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OWNERSHIP OF HUMAN BIOLOGICAL MATERIAL AND THE PROTECTION OF RESEARCH PARTICIPANTS IN THE CONTEXT OF BIOBANKING: A BIOETHICAL ANALYSIS

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A Research Report submitted to the Faculty of Health Sciences,
University of the Witwatersrand, Johannesburg,
in partial fulfilment of the requirements for the degree,
Masters of Science in Medicine in Bioethics and Health Law.

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Johannesburg. November, 2021

DECLARATION

I, Valerie Jane Beaumont, declare that this Research Report is my own, unaided work. It is being submitted for the Degree Master of Science in Medicine in Bioethics and Health Law at the University of the Witwatersrand, Johannesburg.

It has not been submitted before for any degree or examination at any other university.



_____

Valerie Jane Beaumont

Signed this 15th day of November, 2021 in Johannesburg.

DEDICATION

In memory of Alice Rita Scorer (1923-2017)

.

My mother's principles, courage, and sense of adventure inspire me.

"*Never mind about what <u>they</u> say.*

Things are never as bad as they seem.

Never let material possessions take hold of you."

ABSTRACT

The effectiveness of biobanks in supplying human biological material (HBM) for human health research depends on the provision of HBM by research participants.

International and South African policy and legislation on biobanking are not clear on ownership rights of research participants in “donated” HBM and hence, on the extent to which research participants have rights in their HBM.

This ethical and legal analysis of ownership of HBM explores how informed consent, material transfer agreements (MTA) and benefit sharing arrangements protect research participants. The ethical principles as they pertain to biobanking were analysed. The South African National Health Research Ethics Council MTA template was evaluated to determine the extent to which it protects research subjects and gaps were identified. Ownership of HBM was considered.

The study concluded that:

- The principles of autonomy, beneficence, non-maleficence and care should guide informed consent processes. The principle of distributive justice and communitarianism, particularly in communities where collective ownership is a societal value, should inform benefit sharing arrangements.
- The right to privacy must be respected in biobanking.
- The South African MTA, whilst not perfect, is an effective framework for protecting research participants and is in line with global best practice.
- An act utilitarian approach was identified as being the appropriate ethical theory to take account of and find a balance between the risks and benefits of research to all stakeholders and to protect research participants. Such an approach could take account of limitations on the autonomy of the consent process and the potential for failure to protect research participant privacy in biological research whilst benefitting the societal good.

Keywords

Biobanks, bioethics, human biological material, informed consent, material transfer agreements, ownership.

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TABLE OF CONTENTS

1 CHAPTER 1: INTRODUCTION 1

1.1 Background 1

1.2 Literature Review 2

1.2.1 Biobank 2

1.2.2 Areas for protection: Consent, ownership and exploitation 3

1.2.3 International efforts to protect research participants in research on HBM 4

1.2.4 Ownership of Human Biological Material (HBM) 5

1.2.5 Informed consent 6

1.2.6 Material Transfer Agreements (MTAs) 7

1.3 Research Questions 8

1.4 Rationale for the study 8

1.5 Research Aim 9

1.6 Research Objectives 9

1.7 Research Design 9

1.8 Research Methods 9

1.9 Argumentative Strategy 11

1.10 Ethics 11

2 CHAPTER 2: OWNERSHIP OR ETHICAL USE OF HBM stored in biobanks 12

2.1 International perspectives on ownership and ethics in biobanking 12

2.1.1 Ownership vs. control of human biological material 12

2.1.2 Informed consent by the research participant 15

2.1.3 Benefit sharing 17

2.2 South African perspectives on ownership and ethics in biobanking 19

2.2.1 Ownership vs. control of human biological material 20

2.2.2 Informed consent 21

2.2.3 Benefit sharing 21

2.3 International biobanking guidelines....22
2.3.1 Declaration of Helsinki by the World Medical Association 23
2.3.2 Declaration of Taipei by the World Medical Association 23
2.3.3 OECD Guidelines for human biobanks and genetic research databases (HBGRD) (2009) 24
2.3.4 Council for International Organizations of Medical Sciences (CIOMS) 24
2.3.5 The National (United States) Commission for the Protection of Human Subjects of Biomedical and Behavioural Research – The Belmont Report 25
2.3.6 Singapore Statement on Research Integrity 26
2.3.7 American Medical Association 26
2.4 South African biobanking guidelines 27
2.4.1 Ethics in Health Research: Principles, Processes and Structures (DoH Guideline) 27
2.4.2 Health Profession's Council of South Africa (HPCSA) guidelines for health researchers 29
2.4.3 University of the Witwatersrand Human Research Ethics Committee Medical: Biobanking Policy. 29
2.4.4 The San Code....30
2.5 Ethical Principles relating to donation of HBM and informed consent....31
2.5.1 The principle of autonomy in the granting of informed consent....31
2.5.2 The principle of duty of care towards the participant in the informed consent process....32
2.5.3 The principle of communitarianism where research is conducted in communities where communal ownership is a societal value 33
2.5.4 The principle of societal good 33
2.5.5 The principle of distributive justice in sharing the benefits of research 34
2.5.6 The principle of the right to privacy of personal information....35
2.6 Summary on ownership and ethical use of HBM 35

3 CHAPTER 3: LEGAL ISSUES RELATING TO OWNERSHIP OF HBM STORED IN BIOBANKS 37
3.1 International legal frameworks 37
3.1.1 International case law and theories as regards ownership 37
3.1.1.1 Moore v. Regents of the University of California (UCLA) 38
3.1.1.2 Washington University v. Catalona 38
3.1.1.3 Arizona University's settlement with the Havasupai tribe 39
3.1.1.4 Yearworth v North Bristol NHS trust 2010 (Court of Appeals for England and Wales) 39
3.1.1.5 Piljak Estate v. Abraham 2014 (Ontario Superior Court of Justice) 40
3.1.1.6 Relevance of case law to ownership of HBM 40
3.2 South African legal system 42
3.2.1 The Constitution, 1996 42
3.2.2 South Africa's Health Law framework as it applies to biobanking 43
3.2.2.1 The Health Professions Act 56 of 1974 and Ethical Codes 43
3.2.2.2 The National Health Act and Regulations to Chapter 8 43
3.2.3 Material Transfer Agreement of Human Biological Materials 46
3.2.4 South Africa's Privacy and intellectual property framework 49
3.2.4.1 The Protection of Personal Information Act, Act 4 of 2013 (POPIA) 49
3.2.4.2 Intellectual property policy in South Africa 51
3.2.4.3 Publicly-funded research 52
3.2.5 Summary of legal issues relating to the use of HBM in research 53
4 CHAPTER 4: PROTECTION OF RESEARCH PARTICIPANTS BY THE MATERIAL TRANSFER AGREEMENT 54
4.1 Introduction 54
4.2 Evaluation of the WITS MTA in protecting research participants regarding ownership of HBM 56
4.3 Analysis of the National SA MTA template 56
4.4 Gaps in the National SA MTA template and recommendations 62
4.5 Gaps in the legislative provisions and the MTA regarding informed consent and recommendations 62
4.6 Summary of evaluation of National SA MTA template 63

5 CHAPTER 5: DISCUSSION, RECOMMENDATIONS AND CONCLUSIONS 64
5.1 Discussion of ethical principles and human rights considerations in biobanking 64
5.1.1 The principle of beneficence in considerations of the societal good and informed consent 65
5.1.2 The principle of non-maleficence in assessing the risks to research participants 65
5.2 An Act Utilitarian approach to Biobanking 66
5.3 Considerations related to ownership of HBM 67
5.4 Recommendation on whether ownership of HBM ought to remain with research participants 69
5.5 Recommendations for improving the National SA MTA template 69
5.6 Recommendations for further research 70
5.7 Conclusions 70

NOMENCLATURE

BEC:	Biobanks Ethics Committee of the University of the Witwatersrand
CIOMS:	The Council for International Organizations of Medical Sciences
DoH:	National Department of Health
DoH Guideline:	National Department of Health: Ethics in Health Research, Principles, Processes and Structures (2015)
Donor:	Research participant and vice versa; it is a person who has donated human biological material and data to be used for health research purposes and/or teaching (RSA, 2018)
H3 Africa:	Human Heredity and Health in Africa
HBM:	Human Biological Material
HBGRD:	Human biobanks and genetic research databases
Helsinki:	Declaration of Helsinki by the WMA: Ethical Principles for Medical Research involving Human Subjects (2013)
HPCSA:	Health Professions Council of South Africa
HREC:	Human Research Ethics Committee
Materials:	HBM and associated data
MTA:	Material Transfer Agreement
National SA MTA Template	Material Transfer Agreement of Human Biological Materials
NHA:	National Health Act 61 of 2003
NHREC:	National Health Research Ethics Council
OECD:	Organization for Economic Co-operation and Development
POPI:	Protection of Personal Information (Act)
Provider/providing institution:	The biobank providing the material subject to a MTA
Recipient/receiving institution:	The biobank or researcher receiving the material subject to a MTA
(R)SA:	(Republic of) South Africa
SAMRC:	South African Medical Research Council
Taipei:	Declaration of Taipei by the WMA on Ethical Considerations Regarding Health Databases and Biobanks (2016)

Tissue:	Refers only to human tissue and does not include reference to associated data
UK:	United Kingdom
USA:	United States of America
WCRI:	World Conference on Research Integrity
WHO:	World Health Organization
WITS:	University of the Witwatersrand
WMA:	World Medical Association

LIST OF FIGURES

Figure 4.1: Relationships between stakeholders and the flows of HBM and data in biobank research 55

LIST OF TABLES

Table 4.1: Analysis of provisions in the National SA MTA template pertaining to aspects of ownership and control over HBM.....56

Table 4.1: Analysis of provisions in the National SA MTA template pertaining to aspects of ownership and control over HBM (continued).....57

Table 4.1: Analysis of provisions in the National SA MTA template pertaining to aspects of ownership and control over HBM (continued).....58

Table 4.1: Analysis of provisions in the National SA MTA template pertaining to aspects of ownership and control over HBM (continued).....60

Table 4.1: Analysis of provisions in the National SA MTA template pertaining to aspects of ownership and control over HBM (continued).....61

CHAPTER 1: INTRODUCTION

1.1 Background

Biobanks are organised institutions for the collection, storage and dissemination of human biological material (HBM) and associated data and are an important resource in research for the advancement of human health. The scope of biobanking is growing rapidly with increasing interest in and opportunities for commercialisation. Multiple stakeholders have competing interests and include sample donors/research participants, biobanks, ethics committees, researchers, and research institutions. Effective international collaboration between researchers depends on “donations” of human biological material (HBM) to biobanks and the onward sharing thereof for health research.

The main risk to individuals and communities involved in biobank research would be a breach in privacy of their data and data derived from their HBM. In biobank research there is typically little clinical risk to participants. The protection of the rights of research participants/donors by biobanks is essential.

There is growing literature in South Africa on ethical issues related to biobanks and sample storage, but there is a scarcity of published literature on the ethical and legal perspectives of ownership of HBM and protection of research participants in the context of ownership. Even though several biobanks have been identified in South Africa (Abayomi et al., 2013), they are often confused with pathology laboratories and other types of tissue repositories. Biobanks are generally not well understood by even health professionals.

Mahomed, Nothling-Slabbert and Pepper (2017) support the commonly-held view that South African legislation relating to human tissue should be amended to give clarity on ownership as confusion is expressed by researchers in the field with respect to possession, custodianship, ownership, database rights and intellectual property.

It was thus important to conduct a critical bioethical analysis on ownership of biobanked HBM and the protection of research participants in the context of biobanking, in order to gain an understanding of measures that ought to be in place to protect research participants in the context of ownership relating to biobanking of HBM in South Africa.

An analysis of international literature, ethics policy documents and legislation on biobanking was necessary to determine alignment. This research explored international and South African legislation and ethical norms in biobanking to identify key issues related to biobanking in the context of ownership rights in HBM.

1.2 Literature Review

The literature review aimed to give an overview of the most important aspects relating to this analysis. The review explores the concepts of a biobank, the informed consent, ownership and exploitation of HBM and material transfer agreements (MTA).

