need them for new studies, they should be consulted before any third party utilizes the samples for research (Zhang et al., 2010), and they should be regularly updated on the state of the samples.

Researchers and other stakeholders also believed that researchers, participants and communities should benefit from biobank research. Many participants donate their samples with altruistic intentions and the desire to contribute to the community (Allen & McNamara, 2011; Kettis-Lindblad et al., 2006; Petersen et al., 2014). A sizable proportion of them expect personal benefit from research participation (Moodley et al., 2014; Petersen et al., 2014). The sharing of benefits resulting from the research should be fair and equitable to all stakeholders. Though there may not be any tangible benefits, international collaborative research should make available opportunities for enhancing the scientific capacity of the local institution as a benefit (Tindana et al., 2014).

The issue of sample/data ownership and intellectual property rights was also raised. Researchers and other stakeholders suggested that sample/data ownership and intellectual property rights should be negotiated between institutions under MTAs and MoUs between the provider and the user. One researcher felt that the ownership of biological samples and data should be retained by South Africans. A majority were of the view that a participant who donates a specimen for scientific research retains control of his/her sample and they believed that donors have the right to set limits on the research that can be conducted using their samples even after they have been made completely anonymous. Most potential sample donors expect to have a say in the utilization of their biological samples and associated information (Chen et al., 2005; Trinidad et al., 2010).

If research is to benefit society and permit advancements in science, there must be a balance between the control participants desire and societal interests (Foe, 2014). Most countries emphasize export of samples and ignore in-country research collaborations. This probably arises from the lack of guidelines on this issue, especially on the African continent (Nnamuchi, 2015). The insistence of developing countries on the inclusion of provisions for benefit-sharing and ways of handling intellectual property rights in standard MTAs has often been rebuffed by Northern research partners (Zhang et al., 2010). This is further compounded by variations (national and institutional) in intellectual property policies on the sharing of HBM and associated data (Vaught & Lockhart, 2012). For example, the issue of ownership of HBM in South African law is not clearly defined and this could potentially lead to exploitation of local researchers and participants. Hence, according to Mahomed et al. (2015), there is a need to amend South African legislation to provide a clear and reliable message regarding any proprietary claims in respect of HBM.

From the discussion above it can be deduced that stakeholders in the biobank research industry in South Africa have a range of perspectives on informed consent and ethics review of biobank research, comprising both convergent and divergent views.

5.8 Study limitations

There were several study limitations. Implementation of this study was delayed because of the need to obtain institutional permissions and full ethical approval from two Universities (Stellenbosch HREC and UKZN BREC) before commencement of the study; this process took almost nine months (July 2014 - May 2015). Therefore, data collection only started in June 2015. Shortly after commencement (August 2015), the UKZN server that was being used to distribute the survey crashed and three months were lost as efforts were made to rectify the technical problem, in vain. Eventually, subscription was made to the SurveyMonkey® online survey program and the study resumed in November 2015.

Another major limitation to this study was the requirement for submission of the protocol for full ethical review by institutional RECs of the different universities contacted. For instance, an attempt to gain access to the H3Africa consortium failed because when contact was made with the University of Cape Town, the principal investigator was requested to make a full submission for ethical review although the study had already obtained full ethical approval from UKZN BREC and SU HREC.

The principal investigator was also required by UKZN BREC to apply for protocol amendment for every research site that agreed to participate in the study before contacting any potential respondents from that particular site. Thus, a lot of time and effort was lost because of these multiple regulatory requirements from institutions and the REC of record; this greatly affected the number of sites that eventually participated in the study. In addition, some RECs and universities that were contacted did not give any feedback.

The response rate was rather low thus the results of this study might not be generalizable. The low response rate can be attributed to several reasons. First, as we dispatched the survey to a rather wide audience (university academic staff), several recipients may have thought this was not applicable to them. Second, the questionnaire was estimated to take 10 to 20 minutes to complete. Third, we lost a lot of time (more than three months) at the time the UKZN server crashed; many respondents tried to access the survey but could not, and this might have led them to give up. Third, the low return rate for questionnaires among professionals is well documented (Ruiz-Canela, Valle-

Mansilla, & Sulmasy, 2009). In addition, self-administered email-based surveys have been associated with poor response rates (Burgess, 2001). The response rate for REC members was especially low and it was difficult to ascertain whether REC administrators/coordinators distributed the survey link to members as requested. To mitigate this, potential respondents were sent follow-up emails and REC administrators/coordinators were also requested to send reminders thanking members for their participation and to remind them to complete the survey if they had not already done so. On average, five reminders were sent in an effort to improve the response rate.

The time and effort wasted in this study could have been avoided if the ethical review process for multi-site studies in South Africa was standardized. This would also reduce the unnecessary distortion of research protocols since different RECs request varying changes that could potentially impact on the science and ethics of the study. For future studies, it is recommended that institutions of research (e.g. universities) recognize ethical approval from any accredited REC within the country. However, investigators should submit the protocol and regulatory documents to the different study sites, just seeking permission, rather than ethical approval. In the event that any site has scientific and/or ethical concerns, the principal investigator should be in a position to respond in concert with the REC of record. In the long run, this will reduce unnecessary multiple ethical approval of research.

CHAPTER 6: CONCLUSIONS AND RECOMMENDATIONS

6.1 Conclusions

This was a pilot study with a small sample size therefore no definite conclusions can be drawn. However, the results of this study document the perspectives of REC members, researchers and other stakeholders on informed consent and the ethics review process of biobank research in South Africa. Generally, the attitudes of REC members, researchers and other stakeholders on informed consent, ethics review of biobank research, and the protection of human participants in biobank research are positive and ethically informed. Stakeholders believe that there is a need for functional regulatory frameworks to govern the collection, storage, sharing and future use of HBM both within South Africa and across borders. Ethical guidelines and regulatory processes across countries should be harmonized to facilitate international collaborative research and the sharing of HBM and associated data.

To assure adequate protection for human research participants, stakeholders suggested a rigorous ethics review process with appropriate guidance to investigators, and a comprehensive informed consent process. They think broad consent is suitable for biobank research. Ethics review of biobank research is negatively perceived in some instances. These negative perceptions include: reservations on the competency of some RECs to review biobank-related research; a view that RECs sometimes place restrictions on research that are too strict; and the high cost of translating informed consent forms and other research-related documents. Ethics review is also perceived as placing a great deal of emphasis on sample storage and participant confidentiality.

6.2 Recommendations

The following recommendations can be drawn from the findings of the study:

1. Research ethics committees should be strengthened to ensure comprehensive research ethics review of biobank research. Research and academic institutions, and research regulatory agencies, should organize continuing professional development activities for REC members and researchers, to ensure that they keep abreast of current advances in this type of research and associated ethical, legal and social implications.
2. Research ethics committees should provide sufficient information and support to guide investigators through the ethics application and review process, to ensure that adequate measures are put in place to safeguard the safety, rights and welfare of research participants and communities.

3. Research ethics committees should develop broad or tiered consent templates, to ensure that participants are given a range of consent options to facilitate informed decision-making.
4. Research ethics committees should ensure that biobank-related protocols (where applicable) have an adequate community engagement (CE) plan. Research ethics committees should also remind/create awareness amongst researchers regarding the value of CE; they should encourage them to explore different CE strategies.
5. Research ethics committees should strengthen continuing review and monitoring of approved research. They should be encouraged to make field visits and on-site inspections of research, to ensure that researchers comply with ethical standards.
6. Research ethics committees, with the help of local researchers, should establish mechanisms for effective tracking and monitoring of HBM/data both within South Africa and across borders. Where possible, sample analyses should be conducted in South Africa; this will help enhance local human resource and infrastructural capacity.
7. Legislation and guidelines specific to biobanking and genetic research in South Africa should be developed. Among others, the regulations should address pertinent issues in pediatric biobanking and genetic research, and biobank governance issues. There should be harmonization of ethico-legal frameworks for the sharing of human biological materials and associated data between institutions within the country and with other nations. This will facilitate easy transfer and future use of these resources.
8. More in-depth research should be conducted to explore the perspectives and attitudes of all stakeholders towards biobanking and related research. Information from such research may be important in the planning and implementation of continuing professional development activities and could contribute to the harmonization of guidelines for governing biobank research in South Africa.

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Welcome to My Survey

Dear Colleague,

My name is Dr. Erisa Mwaka and I am a research clinician currently doing a Masters' degree through the SARETI programme at UKZN. The topic of my study is Stakeholder perspectives on informed consent and ethics review of research involving human specimen resource repositories (biobanks) in South Africa. I am asking both scientists and REC members to assist me with this project by completing a short online anonymous questionnaire. More details of the project can be found at http://thrive.or.ug/downloads/Participant_information_Consent_form.pdf. You do not need to sign the consent form as completion of the questionnaire will be interpreted as consent. Responses are anonymous and are de-linked from email addresses.