1.2.1 Biobank

According to the National Health Act 61 of 2003 Material Transfer Agreement for Human Biological Materials, published in 2018, a biobank is an organised institution or unit that safeguards collections of biological material and associated data for research purposes, for an unlimited time (RSA, 2018). Biobanks are a critical resource for international co-operation in advancing biomedical research (Tindana et al., 2014).

They rely on participation from large numbers of participants contributing HBM for research purposes (Nisbet & Fahy, 2013). Biobanks are most typically used either for the long-term storage of biological samples for the individual donor's future private use or as collective biological sample repositories as a resource for genetic and genomic research (Dhai & Mahomed, 2015).

According to the University of the Witwatersrand Biobanks Ethics Committee (BEC) (2020), the nine biobanks approved by the BEC include five in South Africa (Clinical Laboratory Services, BARC, Sydney Brenner Institute for Molecular Bioscience, Consortium of TB Biomarkers, South African Medical Research Council) and those in the United States of America (USA) (Vanderbilt University Medical Centre (VANTAGE), Biomedical Research Institute, the BioStorage Technologies North American Operation) and in the United Kingdom (UK) (Fischer Bioservices).

The focus of this study was those biobanks that store and share samples for future research, either for specific studies or for non-specified future use. Amongst other responsibilities, biobanks must implement policies to protect the research participants and ensure access to and the best use and control of samples and sample distribution.

In an agreement between two biobanks for the transfer of HBM for health research, the biobank that stores donated HBM by a research participant in terms of an informed

consent agreement is the “provider” or “providing institution” and the biobank that receives the transferred material from the provider, subject to an MTA, is the “receiver” or “receiving institution” (RSA, 2018).

Macilotti (2011) identified multiple stakeholders that may claim some rights in HBM in biobanking, including: individuals (research participants and their communities); researchers (scientists using biobank stored HBM for health research); biotechnology companies (involved in commercialisation of the products of research); health care systems (benefitting from the research). From these, Macilotti (2011) identified biobanks as being the appropriate agents for controlling HBM sample distribution.

However, there are diverse and sometimes competing rights and interests in the material, of which ownership rights are but one.

Caulfield and Murdoch (2017) alluded to the increased interest in the collection and analysis of HBM. Nisbet and Fahy (2013) estimated that by 2015, the commercial value of the sector would have grown to exceed $2.25 billion. As projected by Nisbet and Fahy, this market has experienced rapid growth, beyond their anticipation in 2013 and was valued at $25.09 billion in 2018. Furthermore, as a result of the important medical role biobanks are playing in the development, particularly of vaccines for the Covid-19 pandemic, current projections by Fortune Business Insights (2020) are that the value of this market could reach $49.46 billion by 2026.

1.2.2 Areas for protection: Consent, ownership and exploitation

The increasing potential for commercialisation and profit taking made possible by the biobanking of HBM raises the question of who owns the donated material. It is therefore important to ensure that there is clarity on ownership of samples and that there is implementation and enforcement of ethical policies in the biobanking chain. This problem was highlighted by Caulfield and Murdoch (2017), who raised concerns over the nature of the consent for use and control of tissue samples in this growing market. According to Caulfield and Murdoch (2017), new ethical strategies, that should have been adopted for obtaining consent from research participants, do not appear to be universally supported, ethically or legally, giving rise to uncertainty around the ownership of HBM and what type of consent is legally appropriate. The key issues of ownership of the HBM and the rights vested in the HBM need to be dealt with when the donor gives consent for the storage and use of the materials.

Caulfield and Murdoch (2017) also projected that the growing interest in the concept of “biorights” could hinder access to biobanked HBM for researchers. This is illustrated in the case of Henrietta Lacks, whose cancer cells, removed without her permission during surgery, survived outside of her body to be exploited by the medical research fraternity (Nisbet & Fahy, 2013). The Lacks family sought and continue to fight for rights and financial compensation for the controversially biobanked cells (Caulfield & Murdoch, 2017). A legal representative of the Lacks family initiated litigation to attain guardianship of the cells (Brown, 2018). An outcome is not yet known.

A balance needs to be obtained between creating access by researchers to biobanked HBM for health research and protecting the research participants from exploitation by biobank stakeholders.

1.2.3 International efforts to protect research participants in research on HBM

Internationally, research participants involving HBM are protected by the World Medical Association (WMA) Declaration of Helsinki in respect of research in general and Declaration of Taipei in respect of biomedical research, the Council for International Organizations of Medical Sciences (CIOMS) publications, as well as the MTAs.

The WMA Declaration of Helsinki (WMA, 2013) places on physicians and researchers who are doing research on biobanked HBM, an obligation to seek informed consent, for amongst others, the reuse of identifiable HBM and data (material). A subsequent WMA declaration, the Declaration of Taipei (WMA, 2016) on *Ethical considerations regarding Health Databases and Biobanks*, established principles and obligations specific to the governance of biobanks.

The Council for International Organizations of Medical Sciences (CIOMS) published guidelines on biomedical research. In the 2002 publication, the Helsinki principles were followed with the intention of supporting the development of national policies in the developing world. The update to the guidelines was published in 2016 with a broader scope reflecting the increase in biobanking: *International guidelines for health-related research involving humans*. This version has an additional guideline, i.e. *Collection, storage and use of biological materials and related data* (CIOMS, 2016). It sets the requirement for biobanks to have a specific governance system in place to obtain authorisation for the future use of biobank samples in research to protect the rights and welfare of HBM donors.

Protection of research participants in biomedical research, including in the context of biobanking, extends from obtaining informed consent from participants prior to commencement of research to sharing beneficial research outcomes. Further, consent for secondary testing of samples, sharing of results and information, disposition of samples, governance of biobanks and legal and social issues are important for the protection of participants with respect to ownership of biobanked HBM (Mungwira et al., 2015). Ethical standards have always set the privacy of research participants as a high priority. The protection of personal information will become increasingly important in biobanking to protect research participants. International requirements for biobanking now require that material, including the associated data, may only be transferred to countries and biobanks where this protection is in place. These requirements are generally enforced through a material transfer agreement (MTA), which passes obligation to comply with donors' requests, from one biobank to another with the transfer of samples (RSA, 2018).

1.2.4 Ownership of Human Biological Material (HBM)

The Declaration of Taipei (2016) describes biological material as "a sample obtained from an individual human being, living or deceased, which can provide biological information, including genetic information, about that individual". It calls for ownership rights and privileges to be contractually defined before collecting and sharing material. The ownership of HBM in the context of biobanking is subject to extensive ethical debate.

Yassin et al. (2011:1012) identified the central issue in the ownership controversy as the "failure to appropriately account for and manage potential differences between stakeholders involved in the biospecimen research process". Mahomed (2018) highlighted the distinction between the ownership of human tissues and human tissue-related inventions which become the subject of benefit sharing.

Importantly, in South Africa, legislation governing research on HBM and all health-related research must be approved by a Health Research Ethics Committee (HREC) registered with the National Health Research Ethics Council (NHREC), established in 2006 in terms of S72 of the National Health Act (NHA) (2003).

According to Thaldar, Botes and Nienaber (2020), there are currently 46 such HRECs. These HRECs are governed by the National Department of Health (DoH) guidelines

(*Ethics in Health Research: Principles, Processes and Structures)* (RSA DoH, 2015) which apply to all research on HBM and associated data.

The South African National Health Research Ethics Council (NHREC) guidelines for ethics in health research (RSA, DoH, 2015) require that proposals to conduct research involving humans must be approved by an independent research ethics committee registered with the NHREC. The guidelines are silent on the question of ownership and do not comprehensively address ethics in biological research or storage of biological samples for future research (Dhai & Mahomed, 2015). Mahomed and Sanne (2015) advocated for a custodian role for biobanks in combination with benefit sharing agreements so that developing world institutions and communities may benefit from research. However, the National SA MTA template (RSA, 2018), which has legal standing takes a clear position that the ownership of samples remains with the donor until destroyed.

The Health Professions Council of South Africa (HPCSA) *Ethical Guidelines for Health Researchers* (2016) do not give guidance on ownership of HBM but specify a requirement for the submission to an ethics committee of an MTA for approval for samples to leave the country. The MTA must be signed by the approving ethics committee. The HPCSA *Ethical Guidelines for Biotechnology Research* (2008) require that where biological specimens are collected during research, participants must be made aware that they have the right to decide about the future use of such specimens.

The now superseded South African Medical Research Council (SAMRC) *Guidelines on the Responsible Conduct of Research* are silent on the question of ownership of HBM (SAMRC, 2018).

International policies on biobanking generally overlook the matter of ownership. The Council for International Organizations of Medical Councils (CIOMS) (2016) *Guidelines for Biomedical Research Involving Human Subjects* require an MTA, informed consent and benefit sharing provisions to be in place but do not refer to ownership. The Singapore Statement (WCRI, 2010) describes the responsibility on researchers to share data and findings openly and promptly as soon as ownership claims have been established, but it does not give guidance on how to manage ownership issues.

1.2.5 Informed consent

Informed consent is the instrument used in health research to inform a research participant of the research and to get permission for the researcher to proceed.

Consent granted by research participants for research on HBM is only valid, in terms of the Declaration of Taipei (WMA, 2016), if participants have been fully informed, including with respect to possible future commercial use and benefit sharing, intellectual property issues and the transfer of data or material to other institutions or countries. The biobanking requirements for the management of matters related to ownership of donated material are not explicit (WMA, 2016).

According to Staunton and Moodley (2016), an inadequate level of public education and awareness on the possible future use of donated samples for genetic research and the potential personal, family or community impact of this research, has the potential for the exploitation, deliberate or unintended, of vulnerable populations. Issues around ownership should therefore be clarified and confirmed with participants before commencement of a study and included in informed consent documents.

With respect to ownership, Macilotti (2011) found that informed consent is not an instrument of total transfer of ownership of HBM, but a matter of transfer of control of the material to an entity such as a biobank in a “trust relationship” to manage the material including adjudicating on the best use of the material. Tindana, Campbell et al. (2017) described a framework for “entrustment of samples” to protect research participants. This involves assigning materials and responsibilities to institutions thus creating a “moral relationship” to protect research participants.

There is limited information available in South Africa (Sections 1.2.2; 1.2.5; 1.2.6; 2.2.1; 2.2.2; 2.2.3;) on the extent to which informed consent practices and documents like MTAs address these critical and globally mandated issues, specifically pertaining to ownership.

1.2.6 Material Transfer Agreements (MTAs)

MTAs are legally binding contracts governing the transfer of materials between institutions (Sathar & Dhai, 2012) and are an appropriate tool to reflect arrangements for the transfer of material and data to researchers and for transfer across international boundaries (Vaught & Lockhart, 2012).

According to the NHA regulations relating to the National SA MTA template (RSA, 2018), it is compulsory in respect of all studies using HBM to govern material and data transfers through an MTA, negotiated between the parties.

It is important that access to biobanked HBM material and data is available to researchers. Macilotti (2011) raised the importance of decisions on allocation of HBM samples to maximise scientific value as a priority over ownership issues.

The Declaration of Taipei (WMA, 2016) requires intellectual property issues related to all stakeholders to be covered in a policy document and communicated in a transparent manner.

The University of the Witwatersrand (WITS) HREC MTA template (2015a) required for the approval of human research, must contain, amongst other requirements, details of third-party transfers, benefit sharing arrangements and intellectual property rights (statutory and other proprietary rights resulting from creations of the human mind such as copyright, patents, scientific works and discoveries, and trade marks). The National SA MTA template (RSA, 2018) now binds all NHREC research to the use of and agreement on an MTA for the transfer of materials.

The SAMRC guidelines (2018) stipulate that agreements on samples shared/transferred for research purposes must be subject to negotiation but no framework is provided.

1.3 Research Questions

Against the background given above, the following research questions arose:

- Ought ownership of HBM remain with the research participant?
- What bioethical measures ought to be in place in the governance of biobanking with respect to ownership, to protect research participants?

1.4 Rationale for the study

Biobanks are an important resource for biomedical research and the sharing of HBM samples nationally and internationally to facilitate ground-breaking research, much of which will potentially benefit the public good. Despite concerns expressed by Sathar and Dhai (2012) that HBM samples may be leaving South Africa without explicit consent from research participants, there is still limited information available on current practices. The South African literature on the ethical and legal issues pertaining to the ownership of biobanked HBM and the protection of research participants is limited and it was therefore important to conduct a bioethical analysis on the ownership of HBM and the protection of human subjects in the context of biobanking to inform ethical research practices in South Africa.

1.5 Research Aim

The aim of this research study was to critically examine the ethical and legal aspects of the ownership of HBM in South Africa and to examine whether the WITS MTA (WITS HREC, 2015a) adequately protects research participants from the perspective of ownership.

1.6 Research Objectives

This research study had the objective:

- To critically analyse the ethical and legal aspects of ownership of HBM stored in biobanks, including but not limited, to informed consent, MTAs, intellectual property rights and benefit sharing;
- To critically evaluate the extent to which the WITS MTA (WITS HREC) and the National SA MTA template (RSA, 2018) protect research participants from the perspective of ownership of HBM; and
- To identify the gaps in the measures which ought to be in place to protect research participants in the context of ownership of HBM in South Africa.

1.7 Research Design

The chosen research design is a bioethical study using normative analysis. Normative ethics is the branch of philosophical enquiry that sets out to give answers to the following questions: What ought to be done? What ought not to be done? Normative ethics sets out to answer these questions, in a systematic critical fashion and to justify the answers that are offered (Sugarman & Salmasy, 2011). In this study, the questions asked were: “Ought ownership of HBM to remain with the research participant?” and “What bioethical measures ought to be in place in the governance of biobanking with respect to ownership, to protect research participants?”

1.8 Research Methods

The study was based on desktop and library-based research. No new data was collected or analysed, and the research did not involve human participants. Findings from the literature were discussed and ethically analysed in a systematic, critical fashion to justify whether ownership of HBM ought to remain with the research participant. It involved the interpretation and critical analysis of the most important texts, postings and relevant international and South African legislation and policy, to

answer the research questions. This analysis defined and clarified concepts, identified and criticised assumptions, analysed and evaluated theoretical frameworks and articulated the most reasonable interpretation of concepts. Sources included but were not limited to research articles, bibliographies, books, Google Scholar, PubMed, government legislation and policy, the WITS MTA (WITS HREC, 2015a) and National SA MTA template (RSA, 2018), Academic institution web sites and other academic search engines.

Key search terms used in different combinations included, amongst others, the following: biobank; biobanking; confidentiality; closure; consent; data sharing; human biological material; indigenous; material transfer agreement; ownership; storage; tissue banks.

Research articles were stored and referenced using Zotera software. A large number of papers were accessed and read and the debates they raised were found to be aligned in nature and in position. The latest papers accessed did not raise new issues.

Key information referenced in the report includes:

- International perspectives and guidelines on biobanking
    - Literature review – chapter 1
    - Section 2.1
    - Section 2.3
- International legislation
    - Section 3.1
- South African Perspectives and Guidelines on biobanking
    - Literature review – chapter 1
    - Section 2.2
    - Section 2.4
- South African legal system
    - Literature review – chapter 1
    - Section 3.1.8
    - Chapter 4
- Publications related to ownership of HBM in biobanking
    - Literature review – chapter 1
    - Section 3.1.8

1.9 Argumentative Strategy

An analysis of the literature on the ownership of HBM in biobanking identified bioethical issues that should be considered in the protection of research participants in the context of ownership in biobanking.

The researcher analysed the potential for benefits and risks to researchers, biobanks and research participants, and also the rights of research participants, in the context of ownership of HBM in biobank research. An act utilitarian approach was used to argue for the overarching importance of social benefit deriving from biomedical research conducted on HBM and justification for the removal of HBM from research participants.

The researcher argued for the respect and application of autonomy in decision-making in the administration of and granting of informed consent by research participants with respect to the removal and use of HBM.

The researcher argued for the protection of the rights of participants to privacy of personal information.

The principle of distributive justice was applied in the arguments that were made in the context of benefit sharing as key to protection of research participants.

The principle of communitarianism was applied to community based research and the principle of care in the informed consent process.

These ethical principles were also applied to the analysis of the WITS MTA (WITS HREC, 2015a).

1.10 Ethics

An ethics review and waiver were not required as there were no human or animal participants in the study.

CHAPTER 2: OWNERSHIP OR ETHICAL USE OF HBM STORED IN BIOBANKS

This chapter highlights the uncertainty regarding ownership of HBM in biobanks. The researcher first reviewed the international and local perspectives on ownership and ethics in biobanking. Then the researcher analysed the international and South African policy documents for guidance on the ethical use of HBM in biobanking and discussed how the ethical principles relate thereto.

In particular, this chapter explores the extent to which informed consent, MTAs and benefit sharing arrangements impact on ownership rights in HBM in biobanking and clarifies the separate benefits accruing as intellectual property.

2.1 International perspectives on ownership and ethics in biobanking

2.1.1 Ownership vs. control of human biological material

In general terms, ownership gives exclusive rights to and control over property. Ownership can be gained, lost and transferred in multiple ways, subject to legislation and separate agreements. In the context of biobanking, such an agreement is the informed consent agreement between the research participant and the biobank.

International policy documents and legislation, provide little clarity around rights and obligations of ownership of HBM in biobanking. The ethical question of who owns HBM in biobanks is a much debated topic in publications. It is apparent from the literature that, as a result of this lack of clarity, diverse governance standards and systems have been implemented by biobanks to protect research participants and to facilitate access to biobanked HBM for research purposes.

Biobanks referred to in published literature have generally applied key global policy imperatives and applicable legislation and have implemented some or all of these standards in their governance systems.

There is little evidence in the literature on enforceable systems for ongoing monitoring and enforcement of standards and systems adopted by biobanks.

The role of biobanks is important to the debate considered in this section. Their purpose is to foster research and to this end, they can be seen as a force for good. Biobanks are an essential source of health research material. The sharing of materials

between biobanks and beyond further enhances the value of these collections. The outcomes of research on biobanked samples has societal benefits and the information derived is generally accepted to be for the societal good. In the opinion of the researcher, whilst there is a lack of clarity on ownership of the HBM samples, it is a well-established principle that products or information derived from research on HBM may lead to property rights in the material, including the right to commercialisation for the benefit of the persons that have added value in the research process. These benefits may or may not be shared with research participants.

Ethical policies for biobanking and relevant legislation are not clear on ownership rights. Biobanks seek to deal with this ambiguity through the architecture or wording of informed consent processes and MTAs.

The heart of the current ethical debates around who owns HBM samples in biobanks is inextricably tied to the following questions:

- Who has the right to decide what the sample may be used for?
- Who has control over the samples?
- Who is accountable to the donor for the storage and sharing of samples?

Local and international authors on the subject are concerned that there are no common or universal answers to these questions. The overall tendency is for the question of ownership to be submerged in favour of a focus on mechanisms to ensure research participant protection and access to biobanks by researchers. This pragmatic approach, although questionable in terms of governance standards, has created a workable framework for facilitating access by researchers to HBM in a controlled environment.

This is borne out by Cadigan et al. (2017) in their survey of United States biobank policies. They found that, generally, best practice guidelines do not adequately address ownership of specimens. Instead, the focus is more on the question of who has the right to control the use and storage of specimens. It seems that the answer is that biobanks, as custodians of specimens, are accountable for use and storage and that this accountability is extended to those to whom the HBM may be transferred.

Accountability for respecting the informed consent agreements of research participants is transferred to the biobank, which in turn can then make decisions around the use and transfer of samples. Such a mechanism is intended to protect research participants and increases access to HBM for research purposes and for the potential

for societal benefits and the common good. However, it limits the control of the research participant to what is recorded in the informed consent document. This control of the research participant is further limited when research will involve use of samples at some future time; introducing an element of the unknown for the research participant, which cannot be properly covered in the informed consent process.

Ballantyne (2018) emphasised the importance of autonomy of research participants in granting informed consent. This article highlights differences between “interest in” and “rights to” the outcomes of research. It also distinguishes between legal rights to control access and the importance of the capacity for data subjects to be autonomous in their decision on the future use of the samples and research data.

The competing interests and expectations of stakeholders in relation to privacy (or protection of information), control of and appropriate use of the generated data must also be considered. Ballantyne (2018) also highlighted the importance of aligning social licence, ethics, and the law to ensure that data use is *publicly acceptable, normatively justified and legal* and cautions against misalignment. The inherent value in the data from HBM research is the social value created through the contribution to knowledge and innovation, amongst others, and that data users need to be safe stewards of the data.

Vayena and Blasimme (2017) proposed that the data intense requirements of medicine cause attention to be focused on the informed consent process and the confidentiality undertakings in respect of donors. They proposed mechanisms to increase control by research participants over data access, data use and governance of data. These include data portability rights to control data access, control of data use through new mechanisms of informed consent and having direct involvement in data governance.

However, Vayena and Blasimme (2017) conceded, that even with additional controls, control by the participant is not absolute as it can be waived, for example, where public health, national security and criminal investigations may require information to be released to third parties. They proposed electronic informed consent as a tool to facilitate access to data and the ability to delete an individual’s data where appropriate and if required by the research participant.

It is apparent from the literature, that policies and practices in biobank governance are tending towards finding a solution to the application of rights of ownership through using the informed consent process to articulate the wishes of research participants

and to establish agreements between research participants and biobanks in respect of the use of material for specific projects and for the future use of samples.

To sum up this section, common best practice does not anticipate that the research participant has full ownership rights in the material. It also does not appear from the literature that the biobanks gain ownership rights in the material.

The informed consent process serves to create an agreement around the donated HBM that protects the research participant's rights to decide how the material will be used and transfers accountability for the storage, transfer of samples and compliance with the informed consent to the biobank.

The research participant does not have further ownership rights in the HBM or the outcomes of research unless otherwise agreed. This approach (on condition that the informed consent process is ethically and legally conducted to ensure autonomy of the research participant), will allow for HBM to be available in an ethical and legal manner for health research, subject to the proviso that informed consent has been properly given to ensure the autonomy of the research participant in making research-related decisions.

2.1.2 Informed consent by the research participant

According to Grady et al. (2017), informed consent is a means to protect the rights and welfare of participants in medical research, whilst contributing to the advancement of knowledge. It is an opportunity for the donor in biobanking to decide whether participation in the research is in their interest, and whether sufficient provision is made to protect the person from exploitation and harm. Biobanks must have policies on informed consent in place to improve sharing and to protect confidentiality (Andanda & Govender, 2015).

Requirements for informed consent of research participants have been mandatory in health research since the implementation of the Declaration of Helsinki in 1964 and its subsequent updates (WMA, 2013). Additional requirements have been introduced in terms of the OECD guidelines for biobanking (2009), the Declaration of Taipei (WMA, 2016) and other international policy documents.

Despite the fact that international policy documents set requirements for informed consent (including the importance of the ethical principles of autonomy and distributive justice), there is scant guidance on the role of the informed consent document in transferring rights in the material, other than the right to decide how it is used.

It therefore appears that informed consent policies assume that the research participant does not have full ownership rights in the HBM after it has been removed and that the only right the participant has is the right to direct what it can be used for.

In general therefore, we see that current policy documents are aligned in that research participants have the right to decide whether or not to participate in a specific research project and also to indicate purposes for which they would grant permission for the samples to be used or shared. They also have the right to withdraw their consent and the material.

To effectively make the necessary decisions, research participants need to have adequate and understandable information on the research project. The informed consent process is intended to manage this and should include a full account of the research project and a declaration of the potential benefits of research and the extent to which benefits will be shared with the research participant. Potential risks to the donor must be explained.

The ethical principle of *autonomy* is separate from, but closely linked to *informed consent*. The principle of autonomy requires that information given to potential donors in the informed consent process is transparent, sufficiently detailed and delivered in a fully understandable manner and that the donor should independently decide on how the HBM may be used.

The challenge with consent for research on HBM is that, due to the very nature of biobanked material, consent may be for use in a particular project but very commonly, is also needed for future research. To address this dynamic, biobanks implement different levels of informed consent, namely consent for a specific project, tiered consent, broad consent and blanket consent (RSA DoH, 2015) as explained below.

Consent for use of the HBM only for a specific project limits the use of the material to that particular project and could, if correctly done, be considered to be truly informed consent.