I do hope that you will assist me by taking the time to complete the survey
Many thanks in Advance

Dr Mwaka Erisa Sabakaki, MMed, PhD
South Africa Research Training Initiative (SARETI)

University of KwaZulu-Natal

Dr Lyn Horn
Stellenbosch University
Supervisor

There are 18 questions in this survey.

Click on the button to begin survey

Any questions can be addressed to erisamwaka@gmail.com

DEMOGRAPHIC INFORMATION

1. What is your gender?

Female

Male

2. What is your race?

Please choose only one of the following:

- Black
- White
- Coloured
- Indian

Other (please specify)

3. Highest degree attained

- PhD
- MMed
- MPhil
- MSoc Sci
- MSc
- MBChB
- Honours
- Bachelors

Other (please specify)

4. What is your institution of affiliation?

Please choose all that apply:

- University
- Research institution
- Hospital/Health facility
- Public Health
- Repository/Biobank
- Other academic institution

Other (please specify)

5. What is your most frequent work activity?

Please choose only one of the following:

- Research
- Clinical
- Academics/Lecturing
- Administration
- Not applicable

Other (please specify)

6. Have you ever participated in research involving the collection, storage and future use of human biological materials?

Please choose only one of the following:

- Yes
- No

7. What is/was your role in repository/biobank research?

Please choose all that apply:

- Principal Investigator
- Co-Principal Investigator
- Researcher
- Clinician
- Pathologist
- Laboratory/Repository personnel
- Bioethicist/REC member

Other (please specify)

8. How long have you been involved in repository/biobank research?

Please choose only one of the following:

- Never been involved
- Less than 1 year
- 1-2 years
- 3-5 years
- 6-9 years
- More than 10 years

9. Have you ever served on a Research Ethics Committee?

Please choose all that apply and provide a comment:

- Yes
- No

10. If yes for how long?

INFORMED CONSENT

This section explores your perspectives on informed consent in human research that involves the collection, storage and future use of human biological specimens.

Please indicate your level of agreement with each statement on a scale from strongly agree to strongly disagree.

11. Studies that involve the storage of human biological materials for future research require separate informed consent forms for the current study and another one for each new study using the stored sample.

Please choose only one of the following:

- Strongly Agree
- Somewhat Agree
- Neutral
- Somewhat Disagree
- Strongly Disagree
- Don't know

The next set of questions is about broad consent and general consent.

In **general consent**, at the time of sample collection participants consent for the use of their samples in any and all future studies with no restrictions on the purpose of the research.

In **broad consent**, at the time of sample collection participants consent for the use of their samples in the current study and a wide range of future research studies based on a broad category and whose specifics are unknown.

12. What is your opinion on the type of consent that is applicable to biobank-related research?

Please choose the appropriate response for each item:

	Strongly Agree	Somewhat Agree	Neutral	Somewhat disagree	Strongly Disagree
The use of a broad consent for research that anticipates future (unknown) research studies is acceptable.	<input type="radio"/>				
A general consent should only be accepted when samples are anonymous.	<input type="radio"/>				
A research participant has the right to establish limits regarding the research that can be done using his or her tissue.	<input type="radio"/>				
The limits should apply even after the tissue sample has been completely made anonymous	<input type="radio"/>				

13. I believe it is ethically necessary to obtain re-consent from research participants if:

Please choose the appropriate response for each item:

	Strongly Agree	Somewhat Agree	Neutral	Somewhat Disagree	Strongly Disagree
The researcher wants to investigate a different, but related, condition or clinical manifestation.	<input type="radio"/>				
The researcher wants to investigate an unrelated condition or clinical manifestation.	<input type="radio"/>				
The researcher wants to add genetic measures to a study that did not originally include them.	<input type="radio"/>				
The researcher wants to share the participant's de-identified sample or data (without a linkage file) with an investigator at another institution.	<input type="radio"/>				

14. In case re-consent is not possible would REC approval for all new studies suffice?

Please choose only one of the following:

Yes

No

INFORMED CONSENT

The following questions address consent and assent from minors (< 18 years)

15. Please indicate your level of agreement with each statement on a scale of "Strongly agree to Strongly disagree".

Please choose the appropriate response for each item:

	Strongly Agree	Somewhat Agree	Neutral	Somewhat Disagree	Strongly Disagree
Parental consent is sufficient for storage of biological samples for genetic research of any child who cannot assent (give permission) because he/she cannot understand the nature of research.	<input type="radio"/>				
Once a child can understand the implications of biological sample storage and genetic research, he/she must be allowed to assent (give permission).	<input type="radio"/>				
A child should have the right to withdraw their biospecimen/data from a repository when he/she is 18 years old.	<input type="radio"/>				

16. From which age do you think children can understand the implications of storage of biological samples for future genetic research?