Tiered informed consent is intended to facilitate the ongoing granting of consent for further projects, but it is administratively more complex and burdensome and presents difficulties for biobanks to implement into the future.

Broad consent provides for future unknown use of samples in line with specific guidelines to be agreed and, as highlighted by Mahomed et al., (2015), must not be confused with blanket consent, which provides no protection to research participants.

The donor must have the right to withdraw consent at any time. Practically this is logistically not always possible. Research participants should be advised of the limitations or difficulties to withdraw samples when consent is withdrawn, particularly where onward transfer has taken place.

It is arguable that broad consent cannot fully meet the needs of “informed” consent in that future use and potential benefits from the research cannot be known at the stage broad consent is given and the HBM is donated. Dhai (2019) referred to such situations as “permission” rather than “consent”, indicating that the donor’s rights may not be fully respected in the informed consent.

Where materials are collected and stored for future use, the use or whereabouts of the material in the case where transfer has taken place may not be known if material or data is de-identified (WMA, 2016). This would limit opportunities for research participants and biobanks to have control over samples. One possible solution lies in anonymising the samples when they are transferred but ensuring that the providing biobank has access to the code to facilitate the removal of samples when required by the research participant.

2.1.3 Benefit sharing

The aim of research is to discover a benefit of some sort as the outcome or result of the research. What is regarded as a benefit may not be the same for all stakeholders. This discussion of benefit sharing does not embrace the sharing of benefits as a result of the creation of intellectual property or the commercialisation of products.

Benefit sharing is also distinct from ownership rights and anticipates the treatment of benefits which may be derived following research on HBM (Mahomed, 2018).

The principle of *distributive justice* must apply but can only be served if the research participant is fully informed of the potential benefits to themselves and to stakeholders and the community and if potential benefit sharing is clearly explained and documented in the consent form (Beauchamp & Childress, 1994).

Benefit sharing in research has various connotations in the literature and practices are diverse. There is an altruistic contribution made by donors, as societal value and the societal good are generally considered to be the principal benefits arising from research. Publications report that, generally, research participants acknowledge and accept societal value and the societal good as benefits and are willing to contribute samples to research on this basis. On the other hand, benefits accruing to researchers

arising from value added during research become the subject of intellectual property rights and are separate from any rights the research participant may have in the donated HBM.

Ballantyne (2018) reported that the term “benefit sharing” was first used in relation to non-human genetic resources. It requires the equitable sharing of benefits among data providers and the donor community. Recent trends in “benefit sharing” show a shift towards “power sharing” arguing instead for decision-making of communities in the governance of biobanks, rather than the sharing of rights in the material. This shift emphasises the importance of the information given to and the consent provided by the research participant.

A benefit may contribute to and promote the welfare of individuals or communities and through a process of consultation should consider people’s needs, priorities and cultural experiences. Benefits include therapeutic and monetary benefits and can also include capacity building (Dhai, 2019).

Joly et al. (2015) found that respondents attributed a high degree of importance to receiving clear and specific information about who should profit financially from biobanking and genetic database projects. The majority of participants preferred equitable sharing models favouring all stakeholders. Value exists in the sharing of public information on the progress of the research in the context of a societal good, from which research participants and the community would derive benefits through contribution to science and humanity.

The value of biobanks lies in maximising researcher access to biobanked material and data. The challenge lies in finding a balance between protecting research participants and creating access. It is therefore important in establishing informed consent and benefit sharing policies and legislation, that a balance can be found to maximise the societal benefits.

Benefit sharing may involve multiple stakeholders. An example is a local community in addition to the research participant. These two parties may or may not share similar needs and values.

This is an important consideration in framing informed consent processes and in adjudicating on what might be considered a benefit. These considerations should not, however, lead to research restrictions for indigenous communities for whom research is equally important. Instead, sensitivity and an understanding of community values

are important in ensuring that the dignity and values of the participants are protected. Researchers have proposed schemes for consultation coupled with education within indigenous communities in an effort to support the informed consent process and to gain buy-in. This is illustrated below.

Aramoana and Koea (2020) interrogated the barriers to indigenous peoples' participation in biobanking and genomic research in their literature review. The authors identified that ancestral land, ancestors, culture, and bodily substances are interconnected and can "act on" each other and that the body parts, even after removal, retain a sense of the person and ancestors. To give away their HBM therefore is counter-intuitive and can be likened to the removal of a link to their ancestors.

A further problematic issue that arose in the study by Aramoana and Koea (2020), of relevance to ownership in biobanking, is the link between the present and ancestral past and the connection with immortalisation of cell lines.

These authors proposed that a model for ownership of HBM from indigenous communities should be one of mutual ownership between the community and the researcher/biobank or at least that the HBM is owned by the community with the biobank taking a stewardship role. It is recommended that consideration for the return of biospecimens to the community following the death of the donor should be discussed in the informed consent process (Aramoana & Koea, 2020).

The role played by biobanks in community health research is important and it must be facilitated through appreciation for sensitive approaches to the values, beliefs and needs of a community and for these to be obtained through a deliberate strategy to ensure that the informed consent is meaningful. These steps are important in health research so that indigenous communities do not become excluded from health research of importance to the community.

2.2 South African perspectives on ownership and ethics in biobanking

South African publications on ownership rights in HBM are substantially aligned with what authors are reporting internationally due in the author's opinion to the substantial influence of international biobanking policies on local biobanking research. This congruence potentially allows for international sharing of HBM samples and local participation in global research initiatives.

However, it is interesting to note that a South African empirical study (Moodley et al, 2014) investigated the perceptions of South African research participants around the use of biological samples in research. The researchers found that whilst participants were in the main, supportive of sample donation, questions around future use, benefit sharing and export of samples elicited concerns from participants. The range of answers was wide and complex. Of importance in the context of ownership was a strong preference for choice of a consent process that provides for participant choices in respect of export and future use of samples.

2.2.1 Ownership vs. control of human biological material

In order to protect individual research subjects, clarity is needed on what rights transfer firstly to the biobank on excision of the material and then subsequently through transfer to researchers. In my opinion, because the legal framework in South Africa does not give clear guidance with respect to the transfer of ownership with the excision of tissue. the informed consent processes provide an important opportunity for research participants to direct the future use of a sample insofar as it is possible to direct its use.

Research articles from a sample of South African biobank researchers indicate that biobanks are opting to implement different models intended to protect research subjects and at the same time make HBM available for medical research.

Abayomi et al. (2013) described the challenges that biobank establishments face given the inadequate local regulation on biobanking. The authors reviewed fundamental ethics issues related to biobanking, but they did not address ownership of HBM.

Schneider et al. (2016), in the context of a biobank at Stellenbosch University, advocated the role of the University as a custodian of HBM samples rather than that of owner of HBM samples. The role of the biobank was understood to be that of custodian or caretaker of specimens to ensure privacy of the donor, the integrity of the specimen and associated data and that both conform to the informed consent.

De Vries et al. (2017) in their report on biobanking practices in 22 African countries, found that the ethics documents from only seven countries had guidelines on ownership of HBM. Policies varied from a department of health owning the samples, to the collecting institution assuming custodianship of the samples and to the government owning the samples. Two other countries left the decision to be agreed upon between the research teams and to be reviewed by the ethics review committee.

In the South African context, it appeared to the researcher that the option most likely to protect research subjects would be a model in which the control over the HBM passes to the biobank on removal of the material whilst the research subject directs the future use of the sample using the informed consent document. The responsibility should then rest with the biobank to ensure, including using the National SA MTA template, that the research subjects' requirements on future use of the samples are adhered to for as long as the HBM is used for research.

2.2.2 Informed consent

The informed consent document, an agreement between the biobank and the "donor" of the HBM, gives the donor the right to decide on how the material is used and transfers these obligations to respect donor requirements to the biobank to act as custodian of the material. The control of the material therefore passes to the biobank but not the full ownership rights.

Tindana, Campbell et al. (2017) reported that the Human Heredity and Health in Africa (H3Africa) Initiative consisting at the time of eight collaborative projects, recognised community engagement as a key element of genomic research. This is important in facilitating understanding of research and in underpinning broad consent for research. Appreciation for cultural values and concerns promotes sensitivity and community buy-in and collaboration in research projects.

This is a particularly important consideration in South Africa given our demographic composition.

2.2.3 Benefit sharing

Labuschaigne et al. (2019) reported that African research participants and researchers have not significantly benefited from their contributions to research and that the MTAs do not re-enforce benefit sharing. Their recommendation is that MTAs should be robust enough to provide assurance that the receiving institution is legally obliged to adhere to the MTA requirements, which should include a requirement for details of benefit sharing.

In addition to the comments made above in respect of indigenous communities, in the context of South Africa and the developing world, a policy on benefit sharing should correct the exploitation which has and continues to exist in certain spheres (Mahomed and Sanne, 2015). Afifi et al. (2020) recorded that South Africa, having hosted

significant international studies over the years, is not able to demonstrate the extent to which our population or participants have benefitted from the international sharing of samples.

Thaldar et al. (2020) suggested the development, in consultation with stakeholders, of best practice guidelines for benefit sharing. They argued that the database in a biobank is a form of library and the property of the research institution. The intellectual property rights of the database itself would be distinct from the independent rights to the individual data points. The library or database itself may qualify as a trade secret. Ownership provisions alone cannot solve the ethical and legal challenges of the fair distribution of benefits between all stakeholders in global research collaboration.

These examples illustrate how biobank governance systems have different approaches to the ownership issue and that the custodianship or stewardship model is favoured.

2.3 International biobanking guidelines

This section analyses international policy documents focusing on the extent to which they address ownership in biobanks. The following explores the extent to which these policies and principles have been incorporated into South African policy and legislation.

South Africa is bound by the declarations of the World Medical Association at the 18th and 53rd General Assemblies to which it is signatory. These documents are thus directly relevant to this study and to biobanking in South Africa. Further, the following quote from Mahomed, Behrens, Slabbert et al (2015) highlights the relevance of and need to consider other key global documents dealing with biobanking, "*As there is no precedent in South Africa regarding ownership of human tissues, guidance must be sought from international law in this regard. In terms of S39(1) of the Constitution of the Republic of Africa, 1996, when interpreting the Bill of Rights, courts must consider international law. International case law suggests that when dealing with the issue of ownership of human tissues, there are no firm "rules" per se."* In the researcher's opinion, this highlights the relevance and importance of the World Medical Association documents for biobanking governance in South Africa.

The key questions are whether compliance with the various principles for the protection of subjects in research affect the nature of informed consent required and whether it impacts on the rights of the participants and their communities and on the ownership of the material that is stored in biobanks. Neither the Declarations of Helsinki and

Taipei (WMA, 2013; 2016), nor the CIOMS (2016) principles provide this much-needed clarity.

2.3.1 Declaration of Helsinki by the World Medical Association

The Declaration of Helsinki (WMA, 2013) places responsibility on research physicians for protection of the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of the personal information of research subjects. It stipulates that involvement in medical research must be voluntary and that subjects capable of giving informed consent must be adequately informed of the study. Information to be provided to subjects should include, but not be limited to, the study aims, methods, funding sources, possible conflicts of interests, institutional affiliations, the anticipated benefits and potential risks of the study and the discomfort it may entail for research participants. Subjects must be informed of their rights to refuse to participate in research or to withdraw the consent at any time (WMA, 2013).

Where a potential subject is incapable of giving informed consent and only if the subject can potentially benefit from the study, can informed consent be sought from a legally authorised representative (WMA, 2013).

The Declaration of Helsinki (WMA, 2013) places ethical obligations for the publication and dissemination of the results of research in human subjects, on all researchers, authors, sponsors, editors and publishers. Research results must be made publicly available and researchers are responsible for the completeness and accuracy of reports. Negative, positive and inconclusive results must be made known. This sharing of information is an aspect of contributing to the societal good.

2.3.2 Declaration of Taipei by the World Medical Association

Activity related to health databases and biobanks should be to the benefit of society and in particular, public health objectives (WMA, 2016).

The World Medical Association gives further guidance specific to health databases and biobanks in the Declaration of Taipei (WMA, 2016). The dignity, autonomy, privacy, and confidentiality of individuals must be respected by physicians charged with ethical and legal obligations towards patients. Information provided by patients and the rights of autonomy, privacy and confidentiality must be protected in exercising control over the use of personal data and biological material. The collection, storage and use of data and biological materials must be voluntary. Specific, free, and informed consent

must be obtained. The Declaration of Taipei (WMA, 2016) stipulates that, before HBM is collected or shared, the ownership of materials and rights and privileges of participants should be discussed and contractually defined. Principle 18 specifically states in the declaration that, “special considerations should be given to the possible exploitation of intellectual property” (WMA, 2016).

In the event that commercial gain may arise from the research, potential participants should be made aware of this and of provisions for benefit sharing and intellectual property issues that could arise with the transfer of data or material to other institutions or third countries (WMA, 2016). The interests and rights of communities, particularly vulnerable communities, in the outcomes and benefits arising from the research must be protected (WMA, 2016). Although the declaration states that a transparent policy covering the intellectual property rights should be available and communicated, it does not include detailed guidelines (WMA, 2016).

2.3.3 OECD Guidelines for human biobanks and genetic research databases (HBGRD) (2009)

In 2009, the Organization for Economic Co-operational Development (OECD) established a set of guidelines for human biobanks and genetic research databases (HBGRD). This comprehensive set of guidelines on biobanking recommends best practices for the establishment and management of biobanks. The guidelines do not address ownership directly. However, it recommends that where applicable, the HBGRD will be the legal custodian of the HBM (and data and the collection) and that the participant may not retain all rights in these.

There should be clearly articulated policies on benefit sharing which should include details of whether products which may arise form research might be shared with participants or the community, and how sharing would take place. Benefit sharing arrangements should be negotiated before a study begins and covered in the informed consent document.

2.3.4 Council for International Organizations of Medical Sciences (CIOMS)

The Council for International Organizations of Medical Sciences (CIOMS) is an international non-governmental organisation. In collaboration with the World Health Organization (WHO), CIOMS published a statement of general ethical principles and guidelines (CIOMS, 2016) to support the development of national policies, especially in the developing world, on biomedical research and incorporating the principles of the

Declaration of Helsinki (WMA, 2013). The CIOMS document identifies minimum criteria for obtaining informed consent for general research and the minimum information which must be provided to participants potentially participating in biomedical research, specifically involving biobanks. In respect of ownership and benefit sharing this includes but is not limited to:

- Options to withdraw from the study at any time without repercussions and details of whether biological specimens taken will be destroyed or stored after the study and whether transfer may take place;
- Details of storage and future use and the subject's right to decide on these matters;
- Details of any reimbursement for study, participation and, where a possibility exists of development of commercial products from biological specimens, potential payments, or benefits; and
- Potential benefits to the individual and community.

Further to these principles, sponsors and investigators have obligations in terms of CIOMS to refrain from unjustified deception, undue influence or intimidation. These parties also need to ensure that the subject fully understands the facts around the research and has time to consider the matter before obtaining consent which should be documented, signed and renewed if conditions or research procedures change. Long-term studies should provide for informed consent to be renewed at predetermined intervals, even if nothing has changed. Subjects must have an opportunity to question investigators and, in some situations, counselling may be beneficial.

2.3.5 The National (United States) Commission for the Protection of Human Subjects of Biomedical and Behavioural Research – The Belmont Report

The Belmont Report (USA, 1979) is a statement of basic ethical principles for the conduct of research in humans. It attempts to address ethical questions arising from reported abuses in research during the Second World War and other incidents.

The document highlights the importance of three ethical principles relevant to human research ethics:

- Respect for persons: Individuals should be treated as autonomous persons. In the situation where a person's autonomy is diminished, they should be protected.
- Beneficence: Benefits from research should be maximised and harm should be minimised to ensure the well-being of research participants.
- Justice should prevail with regards to equity in the sharing of benefits and risks.

In the context of biobanking, autonomy is important in the granting of informed consent. Beneficence relates to attaining a balance between the benefit to society of the research versus the burden and risks born by research participants and researchers. Justice must be done in the sharing of risks and benefits and in the placing of research sites.

2.3.6 Singapore Statement on Research Integrity

The Singapore Statement on research integrity (WCRI, 2010) recommends that data sharing should first allow an opportunity for parties to establish priorities and ownership claims. The Singapore Statement does not deal further with ownership.

2.3.7 American Medical Association

The following reference published by Petrini (2012), in reference to the Code of Medical Ethics of the American Medical Association (2007) recommends that physicians contemplating the commercial use of human tissue should abide by guidelines which include the following:

- Informed consent should be obtained for the use of organs or tissues;
- Details of potential commercial applications arising from the HBM must be disclosed before profit is realised;
- HBM may not be used for commercial purposes without informed consent of the donor;
- Profits from the commercial use may be shared with patients in accordance with lawful contractual agreements.

It is interesting to note the inclusion of specific mention of requirements in respect of potential commercial applications, permission for commercial purposes and the mention of profit-sharing from commercial use. These requirements have not been so explicitly detailed in other policy documents which have been referenced by the researcher. These requirements place specific demands on biobanks where there is

intent to use HBM for commercial use. Whilst this seems to respond to the directives of the World Medical Association Declaration of Taipai it could, in the opinion of the researcher when published in this format, impose a barrier to access to biobanked HBM as the future use is not easily quantified at the time of informed consent.

2.4 South African biobanking guidelines

The SA Department of Science and Technology compiled the *Bio-economy Strategy* (RSA, 2013). The following excerpt highlights the importance of biomedical research in the SA economy:

> *For the Bio-economy Strategy to achieve its objectives, the regulatory landscape should address the ethical implications of all innovations, while taking care not to stifle research and innovation. The country should strike a healthy balance between recognising the potential benefits of biotechnology and ensuring that research is ethically conducted. This will require constantly evolving ethical and regulatory frameworks.*

In respect of research on HBM, the DoH guideline, *Ethics in Health Research: Principles, Processes and Structures* (RSA DoH, 2015), is the most important policy document.

2.4.1 Ethics in Health Research: Principles, Processes and Structures (DoH Guideline)

The Department of Health (DoH) guideline, *Ethics in Health Research: Principles, Processes and Structures* (RSA DoH, 2015), published in terms of the NHA legislation by the NHREC has legal status.

This guideline applies to all research that involves living persons and the use of animals. S3.3 deals specifically with data and HBM for research purposes (biobanks) (RSA DoH, 2015).

Research on biological materials involves either the collection of data and biological materials from research participants or the use of previously-collected diagnostic or therapeutic biological materials for research. Ethical considerations on the use of the material and associated data should include provisions regarding access to and appropriate use of material and privacy considerations. It should take account of the special status attributed by some segments of the population to the management of the human body and its parts.

For consent to be “informed”, research participants must be fully informed on all choices before the research commences and participation should be voluntary. The nature and quality of the information to be made available to the participants is important. The proposed process for informed consent and the information to be provided must be assessed by the HRECs. However, the policy does not deal with the matter of ownership of donated material and data in the context of informed consent.

The use of biological materials and/or data for research purposes must be distinguished in the consent documentation from material and data collected for clinical purposes. In the event where narrow consent for single use only has been granted by the research participant, new consent would be required for further use. Tiered consent provides for consent for a primary study and allows a choice of whether to open storage for future use. Broad consent from a donor allows for the use of the specimen for current and future research and is advocated by the policy where future use (secondary use) is intended. It provides remedies to be applied in the absence of broad consent for secondary use. Blanket consent is not recommended as it is difficult to implement the ethical principles and respect the wishes of donors. In order to protect the subject, such remedies would need to be clearly mandated by the donor and controlled through HREC procedures.

Dhai (2019) raised the question as to whether broad consent can be considered as informed consent or just “permission”. If the latter description indeed applies, then broad consent may provide inadequate protection to research participants.

Benefit sharing: The DoH guideline (RSA DoH, 2015) gives guidance on benefit sharing in health research. The guideline calls for distributive justice or equality and a fair balance between the risks and benefits amongst all stakeholders, including research participants, communities and South African society, who should all have a reasonable chance of benefiting from research results.

Benefit sharing strategies of a biobank must be approved and annually reviewed by an independent HREC registered with the NHREC. Specific guidelines are not articulated.

MTA: The DoH guideline (RSA DoH, 2015) requires the transfer of materials between the provider and recipient to be governed by an MTA approved by an HREC. These guidelines are further discussed in S3.2.2.2.

2.4.2 Health Profession's Council of South Africa (HPCSA) guidelines for health researchers

The HPCSA *General ethical guidelines for health care professions: Booklet 13 Guidelines for health researchers* (HPCSA, 2016) on data and specimen storage require the use of an MTA for the export of samples. The agreement must be approved by an HREC and must justify reasons and benefits in respect of samples leaving the country.

In alignment with the principle of autonomy, the guidelines for informed consent address amongst others, the importance of information being provided in an understandable language, avoidance of dependent relationships in the consent process, that consent is an ongoing process, and the importance of a witness where a potential donor is illiterate. Ownership is not addressed. These guidelines are further referred to in S3.2.2.1.

2.4.3 University of the Witwatersrand Human Research Ethics Committee Medical: Biobanking Policy.

The Human Research Ethics Committee Medical (HREC) of the University of the Witwatersrand (WITS) has a policy on biobanking known as "The Human Research Ethics Committee Medical; Principles and Policy on Biobanks, (WITS HREC, 2015b). This policy applies to biobank related research approved by the WITS HREC. Arrangements for the transfer of samples between biobanks and researchers must be recorded and agreed in the WITS MTA template (WITS HREC, 2015a).

The need for a Wits biobank policy arose as a result of applications to the Wits HREC for permission to store or export HBM. The committee needed additional information on the storage and disposition of samples and the policy and MTA template were drafted and made available to the committee by Mahomed, S., in 2014 (Mahomed, S, 2018). The WITS MTA template is a key document intended to protect the rights of research subjects whilst facilitating research through the transfer of HBM.

The WITS MTA template was the initial focus of this bio-ethico analysis.

Subsequent to the commencement of this research on the WITS MTA template, Mahomed S, (2018), made recommendations for draft regulations for human biobank research in South Africa. These recommendations included amongst others, the use of a MTA for the transfer of HBM outside of the South African borders, for the recording of benefit sharing arrangements in biobank research and for collaborative projects

using HBM. The WITS MTA was published as part of Mahomed's research and made available to the Department of Health for the purpose of drafting regulations. The National SA MTA template was gazetted in 2018 and is now a binding document for use in research or clinical trials under the auspices of the HRECs for the transfer of HBM. The National SA MTA template is based on the WITS MTA and is very similar. This research will therefore focus on the binding National SA MTA template.

The WITS policy (WITS HREC, 2015a) requires that research must benefit research participants and their communities. Details of benefit sharing must be negotiated between provider and recipient and documented in the MTA. Guidelines are not provided. The *WITS MTA* on the otherhand emphasises the importance of benefits to providers and defines "benefits" as follows:

> *…the benefit that will be received by the **Provider** from the use of the Materials by the Recipient. Benefits may include, amongst others: the sharing of information; use of research results; royalties; acknowledgement of the Provider as the source of the materials; publication rights; transfer of technology or materials; and capacity building.*

The WITS policy and MTA template (WITS HREC, 2015b; 2015a) require that all transfers and exports of HBM and data for specific research purposes must be approved by the WITS HREC against documented transfer procedures. The WITS MTA (WITS HREC, 2015a) describes a "custodian" as a person or entity entrusted by the donor with safeguarding and protecting the donated HBM. It is silent on ownership.

2.4.4 The San Code

Of interest in the South African context is the relevance of communitarianism to a discussion on ownership of HBM. This is contextualised in the San Code of Ethics (SA San Institute, 2017) a statement of ethical principles to guide research involving the San people, a South African indigenous population. This Code does not deal with ownership per se, but calls for the values of respect, honesty, justice, fairness, and care. In particular, the document highlights the importance for individuals and community of consideration for culture, history and sensitivities, privacy, and engagement around research. It is significant that the document stresses that promises made by researchers need to be kept. Transparency and honesty with respect to research benefits and opportunities to collaborate in research are important. Research should be aligned with improving the lives of the San.