Please choose only one of the following:

- 0-3 years
- 4-6 years
- 7-9 years
- 10-12 years
- 13-15 years
- 16-18 years

17. From which age do you think children can understand the implications of genetic research?

Please choose only one of the following:

- 0-3 years
- 4-6 years
- 7-9 years
- 10-12 years
- 13-15 years
- 16-18 years

HUMAN PARTICIPANT PROTECTION

This part is about the protection of human participants in research involving the use of their biospecimens.

18. For the following questions where the term "coded" is used, it refers to de-identified/anonymized specimens, samples, or data in which the original investigator maintains a linkage file (with study numbers and personal identifiers) separate from the specimens/samples/data. This linkage would not be available to other investigators.

Please choose the appropriate response for each item:

	Strongly Agree	Somewhat Agree	Neutral	Somewhat Disagree	Strongly Disagree
The storage of human biological specimens and data for future genetic research is acceptable as long as they are anonymized.	<input type="radio"/>				
A participant who donates blood for scientific research remains in control over his/her blood.	<input type="radio"/>				
Use of coded human tissue specimens constitutes human subject research (Assume researchers do not have access to the link between the original and coded data).	<input type="radio"/>				

19. We would appreciate your opinion concerning the following statements.

Please indicate your level of agreement with each statement on a scale of very likely to very unlikely.

Identifiability and possible harms:

Please choose the appropriate response for each item:

	Very Likely	Somewhat Likely	Neutral	Somewhat Unlikely	Strongly Unlikely
How likely is it that a research participant would be personally identified in a study involving coded data?	<input type="radio"/>				
How likely is it that a research participant would be harmed as a result of identification from coded data?	<input type="radio"/>				
How likely is it that a government agency or other law enforcement agency might compel investigators to disclose information about genetic research participants?	<input type="radio"/>				

20. Improper handling of research results can cause harm to the community from which a sample donor belongs

Please choose only one of the following:

- Strongly Agree
- Somewhat Agree
- Neutral
- Somewhat Disagree
- Strongly Disagree
- Don't know

REC REVIEW PROCESS

This section addresses the ethics review process.

21. Which of the following issues (if any) have required considerable discussion between researchers and REC in the review of research involving the future use of biospecimens e.g genetic research? By 'considerable discussion' we mean more than 2 or 3 back-and-forth rounds and/or more than a 1-hour conversation

Please choose all that apply:

- Procedures for protecting personal information and samples
- Informed consent process and documentation
- Re-consent for use of sample/ data for a new study or change in purpose
- Independent ethical review of all new studies on stored samples
- Plans or lack of plans to deal with community harm or benefits
- None of the above
- Other (please specify)

22. Which of the following issues (if any) have required considerable discussion between researchers and REC in the review of research involving the future use of biospecimens e.g genetic research? By 'considerable discussion' we mean more than 2 or 3 back-and-forth rounds and/or more than a 1-hour conversation

Please choose all that apply:

- Procedures for protecting personal information and samples
- Informed consent process and documentation
- Re-consent for use of sample/ data for a new study or change in purpose
- Independent ethical review of all new studies on stored samples
- Plans or lack of plans to deal with community harm or benefits
- None of the above

CHALLENGES IN ETHICS REVIEW

We would appreciate it if you answered the following two questions

23. Have you ever had any challenges in the ethical review of research involving the use of HBM?

Please choose only one of the following:

Yes

No

24. If yes what challenges did you face? Suggests ways in which such challenges can be overcome?

Please write your answer here:

25. What is your opinion on the export and sharing of biological specimens and associated data e.g in genetic research?

Please write your answer here:

26. Thank you for participating in this study, if you choose, please feel free to offer any comments you would like to share with us

APPENDIX II RESEARCH ETHICS COMMITTEE MEMBERS' SURVEY TOOL

Welcome to My Survey

Dear Colleague,

My name is Dr. Erisa Mwaka and I am a research clinician currently doing a Masters' degree through the SARETI programme at UKZN. The topic of my study is Stakeholder perspectives on informed consent and ethics review of research involving human specimen resource repositories (biobanks) in South Africa. I am asking both scientists and REC members to assist me with this project by completing a short online anonymous questionnaire. More details of the project can be found at http://thrive.or.ug/downloads/Participant_information_Consent_form.pdf. You do not need to sign the consent form as completion of the questionnaire will be interpreted as consent. Responses are anonymous and are de-linked from email addresses.

I do hope that you will assist me by taking the time to complete the survey
Many thanks in Advance

Dr Mwaka Erisa Sabakaki, MMed, PhD
South Africa Research Training Initiative (SARETI)

University of KwaZulu-Natal

Dr Lyn Horn
Stellenbosch University
Supervisor

There are 18 questions in this survey.

Click on the button to begin survey

DEMOGRAPHIC INFORMATION

1. What is your gender?

Please choose only one of the following:

- Male
- Female
- Other

2. What is your race?

Please choose only one of the following:

- Black
- White
- Coloured
- Indian
- Other

3. Highest degree attained

Please choose only one of the following:

- PhD
- MMed
- MPhil
- MSoc Sci
- MSc
- MBChB
- Honours
- Bachelors

Other (please specify)

4. What is your role on the Research Ethics Committee (REC)?

Please choose only one of the following:

- Chair
- Member
- Legal member
- Scientist
- Non-voting Administrator/coordinator
- Voting Administrator/coordinator
- Community representative

Other (please specify)

5. For how long have you served on a REC?

Please choose only one of the following:

- Less than 1 year
- 1-2 years
- 3-4 years
- More than 5 years

6. Are you involved, at any level, in the review or coordination of research that involves the collection, storage and future use of human biological specimens?

Please choose only one of the following:

- Yes
- No

REC APPLICATION AND REVIEW PROCESS

This section addresses specific aspects of the REC application process

7. My REC gives investigators specific ethical guidance on how to prepare a new application in human research that involves the collection, storage and future use of human biological specimens

Please choose only one of the following:

- Yes
- No
- Uncertain

8. For each of the following, do you feel that specific ethical guidance is needed for research that involves the collection, storage and future use of human biological specimens?

	Yes	No
Writing a consent form/ information sheet:	<input type="radio"/>	<input type="radio"/>
Designing procedures for recruiting sample donors:	<input type="radio"/>	<input type="radio"/>
Developing a research study design	<input type="radio"/>	<input type="radio"/>
Developing a repository for biospecimen and associated data	<input type="radio"/>	<input type="radio"/>

9. For applications requiring full committee review, my REC takes more time to review biobank-related research compared with other types of research.

- Strongly Agree
- Somewhat Agree
- Neutral
- Somewhat Disagree
- Strongly Disagree
- Don't know

10. Which of the following issues (if any) have required considerable discussion between researchers and REC in the review of research involving the future use of biospecimens? By 'considerable discussion' we mean more than 2 or 3 back-and-forth rounds and/or more than a 1-hour conversation.

Please choose all that apply

- Informed consent process or documentation
- Procedures for protecting personal information and samples
- Scientific aspects of the study of the study
- Re-consent for use of sample/ data for a new study or change in purpose
- Re-use of stored samples for future studies
- Plans or lack of plans to deal with community harm or benefits
- Shipping of samples abroad
- None of the above
- Other

11. *Please indicate your level of agreement with each statement on a scale of "Strongly agree to Strongly disagree"*

In broad consent, at the time of sample collection participants consent for the use of their samples in the current study and a wide range of future research studies based on a broad category and whose specifics are unknown.

The use of a broad consent form that anticipates future research studies (for example to establish a repository, genetic research, study additional diseases) is acceptable to my REC.

Please choose only one of the following

- Strongly Agree
- Somewhat Agree
- Neutral
- Somewhat Disagree
- Strongly Disagree
- Don't know

INFORMED CONSENT

The following section addresses informed consent issues that are often raised in conduct of research that involves the collection and storage of human biological specimens for future research.

12. Please indicate your level of agreement with each statement on a scale of "Strongly agree to Strongly disagree"

Studies that involve the storage of human biological materials for future research require separate informed consent forms for the current study and another one for each new study using the stored sample.