2.5 Ethical Principles relating to donation of HBM and informed consent

The ethical principles applicable to ownership of HBM and informed consent in biobanking include:

- autonomy in the granting of informed consent;
- duty of care towards the participant in the informed consent process and in respecting the donors directives in respect of the use of the HBM, thereafter;
- communitarianism where research is conducted in communities where communal ownership is a societal value; and
- the societal good.

In the following sub-sections, these ethical principles are analysed in the context of biobanking.

2.5.1 The principle of autonomy in the granting of informed consent

Can compliance with the principle of autonomy be assured in the informed consent process in biobanking? Beauchamp and Childress (1994) reasoned that the primary function and justification for informed consent is to enable and protect individuals' autonomous choices.

Biobanking participants providing HBM should be free to make autonomous choices when consenting to participate in a study. The principle of autonomy dictates that, in personal decision making, a person should be free from controlling influences and have the capacity for intentional action. Participants should not be coerced into consenting or be in a vulnerable or subservient/dependent relationship to the investigator. Participants should also be fully informed on the details of the study, on the potential future use of their HBM, on their rights and on the consequent potential for risks and benefits.

Given that the concept of ownership of HBM lacks certainty in the context of biobanking, a relevant question is whether the informed consent is relevant if issues of ownership, control of, access to and use of HBM are not raised in the disclosure process intended to inform research participants. The answer is probably, no.

An inherent challenge in biobanking is that of conflicting interests between research stakeholders; research participants, biobanks and researchers. Research participants

are unlikely to have personal interest in the research, researchers are dependent on access to HBM for research and HBM stored in a commercial biobank may have potential for commercial value.

Autonomy in the granting of informed consent is important: The risk to the autonomy of research participants is that when biobanks engage with potential research participants, there is a chance that the investigator communicates a biased narrative, and that the information may be inclined towards persuading the individual of the positive attributes of the study. Examples could include inadequate disclosure of information around the potential commercial benefits of the study, over-emphasising the societal benefits to health research or over-stating the ability of the biobank to protect personal information. The possibility of personal information and data becoming discoverable from the HBM is generally the biggest risk to the participant. This possible oversight would undermine research participant autonomy.

Is autonomy absolute? It is generally accepted that respect for autonomy can be overruled by competing moral considerations, as in the case of the absence of informed consent for a future use of HBM. The public interest and the principle of beneficence could be considered as a justifiable reason to limit autonomy. Hence, it is acceptable that, in the absence of broad consent from a research participant, an HREC may make a ruling on future use of the HBM.

In summary, the detail and process of informed consent is fundamental to ensuring that consent is granted autonomously. The principle of autonomy applied to the granting of consent to provide HBM for research purposes recognises the importance of fully informing the participant about the research and ensuring absence of coercion to participate. The principle is not absolute and may be moderated by other considerations, such as the public interest in health research.

The process to obtain informed consent for future use of the HBM may be imperfect and lack detailed content due to the nature of informed consent. Checks and balances on biobank and investigator processes could enhance participant autonomy.

2.5.2 The principle of duty of care towards the participant in the informed consent process

The principle of care is relevant in informed consent. The duty of care in biobanking is to be responsive to health needs and priorities of the population, participating community or proposed participants (RSA, 2015a). It has been highlighted as

important when engaging with research participants, such as in the consent process. A caring approach should be adopted to ensure that the participant is comfortable in engaging. An example is the manner in which it is explicitly documented in the *San Code of Research Ethics* (SA San Institute, 2017).

Biobanks should take reasonable care to uphold and implement the scope of informed consent, and where applicable, community interests, and similarly bind researchers and users of data and HBM.

2.5.3 The principle of communitarianism where research is conducted in communities where communal ownership is a societal value

Can communitarianism be an alternative to autonomy of the individual in indigenous communities? The socio-economic organisation of many indigenous communities is based on the principle of common or collective ownership. Consideration for societal beliefs and for involving the community in the information-sharing and consent process in thus important. It potentially impacts the autonomy of an individual in the decision to participate in a study and in the engagement around arrangements for benefit sharing. This communitarian approach to decision making ought to be considered in the consent process for studies in such communities and, as a minimum, keep the community informed and engaged around arrangements for the sharing of benefits. The needs of the community may, in such cases, prevail over the autonomy of the individual.

The San Code (SA San Institute, 2017) succinctly articulates important values in such communities. It is of relevance in the South African context where research is being undertaken within indigenous communities. It is closely aligned with the principle of care.

Due attention should be paid to cultural beliefs. Communal interests can be real issues and processes should be put in place to provide for community engagement around the informed consent, potential community and societal interests and the sharing of benefits, including relevant and appropriate community information arising from the study.

2.5.4 The principle of societal good

Does the contribution by health research, to the societal good, justify research on HBM? In general terms, study participation will not materially benefit the research

participant. Participation is motivated on the grounds that health research is in the public interest and that society in general will benefit. Without the commitment of research participants to support biological research, or the important role played by biobanks, progress in healthcare development would be inhibited to the detriment of society. Health care research ought to be facilitated for the benefit of society. In this sense the contribution to the societal good justifies research using HBM.

2.5.5 The principle of distributive justice in sharing the benefits of research

Can distributive justice provide for the equitable sharing of research benefits? Guidelines and legislation are aligned on the importance of sharing the information and benefits of research, including amongst research participants and communities. The principles of distributive justice should inform such arrangements. From an ethical perspective, unanimity does not exist on what or how research outcomes, especially those of a negative nature and commercial gains should be shared. This is debated in the study.

The principle of distributive justice is an important consideration in biobanking. It is a group of norms for distributing benefits, risks, and costs (Beauchamp & Childress, 1994). Distributive justice in biobanking must be considered in arrangements for the fair sharing of benefits and burdens or risks from research amongst individuals or groups. The determination of what constitutes a risk or a benefit or equitable sharing is complex. The benefits of HBM use is generally justified by the goal of progress in health research for societal benefit. Research participants may not be paid for HBM and biobanks may have the potential to become a commercial operation and benefit from financial gains. Rewards for researchers include the creation of intellectual property, products and receiving scientific accolades.

The risk to the research participant or their community is principally directed at any personal consequences of a breach in privacy of their confidential information. The potential for compromising autonomy in informed consent could also be considered a risk. The direct risk to the biobank of receiving HBM could be failure to enforce compliance with the informed consent document, which in turn would translate to an additional risk to the research participant. The risk of not obtaining HBM would be significant if research participants do not consent thereto and hence the concern for the balance of information provided in that process.

It appears that in the distribution of benefits, the biobank and researcher benefit the most and in the distribution of risks, the research participant shoulders the greatest risk. The sharing of benefits between the biobank, the research participant and the researchers cannot be truly equitable. The principal benefit to society is indirectly a benefit to research participants and the public good should take precedence in decision making.

Benefit sharing arrangements should be dealt with in the informed consent and discussed with participants. Ethical guidance would be of value in determining the nature of information that should be shared. Whilst the principle is a noble one, determination of what is equitable sharing between the direct stakeholders and how it should be communicated to participants present a challenge. Practicalities in some cases may militate against the overarching principle such as in the case of sharing of results.

2.5.6 The principle of the right to privacy of personal information

Can biological research protocols guarantee that the right to privacy will be respected? The medical and personal information of a research participant and possibly also the data generated from the research is sensitive information. Biobanked HBM is stored together with specific personal information and data relating to the participant. The right to privacy and protection of information is a basic human right and must be protected by all involved research stakeholders. This includes recipients of material, researchers, and eventual users of the data generated.

Study methodologies have been developed to protect this information and data, but the mere nature of biological research means that information about a person may nonetheless be evident to researchers. The research participant may not appreciate this fully. Therefore, whilst health research and biobanking protocols should be such that the confidentiality of patient information is protected as far as is possible through blinding and coding mechanisms, in biological research there is an inherent risk that confidentiality may be broken. Confidentially cannot therefore be guaranteed, which can result in harm to a research subject and possibly even to their communities.

2.6 Summary on ownership and ethical use of HBM

Chapter 2 analyses international and local perspectives, guidelines and legislation on ownership of HBM in biobanking. Generally, there is lack of clarity on ownership of biobanked HBM.

The referenced literature dealing with biobanking perspectives on ownership highlighted similar issues around informed consent and benefit sharing. The review demonstrated that biobanks have implemented mechanisms to protect research participants, whilst making donated HBM available for health research.

The international and local guidelines are generally aligned on their approach to informed consent for research participant protection and the MTA template as a means to transfer biobank accountability for protecting research participants in the transfer of samples. The importance of the autonomy of research participants in the informed consent process was highlighted as was the necessity for benefit sharing arrangements to be highlighted, declared in the informed consent process and documented in the MTA and aligned with the principle of distributive justice.

South Africa is the only country to have an enforceable requirement for a specific MTA format. The legal issues relating to ownership of HBM stored in biobanks are addressed in the following chapter.

CHAPTER 3: LEGAL ISSUES RELATING TO OWNERSHIP OF HBM STORED IN BIOBANKS

This chapter explores the international and South African legal frameworks relating to biobanking. In particular, the SA contexts for HBM, benefit sharing, MTAs and intellectual property are described.

3.1 International legal frameworks

3.1.1 International case law and theories as regards ownership

It is generally recognised that possession and use of legitimately removed cells, tissues and organs passes to the recipient or person removing the tissue, irrespective of ownership. Where the material is processed further, after removal, additional rights including ownership rights may be acquired (Petrini, 2016).

The issue of ownership of HBM by the research participant has however been challenged in courts which have addressed the question of the participants' rights to commercial gains arising from the HBM (Tran, L., 2017).

The principle that a deceased human body cannot legally be owned has applied for centuries since the ruling in 1614 in the Hayne's case in the United Kingdom which held that "there can be no property in a corpse". However, in the case of Doodeward v Spence, 1908, (Australia) the court ruled that a preserved fetus could be possessed. The court found that where a fetus had undergone "the lawful exercise of work or skill so […] that it has acquired some attributes differentiating it from a mere corpse awaiting burial", it should be legally protected. Similarly the case of R v. Kelly and Lindsay, 1998, establishes the principle that because body parts had been the subject of skilled work they could be considered to be property, in this case belonging to the Royal College of Medicine (Petrini, 2012).

More recent international case law does not provide us with consistent view on excised HBM.

3.1.1.1 Moore v. Regents of the University of California (UCLA)

In the case of Moore v. Regents of the University of California in 1990, the patient's removed cells were used without his knowledge or consent, for economic gain. The patient sued the university seeking a share in the profits.

The reason for the removal of the cells was not primarily a research matter but rather related to patient care. The treating doctor had mislead the patient into undergoing successive, unnecessary treatments in order to harvest the patient's rare cells. These were subsequently developed into a commercial cell line and patented.

The court ruled that because the patient had consented to the removal of the tissues, the patient had no property interest in the cell line developed from his cells. The patient's permission was not sought for the development and patenting of the cell line and the doctor was held in breach of his fiduciary duty to obtain the patient's informed consent for doing research on the cells. This decision was reported as being controversial at the time (Szostak, 2010).

3.1.1.2 Washington University v. Catalona

- Charo (2006), in a report on the ownership and use of human tissue, referred to the case, where the control over HBM samples was challenged. Catalona (a researcher) asked patients (donors) to request their samples be transferred from the research centre at Washington University to his new research centre. The court ruled on the basis of the consent forms signed by the participants, that the control of the material vested with Washington University and that the patients' rights were limited to rights to request that samples be destroyed and that they could not direct that the samples be delivered to Catalona or to another university (Charo, 2006).
- Charo (2006) debated the ownership rights in the HBM, describing two approaches. Firstly, it could rest on issues of privacy of medical information or entitlements created through the regulation of research and not on considerations of sample ownership. Secondly, if property rights in HBM do exist in general or through transfer, then such rights would depend on the fairness of the transaction and the quality of the information provided to the participants at the time of consent for the research. Charo recognised that ownership issues have powerful implications for medical research.

- At present some research organisations adopt a theory of autonomy of the research participant which is independent of any property right in the tissue (Charo, 2006). Charo's report also questioned the value of a common practice of requiring a waiver of property rights from the research participants because of uncertainty over the property rights in HBM, and also of the validity of the waiver without the required certainty, and that such waivers may not comply with legal rules for transfer of property.