Please choose **only one** of the following:

- Strongly Agree
- Somewhat Agree
- Neutral
- Somewhat Disagree
- Strongly Disagree
- Don't know

13. Fresh ethical approval is necessary for the re-use of stored samples

Please choose **only one** of the following:

- Yes
- No

14. I believe it is ethically necessary to obtain re-consent from research participants if:

Please choose the appropriate response for each item:

	Strongly agree	Somewhat agree	Neutral	Somewhat disagree	Strongly disagree	Don't know
The researcher wants to investigate a different, but related, condition or clinical manifestation.	<input type="radio"/>					
The researcher wants to investigate an unrelated condition or clinical manifestation.	<input type="radio"/>					
The researcher wants to add genetic measures to a study that did not originally include them.	<input type="radio"/>					
The researcher wants to share the participant's de-identified sample or data (without a linkage file) with an investigator at another institution.	<input type="radio"/>					
The original consent was given by a minor subject's parents and the subject is now old enough to decide for him or herself.	<input type="radio"/>					

HUMAN PARTICIPANT PROTECTION

This part is about the protection of human participants in research involving the use of their biospecimens.

15. For the following questions where the term "coded" is used, it refers to deidentified/ anonymized specimens, samples, or data in which the original investigator maintains a linkage file (with study numbers and personal identifiers) separate from the specimens/samples/data. This linkage would not be available to other investigators.

	Strongly Agree	Somewhat Agree	Neutral	Somewhat Disagree	Strongly Disagree	Don't know
The storage of human biological specimens and data for future genetic research is acceptable as long as they are anonymized.	<input type="radio"/>					

7

16. We would appreciate your opinion concerning the following statements.
Please indicate your level of agreement with each statement on a scale of "very likely" to "very unlikely".

Identifiability and possible harms:

Please choose the appropriate response for each item:

	Very Likely	Somewhat Likely	Neutral	Somewhat Unlikely	Very Unlikely
How likely is it that a research participant would be personally identified in a study involving coded data?	<input type="radio"/>				
How likely is it that a research participant would be harmed as a result of identification from coded data?	<input type="radio"/>				
How likely is it that a government agency or other law enforcement agency might compel investigators to disclose information about genetic research participants?	<input type="radio"/>				

17. Improper handling of research results can cause harm to the community from which a sample donor belongs

- Strongly Agree
- Somewhat Agree
- Neutral
- Somewhat Disagree
- Strongly Disagree
- Don't know

18. Thank you for participating in this study, if you choose, please feel free to offer any comments you would like to share with us:

APPENDIX III UNIVERSITY OF KWAZULU-NATAL BREC ETHICAL APPROVALS



10 February 2015

Dr Erisa Mwaka
South African Research Ethics Training Initiative
School of Applied Human Sciences
University of KwaZulu-Natal
erisamwaka@yahoo.com

PROTOCOL: Stakeholders perspectives on informed consent and ethics review of research involving human specimen resource repositories (BIOBANKS) in South Africa: Degree Purposes (MSocSci). BREC REF: BE412/14.

EXPEDITED APPLICATION

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application received on 01 September 2014.

The study was provisionally approved pending appropriate responses to queries raised. Your responses received on 16 January 2015 to queries raised on 01 December 2014 have been noted by a sub-committee of the Biomedical Research Ethics Committee. The conditions have now been met and the study is given full ethics approval to commence at the following sites only:

- Stellenbosch permission noted, study may commence with Stellenbosch sample.
- Approval is given to commence data with HPCA REC members.

Please note that UKZN permission is pending and study can only commence at UKZN once permission has been submitted to BREC.

This approval is valid for one year from **12 February 2015**. 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 (2004), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at <http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx>.

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

The sub-committee's decision will be **RATIFIED** by a full Committee at its meeting taking place on **10 March 2015**.

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

Biomedical Research Ethics Committee

Professor D R Wassenaar (Chair)

Westville Campus, Govan Mbeki Building

Postal Address: Private Bag X54001, Durban 4000

Telephone: +27 (0) 31 260 2496 Facsimile: +27 (0) 31 260 4809 Email: brec@ukzn.ac.za

Website: <http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx>

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BIOMEDICAL RESEARCH ETHICS ADMINISTRATION
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Private Bag X 54001
Durban
4000
KwaZulu-Natal, SOUTH AFRICA
Tel: 27 31 2604769 - Fax: 27 31 260-4609
Email: BREC@ukzn.ac.za

Website: <http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx>

29 April 2015

Dr Erisa Mwaka
South African Research Ethics Training Initiative
School of Applied Human Sciences
University of KwaZulu-Natal
Private Bag X01
Scottville, 3209
erisamwaka@yahoo.com

Dear Dr Mwaka

PROTOCOL: Stakeholders perspectives on informed consent and ethics review of research involving human specimen resource repositories (BIOBANKS) in South Africa: Degree Purposes (MSocSci). BREC REF: BE412/14.

We wish to advise that your letter dated 16 April 2015 requesting approval of Amendments (addition of new site UKZN) have been noted and approved by a sub-committee of the Biomedical Research Ethics Committee.

This approval will be ratified by a full Committee at its meeting taking place on **09 June 2015**.

Yours sincerely

Ms A Marimuthu
Senior Administrator: Biomedical Research Ethics



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Tel: 27 31 2604769 - Fax: 27 31 2604609
Email: BREC@ukzn.ac.za

Website: <http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx>

12 February 2016

Dr Erisa Mwaka
South African Research Ethics Training Initiative
School of Applied Human Sciences
University of KwaZulu-Natal
erlsamwaka@yahoo.com

Dear Dr Mwaka

PROTOCOL: Stakeholders perspectives on informed consent and ethics review of research involving human specimen resource repositories (BIOBANKS) in South Africa; Degree Purposes (MSocSci). BREC REF: BE412/14.

RECERTIFICATION APPLICATION APPROVAL NOTICE

Approved: 12 February 2016
Expiration of Ethical Approval: 11 February 2017

I wish to advise you that your application for Recertification received on 12 January 2016 for the above protocol has been noted and approved by a sub-committee of the Biomedical Research Ethics Committee (BREC) for another approval period. The start and end dates of this period are indicated above.

If any modifications or adverse events occur in the project before your next scheduled review, you must submit them to BREC for review. Except in emergency situations, no change to the protocol may be implemented until you have received written BREC approval for the change.

This approval will be ratified by a full Committee at its next meeting taking place on 08 March 2016.

Yours sincerely

Mrs A Marimuthu
Senior Administrator: Biomedical Research Ethics



Approval Notice
New Application

20-May-2015

Mwaka, Erisa Sabakaki ES

Ethics Reference #: S15/04/076

Title: **Stakeholder perspectives on informed consent and ethics review of research involving human specimen resource repositories (biobanks) in South Africa.**

Dear Dr Erisa Sabakaki Mwaka

The **New Application** received on **14-Apr-2015**, was reviewed by Health Research Ethics Committee (via Committee Review procedures on) **06-May-2015** and has been approved.

Please note the following information about your approved research protocol:

Protocol Approval Period: **06-May-2015 -06-May-2016**

Present Committee Members:

Weber, Franklin CFS

Unger, Marianne M

Barsdorf, Nicola N

Botha, Paul JP

Decloedt, Eric EH

Rohland, Elvira EL

Hoek, Kim KGP

Werely, Cedric CJ

Hendricks, Melany ML

Ferris, William WF

Welzel, Tyson T

Abulfathi, Ahmed AA

Mukmda, Fidele FK

Please remember to use your **protocol number (S15/04/076)** on any documents or correspondence with the HREC concerning your research protocol.

Please note that the HREC has the prerogative and authority to ask further questions, seek additional information, require further modifications, or monitor the conduct of your research and the consent process.

After Ethical Review:

Please note a template of the progress report is obtainable on www.stm.ac.za/irbs and should be submitted to the Committee before the year has expired. The Committee will then consider the continuation of the project for a further year (if necessary). Annually a number of projects may be selected randomly for an external audit.

Translation of the consent document to the language applicable to the study participants should be submitted.

Federal Wide Assurance Number: 00001372

Institutional Review Board (IRB) Number: IRB0005239

The Health Research Ethics Committee complies with the SA National Health Act No.61 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 Part 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes 2004 (Department of Health).

Provincial and City of Cape Town Approval

Please note that for research at a primary or secondary healthcare facility permission must still be obtained from the relevant authorities (Western Cape

Department of Health and/or City Health) to conduct the research as stated in the protocol. Contact persons are Ms Claudette Abrahams at Western Cape Department of Health (healthres@pgwc.gov.za Tel: +27 21 483 9907) and Dr Helene Visser at City Health (Helene.Visser@capetown.gov.za Tel: +27 21 400 3981). Research that will be conducted at any tertiary academic institution requires approval from the relevant hospital manager. Ethics approval is required BEFORE approval can be obtained from these health authorities.

We wish you the best as you conduct your research.

For standard HREC forms and documents please visit: www.stm.ac.za/ids

If you have any questions or need further assistance, please contact the HREC office at 0219399657.