3.1.1.3 Arizona University's settlement with the Havasupai tribe

In the case of the Havasupai Indian Tribe, the ownership of HBM is not the core issue but rather the failure of researchers to properly obtain informed consent for the study both before commencement of the study and also for secondary use of the material in further research. This failure to obtain informed consent from a community not only harmed the community but also undermined the reputation of the Arizona State University researchers.

A settlement, including return of the samples, financial payments and commitments to support health and education, and economic development, was reached 21 years after the tribe had approached the University to do research and 6 years after the tribe had filed a lawsuit against the University. The research was to have been focused on the incidence of diabetes in the tribe. The apology and acknowledgement made by the University are significant in informing HBM research practices today.

Oversights of the University which were at the heart of the community complaint included "lack of informed consent, violation of civil rights, and intentional or negligent infliction of emotional distress". (Sterling, 2011). Samples were also shared with other researchers without community engagement, for research purposes on subjects which the community found to be offensive. (Mello and Wolf, 2020)

3.1.1.4 Yearworth v North Bristol NHS trust 2010 (Court of Appeals for England and Wales)

The ownership of HBM is debated in the case of Yearworth v. North Bristol NHS trust. In this matter 6 patients of the North Bristol NHS trust had banked their sperm prior to undergoing cancer chemotherapy as a precautionary measure to store the sperm for future use in the event of the men experiencing infertility following the treatment.

The samples were damaged in storage, rendering them unusable. The Trust admitted to breaching the duty of care that it owed the men in terms of the arrangement (Rostill, 2014).

The basis of the men's claims against the Trust was that they owned their sperm and that they therefore had property rights in the sperm. The English Court of Appeal upheld this position despite the fact that the long-held position in law (at that time) was that "*property cannot be held in the human body, living or dead*" (Harmon, 2010). One interpretation of the ruling is that the Judge deemed the sperm to be owned by the men only as far as storage by the Trust was concerned.

Harmon, 2021, reviewed the Appeal Court's decision on a number of points including the proprietary and contractual interests in body and bodily products. Hamon, (2010), concluded that this first instance where an appellate court seriously considered the question of originator property in HBM has extended the right of body-product ownership to originators of the product (HBM) within a specific context. He however highlights the very narrow context of the sperm, productive tissue, and challenges the ruling and its significance for HBM in general.

Rostill (2014), in his interpretation of the case concludes that the decision of the English Court of Appeal establishes the principle that "*in English law persons have, in certain narrow circumstances, a right in rem in their sperm, a right grounding duties on persons generally not to cause by their negligence such damage as would preclude the right-holder (…),.from using it*".

3.1.1.5 Piljak Estate v. Abraham 2014 (Ontario Superior Court of Justice)

Saulnier and Joly, 2016, reported on the findings of the Superior Court of Ontario in the matter of Piljak Estate v. Abraham (2014). The case dealt with ownership of tissue removed from a patient during diagnostic medical testing.

The Court found that the tissue belonged to the hospital where the procedure was performed. Saulnier and Joly (2016) highlight that if the HBM belongs to the hospital, and the tissue is made available for research, the rights of individuals to withdraw consent for future use could be compromised.

3.1.1.6 Relevance of case law to ownership of HBM

In the case of Moore v. Regents of the University of California, the courts ruled that as the patient had consented to the removal of the tissue, the "patient" did not have property rights in the removed HBM and therefore had no further right to control its use or rights

to economic benefits from the research (Szostak, D.C., 2010). In this case it would appear that whilst the patient had given consent for the removal of the tissue he had not given permission for research to be done on the tissue. There had also not been disclosure on the potential benefits that could be derived from such research. The “patient’s” rights to autonomy in making decisions around the use of his HBM were not respected in this case and the principles of distributive justice were similarly not considered.

The ruling of the court in the Catalona case was that control of the samples remained with the biobank (Washington University) and that the patient’s rights were limited to directing the destruction of the material and did not extend to the ability to give other instructions related to the material (Charo, 2006). This ruling aligns with the generally accepted position that control over donated HBM passes to the recipient, in this cae the University.

The matter of the settlement between the University of Arizona and the Havasupian Tribe highlights the challenges in ethically conducting valuable and much needed research on HBM in vulnerable communities and in ensuring autonomy of both the individuals and the community, particularly in the context of fully informing the consent process. Consideration was not given to the need for consent or tribal values relating to future use of their HBM.

The case of Yearworth v. North Bristol NHS Trust was the first case in which a decision of an Appeal court found that, in a limited context, the property could reside with the originator of a bodily product. This decision was specific to sperm due to it being reproductive tissue. The outcome of the appeal has been challenged by various authors and different interpretations of the findings have been debated (Harmon, 2010 Rostill, 2014)

In the case of Piljak Estate v. Abraham (2014), the court found that material removed during diagnostic testing belonged to the hospital where the procedure was performed.

This ruling however challenges the long supported principles that HBM cannot be owned. The decision of the Court has been challenged on various points to the extent that the question has been raised as to whether the ruling can be considered significant (Harmon, 2010).

The rulings in the case law highlight the importance of informed consent in respect of ownership for research as well as when tissue is removed in the clinical environment.

Cadigan et al, 2017 commented that the legal challenges to the physical property of HBM as well as the numerous ownership disputes that are not litigated, highlight the potential for contentious perceptions around ownership of HBM. The authors recommend that biobanks have a policy about ownership of specimens and rights to technology developed from the HBM.

The outcomes of these cases illustrate that whilst in general terms, donors' rights over removed HBM are limited once the material has been removed, the donor does have a right to direct the use to which it is put and its disposition. Also, whilst the long held common principle, internationally, is that there cannot be ownership rights in HBM, the Yearworth v North Bristol NHS Trust case introduced the concept of ownership by originators of body products in specific circumstances and the much-criticised ruling in the Piljak v Abraham case is that ownership can rest in HBM, in this case with the hospital that removed it.

Rhodes (2016) has researched international approaches to ownership and control of human genetic resources. The author found that at the international level, there is no common approach to ownership in respect of "human genetic resources". The author raises the concern that such an approach could mitigate against the potential for these resources to contribute to addressing global health challenges as such free access would mean anyone could access and use the resources and claim property rights therein. Such an approach could advantage private companies as well as scientifically and technologically advanced states.

Until the publication of the National SA MTA for the governing the transfer of HBM, there have been no clearly defined rules on ownership of HBM in South African Law so that the courts would need to have regard for international law. The literature suggests that when dealing with the issue of the ownership of HBM, each case needs to be separately assessed (Mahomed et al., 2015).

3.2 South African legal system

3.2.1 The Constitution, 1996

The South African Constitution is the supreme law of South Africa.The Bill of Rights (Chapter 2) recognises the basic human rights of South Africans. In the context of research involving HBM, relevant Constitutional rights include rights to human dignity; life; freedom and security of the person; privacy and health care (RSA, 1996).

The right to security of the person embodied in the Bill of Rights recognises the principle of autonomy and includes the right "to security in and control over one's body" (S(2)(a)) and to "not be subjected to medical experimentation without their informed consent" (S(2)(b)).

Protection of the right to privacy is particularly important in research on biobanked HBM due to the significant amount of personal information contained in a sample and in the associated data. Particular attention must be paid to protecting the privacy of research subjects.

The right to healthcare requires that "the State take reasonable legislative and other measures, within its available resources, to achieve the progressive realisation of the right to (…) "have access to healthcare services".

3.2.2 South Africa's Health Law framework as it applies to biobanking

3.2.2.1 The Health Professions Act 56 of 1974 and Ethical Codes

Only registered medical technologists or scientists registered in such terms with the Health Professions Act 1964, may remove and use HBM from a living person for research purposes (RSA 2012b). Such registered persons are accountable to the Health Professions Council of South Africa (HPCSA) which publishes ethical guidelines for research including research on HBM (HPCSA, 2008 and 2016). This is also relevant to the S2.4.2 on the HPCSA ethical guidelines.

3.2.2.2 The National Health Act and Regulations to Chapter 8

<u>The National Health Act, Act 61 or 2003 (NHA)</u>

The National Health Act (NHA, 2008) intends to "provide a framework for a structured, uniform health system within the Republic, taking account of the obligations imposed by the Constitution and other laws on the national, provincial and local governments with regard to health services; and to provide for matters connected therewith".

Regulations relating to research with human participants (2014) have been published in terms of S71 read with S90(1). These Regulations dictate ethical research principles that must be adhered to, to ensure respect for the rights of research subjects including the rights to dignity, privacy, bodily integrity and equality, as mandated by the RSA Constitution. In particular, research must comply with the Department of Health's national ethical guidelines for research with human participants. It is the responsibility of researchers to comply with the ethical guidelines and the requirements for informed

consent. Protocols must be submitted to a registered health research ethics committee (HREC) for review and approval.

DoH Ethics in Health Research: Principles, Processes and Structures.

The NHA, 2003, S72, mandates the establishment of a National Research Ethics Council (NHREC) to, amongst others, publish guidelines for health research ethics committees (HRECs) (S72(a)), register and audit HRECs (72(b)), set norms and standards for research on humans (…) including clinical trials (72(c)) and other issues pertaining to ethical issues concerning research.

Guidelines published by the Department of Health provide the ethics framework for health research including research using HBM. These norms and standards are enforced through the National Research Ethics Committee and institutional ethics committees.

Biobanks are required to be registered with an approved Research Ethics Committee, and study protocols and MTAs for HBM transfer arrangements must be approved by an HREC. Details of these guidelines are also discussed in S2.4.1.

Chapter 8 of the NHA

Many of the principles established internationally for health research informed consent are legislated in the NHA (RSA, 2003) intended to give effect to Constitutional rights (RSA, 1996). Every organisation conducting health research must have, or have access to, a health research ethics committee registered with the NHREC to review and approve research protocols that meet ethical standards (NHA, 2003, S73). Research proposals and protocols must be reviewed by an ethics committee, where appropriate, before approval is granted to the research organisation.

Human Biological Materia donated for use in health research

Chapter 8 of the NHA provides for the promulgation of regulations regarding human tissue. The following regulations relevant to biobanking have been promulgated;

- in terms of S90(1) read with S68(1), regulations regarding the general control of human bodies, tissue, blood, blood products and gametes (2012) as amended (2017),
- in terms of S68, regulations relating to the use of human biological material (2012), and
- the Material Transfer Agreement of Human Biological Material (2018).

HBM may only be removed from a living person for medical purposes if written informed consent has been obtained from the donor (NHA, 2003, S55(a)). HBM may not be

removed from a person who is mentally ill, if the tissue is not replaceable by natural processes from a person younger than 18, or gametes from a person under 18 years or, placenta, embryonic or foetal tissue, stem cells or umbilical cord, excluding umbilical cord progenitor cells (NHA, 2003, S56(2)).

HBM may be donated by a living person who has given consent, only for the purposes of training students in health research, for health research, for the advancement of the health sciences or for the production of a therapeutic, diagnostic or prophylactic substance (NHA, 2003, S64). Regulation 4 (a) provides that tissue may be donated to a hospital, a university of Technology, an authorised institution designated in terms of S54 of the NHA, a medical practitioner, dentist or tissue bank. (RSA, 2012, regulation 4). A person who has donated HBM may not receive payment or reward in respect of the donation. Only reasonable associated costs may be reimbursed (NHA, 2003, S60(4))

Regulation 26 (RSA, 2012) of the regulations regarding the general control of human bodies, tissue, blood, blood products and gametes, provides that any person who acquires any tissue, blood or gamete by virtue of the provision of the Health Act and provided the tissue is used for the purposes for which it has been donated, on receipt of that HBM, acquire exclusive rights in respect thereof. This is to be interpreted as being the exclusive rights to the use of the HBM. The scope of this use is covered in the informed consent granted by the research participant.

Regulation 3 of the regulations relating to research with human participants (RSA, 2012), obliges researchers to consult with participating communities and stakeholders about the research. Clear direction must be given as to how information may be used, kept and disclosed and informed consent must be obtained before information is released to health insurers, other healthcare providers or others. The information may only be used for the purpose it was originally intended. Where long-term storage of genetic material is envisaged, written informed consent of the user (of HBM) or donor must be obtained. Records must be destroyed after the purpose for which they were created have been served (RSA, 2012).