Included Documents:

CV L Horn
Protocol Synopsis
Protocol
Institutional Permission letter
Proposed work plan and budget
Questionnaire for REC members
Questionnaire for researchers
Declaration L Horn
Application form
Declaration ES Mwaka
UKZN ethics approval
Checklist
CV ES Mwaka
Participant information leaflet & consent form

Sincerely,

Franklin Weber
HREC Coordinator
Health Research Ethics Committee |

APPENDIX V PARTICIPANT INFORMATION LEAFLET AND CONSENT FORM

TITLE OF THE RESEARCH PROJECT: Stakeholder perspectives on informed consent and ethics review of research involving human specimen resource repositories (biobanks) in South Africa.

REFERENCE NUMBER: BE412/14

PRINCIPAL INVESTIGATOR: Dr. Erisa Sabakaki Mwaka

ADDRESS: University of Kwazulu-Natal, College of Humanities, School of Applied human sciences, Department of Psychology (Pietermartizburg Campus)

CONTACT NUMBER: +256752575050 (Mobile), SARETI Office 0332606162

Date:

Dear colleague, greetings.

You are being invited to consider participating in a study that involves research on stakeholder perspectives on informed consent and ethics review of research involving human specimen resource repositories (biobanks) in South Africa. We are seeking input from research ethics committee members, scientists (researchers), clinicians, repository managers and personnel, pathologists and laboratory staff participating in research that involves the collection, storage and future use of human biological materials. We aim to inform consensus and harmonization of guidelines and repository/biobank governance.

The study is expected to enrol about 400 participants from different research ethics committees (REC) and, clinical and research sites in Kwazulu-Natal and Western Cape provinces, and the Human Heredity and Health in Africa (H3Africa) network. It will involve the completion of an on-line structured questionnaire. The duration of your participation if you choose to enrol and remain in the study is expected to be about 20 minutes. The study is funded by South African Research Ethics Training Initiative (SARETI).

This is a minimal risk study with the no anticipated problems. You might feel uncomfortable answering some of the questions. The study will be of no direct benefit to you however study results may assist with the streamlining of biobank governance in the country.

This study has been approved by the University of Kwazulu-Natal Biomedical Research Ethics Committee (BE412/14) and Health Research Ethics Committee at Stellenbosch University (S15/04/076) and will be conducted according to the ethical guidelines and principles of the

international Declaration of Helsinki, South African Guidelines for Good Clinical Practice and the Medical Research Council (MRC) Ethical Guidelines for Research.

In the event of any problems or concerns/questions you may contact the researcher at erisamwaka@gmail.com or Dr. Lyn Horn lhorn@sun.ac.za or Prof D Wassenaar at Wassenaar@ukzn.ac.za or Stellenbosch University Health Research ethics committee at ethics@sun.ac.za or University of Kwazulu-Natal Biomedical Research Ethics Committee at BREC@ukzn.ac.za

Participation in the study is voluntary. You are free to withdraw from the study unconditionally and at any time. Withdrawal from the study will not affect you in any way.

You will neither incur any cost nor be compensated for your participation in the study.

The information you give will have no personal identification details. Neither you nor your institution will be identified in any way when the results of this study are published. The completed questionnaire will be de-linked from your email address and assigned a special code to protect your identity. Electronic copies of questionnaires and data will be safely stored in a password protected computer files known to the researcher only. Data accruing from the study will only be available to the research team or REC members when the need to inspect research records arises. Research results will be available in the UKZN library and School of psychology. They will also be communicated back to you as well as the general public through peer reviewed publications, presentations at conferences, workshops and invited lectures. Your responses will be treated with confidence and at all times data will be presented in such a way that your identity cannot be connected with specific published data. Only pseudonyms will be used in all disseminated information.

Results of the study will be compiled in a thesis and submitted to UKZN as partial fulfilment for the award of a Master of Social Science degree in Human Research Ethics, and may be published in a peer reviewed journal.

Declaration by participant

By signing below, I agree to take part in a research study entitled *(insert title of study)*.

I declare that:

- I have read or had read to me this information and consent form and it is written in a language with which I am fluent and comfortable.

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

Completion and return of the questionnaire will be considered an implication of acceptance to participate in the study.

Signed at (*place*) on (*date*) 2015.

Signature of participant

Signature of witness

Declaration by investigator

I (*name*) declare that:

- I explained the information in this document to
- I encouraged him/her to ask questions and took adequate time to answer them.
- I am satisfied that he/she adequately understands all aspects of the research, as discussed above
- I did/did not use an interpreter. (*If an interpreter is used then the interpreter must sign the declaration below.*)

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