These regulations do not take account of the transfer of samples from one storage site to another. Morrison, (2020), highlighted the importance of the formation of durable connections that tie bio-objects, novel products formed from living cells and tissues, to places and persons of origin as a condition of transfer or mobility. This is addressed in the National SA MTA published in terms of the NHA.

3.2.3 Material Transfer Agreement of Human Biological Materials

A Material Transfer Agreement of Human Biological Materials (National SA MTA template) (RSA, 2018) was published in July 2018, by the Department of Health in terms of the NHA (RSA, 2003) for the use of all providers and recipients of biological material used in research or clinical trials under the auspices of the Health Research Ethics Committees (RSA, 2018). South Africa is unique in being the only country to regulate the requirement for the use of a standardised MTA when transferring HBM, including when transferring HBM into or out of South Africa (Thaldar et al., 2020). It is required to be used by all providers and recipients of HBM used in research or clinical trials under the auspices of a HREC.

The MTA seeks to address an omission in the law and oblige the biobank to use this as the framework for the transfer agreement. What S26 does not do is answer the question of who owns the donated HBM and what if the biobank transfers the HBM to third party researchers. The MTA clarifies that the exclusive rights of use can be equated with that of a custodian. The rights of custodianship remain with the biobank irrespective of the transfer of HBM to researchers/recipients. It thereby places the duty of care on the biobank to ensure that the terms and conditions of the informed consent are captured in research protocols and approved by an HREC prior to transfer of the HBM. This is partially covered in S3.3 of the MTA.

The MTA defines the relationships between, and places obligations on, the parties to the transfer of materials. It provides a framework for the transfer, use and other processing of HBM. It also addresses obligations at the termination of a project, for dispute settlement, concerning intellectual property, provisions for confidentiality and terms of publication and publicity.

This National SA MTA template (RSA, 2018) is, for historical reasons, remarkably similar to the WITS MTA (WITS HREC, 2015a), the initial focus of this study. This is because the Wits MTA template preceded and informed the development of the SA MTA Template. This is further discussed in chapter S4.2 and 4.3. Points of substantive difference between the two MTAs are limited to:

- The National SA MTA template states that the donor “remains” the owner in the event of a transfer, whereas the WITS MTA is silent on ownership. This is significant in the context of ownership of HBM.

- The definition of benefit sharing in the DoH MTA is broad in scope, whereas the WITS MTA focuses principally on benefits to the provider (biobank). This seems to be an oversight in that the WITS policy itself aligns with the National SA MTA template.

- In this study's assessment of the role of an MTA in safeguarding research participants, the National SA MTA template (RSA, 2018) was referenced as it has legal standing in terms of the NHA and now supercedes the Wits MTA (WITS HREC, 2015a) as an authoritative document.

Sharing the benefits of research on HBM

The South African Biodiversity Act 10 of 2004 provides for the sharing of benefits of indigenous biological resources (RSA, 2004). It does not however apply to human tissue (Mahomed & Sanne, 2015).

There is no legal requirement in South African law for benefit sharing in respect of the actual donation of human biological material (Thaldar et al., 2020). Instead, according to the NHA, it is a legal offence to receive any form of financial or other reward in respect of the donation of human biological material (RSA, 2003: S60(4)). Notwithstanding prohibition on payment of donors, the exclusive rights for the use of donated HBM, for the purpose for which it has been donated, pass to the person that receives the material (RSA, 2012: Regulation 26).

Regulation 3 of the NHA, Regulations regarding the general control of human bodies, tissue, blood, blood products and gametes (RSA, 2014), obliges researchers to disseminate research results in a timely and competent manner, including to participants and participating communities where possible.

The South African National SA MTA template (RSA, 2018) defines "benefit" as, amongst others, the sharing of information; use of research results; royalties; acknowledgement of the provider (biobank) as the source of the materials; publication rights; transfer of technology or materials; and capacity building. Therefore, it follows that benefit sharing means the process or active sharing in the benefits that derive from the project in a manner that is fair and equitable. The National SA MTA template (RSA, 2018) directs that the sharing of benefits should be discussed and negotiated between the provider

(the entity transferring the material) and the recipient (researcher or recipient biobank) of materials.

Any agreement to share benefits must be documented by the parties in the MTA although no guidelines are given in Annexure B to the National SA MTA template (RSA, 2018).

Informed consent for the use of HBM in research

The National SA MTA template (RSA, 2018) describes informed consent as a formal agreement in which a donor gives permission in respect of the use of donated material, after being informed about the project. Relatively detailed processes are prescribed. Information provided to donors should embrace details of ongoing sharing processes and ongoing participation with the ability of the donor to decide on future use of the biological material. The provider, or person responsible for the storage of the biological material, must obtain informed consent from the donor to provide the biological material to an appropriate recipient for the purposes of a research project. The completed consent form and consent for secondary uses of the material must be reviewed by the ethics committee.

Notwithstanding the fact that S3.3 of the National SA MTA template (RSA, 2018) provides that the donor remains the owner of the materials until such time as they are destroyed, the provider remains custodian of the material after the transfer. The MTA must be accompanied by the informed consent provided by the donor for the provider to provide materials to the recipient to undertake the project contemplated and also a consent for secondary use should the need for secondary use arise.

Thaldar et al., (2020) argued that the National SA MTA template (RSA, 2018) is not clear on the scope to which the informed consent is applied. The definition of consent infers that it applies to a specific project, but the scope of the National SA MTA template (RSA, 2018) appears to be broader.

Grady et al. (2017) highlighted the fact that the MTA introduces a dynamic approach to consent and that consent must therefore be obtained on an ongoing basis for new uses of the material. In contrast, the DoH guidelines (RSA DoH, 2015) recommend that consent should be broad enough to allow for secondary use at a future date.

The MTA between the provider and recipient must be signed by the provider, the recipient and the HREC before transfer takes place.

Thaldar et al. (2020) and Labuschaigne et al. (2019) do not agree on the merits or validity of an HREC being a party to an MTA. Thaldar et al. (2020) argued that in the case of most biobanks, they will not have legal capacity to sign an MTA. Labuschaigne et al. (2019), however, argued for the merit of having independent HREC oversight over the MTA agreement. Such oversight would also include the duty of the HREC to review the protocol and consent form.

3.2.4 South Africa's Privacy and intellectual property framework

The protection of a donor's right to privacy as well as the protection of any intellectual property rights created in donated HBM must be respected.

The substantial amount of information about an individual which is discoverable in a sample of HBM and in the associated records, constitute "personal Information" belonging to the donor. Donors have a right to privacy and therefore this personal information must be protected

It is argued in general that in the case of research using HBM, the debates about rights of use should be about the appropriate balance between respect for the research participant and the collective societal value derived from the research. There is an argument for the public right to the HBM provided that the protection of privacy and the interests of the donor are protected (Charo, 2006).

Where the material has been further processed, additional rights including that of ownership, may be acquired.

3.2.4.1 The Protection of Personal Information Act, Act 4 of 2013 (POPIA)

Botha J, et al record that it is a global right for individuals to have their personal information protected against any unlawful collection, retention, dissemination and use. The European Union's General Data Protection Regulation (GDPR) (European Union, 2018b) is intended to protect processing and movement of personal data of natural persons and protect their freedoms and rights and in particular, their right to protection of their personal data. The European Union's Data Protection Directive was first introduced in 1995 and since revised. The United Kingdom (UK) adopted the Data Protection Act in 1998 and the United States of America (USA) has implemented

various related laws since 2001. The authors reported that more than 100 countries had implemented laws to protect information held by governments and private companies and that the South African Protection of Personal Information Act (POPIA), signed in 2013 and only fully implemented on 1st July, 2021, was influenced by the European Union Data Protection Directive, data privacy models in the USA, Canada, Australia and the UK with the intent of stimulating business and cross border transfer.

The relevance of this alignment of principles of protection of personal information to biobanking is that HBM donated and stored in biobanks on one jurisdiction may be transferred to researchers working in other jurisdictions. The protection of the personal information associated with and discoverable in the samples must be protected wherever the research is conducted. This alignment with certain countries is therefore important and relevant.

POPIA aims to promote the protection of personal information by public and private bodies and it is intended that Codes of Practice be published for sectors (Botes, Olckers and Labuschagne, 2021). The authors highlight that whereas personal information can, in a health research context be obtained directly from an individual, subject to informed consent, POPIA limits the sharing of such information. Biometric and health data requires specific consent for release (POPIA S26).

Where a biobank wishes to transfer HBM to a jurisdiction where there is no legislation in place it would be the responsibility of the biobank to secure an undertaking from the recipient to protect the personal information. The mandatory use of National SA MTA template (RSA, 2018) for transfers of HBM is intended to protect the donor's information.

Staunton and De Stadler (2019) highlighted the potential challenge for biobank research in complying with POPIA particularly as health data and biometric data is categorised in the Act as "special information" requiring specific consent. It is recommended that to overcome this hurdle, consent forms should explicitly inform participants that data may be shared with other researchers, locally and abroad.

Thaldar et al. (2020) proposed that a potential solution to compliance with POPIA would be to incorporate the POPIA requirements into the National SA MTA template (RSA, 2018).

Protection of personal information legislation relies on the granting of consent to use personal information. Until the implementation of the POPIA Act it was generally

considered acceptable to rely, in health research, on specific, broad or tiered consent. The POPIA however requires consent to be specific. This presents a conundrum for research on HBM where valuable sample collections have been created based on more generalised approaches to consent (Thaldar & Townsend, 2021) and where future research needs were not yet evident.

Thaldar and Townsend (2021) argue that the provisions of POPIA are likely to apply to most South African health research. At the heart of the problem is that whilst the DoH ethics guidelines advocate for broad consent for biological research, POPIA requires specific consent. The authors argue against relying on an interpretation of specific v. broad consent and propose that mechanisms for exemption from certain POPIA provisions could potentially provide a solution. An argument in support of exemption from POPIA would need to be a human rights debate and would need to incorporate a standard set of privacy clauses or approval by the regulator. Experts do not however agree on the most appropriate approach to make research on HBM POPIA compliant.

3.2.4.2 Intellectual property policy in South Africa

The World Health Organization raised concerns in their *Genomics and World Health Report* (WHO, 2002) that the increasing trends in human DNA patenting favoured developed countries and would retard, rather than stimulate, scientific and economic progress because of related restriction of access. A 2013 study by Rosenfeld and Mason (cited by Rhodes, 2016), found that approximately 41% of human genes are covered by patents.

A patent gives the holder exclusive title to use the patented property. Patents issued in terms of invention are limited in scope, duration and geographical area. For an invention to be patented, it must satisfy requirements for novelty and originality (Petrini, 2012). Directive 98/44 of the European Union (1998a) deals with the biotechnology sector in respect of intellectual property and provides for the patenting of biological material isolated from its source. However, the intellectual property rights apply to the results of research and not to the samples collected.

South African Intellectual Property legislation includes amongst others the Trademarks Act no 194 of 1993 and Trade Mark Regulations, 1995, the Patents Act and Patent Regulations, 1978, and the Copyright Act, 98 of 1978.

Patent protection is obtainable for any new invention involving a patentable step and which is capable of being used or applied in trade, industry or agriculture, through the national filing system (Adams & Adams, 2021).

Intellectual property in HBM can be acquired through the use in research of the HBM by the recipient or a subsequent recipient of the HBM which could lead to commercialisation of product produced from the HBM by the inventor.

Mahomed and Sanne (2015) addressed the subject of ownership and intellectual property rights. They commented that there is no precedent in South Africa and that commercialisation of products from HBM presents a challenge to the courts. It is recommended that legislation is needed to address proprietary claims in respect of HBM. In the absence of guidance in SA law, the informed consent of participants to utilise the HBM is a critical step. Such consent must be informed by clear details of the intended use of the material and of potential gains. Mahomed (2018) advocated against the situation the biobank holds property rights in the HBM (Mahomed, S., 2018).

The information provided in the informed consent process must be clear as to what the potential is for commercialisation and for profits derived from the HBM. The information must be communicated in a transparent and meaningful way (Declaration of Helsinki).

The Copyright Act definition of *literary works* includes tables and compilations. A data set compiled from genetic information derived from HBM would therefore qualify as a literary work in which the originator would have copyright and the capacity to commercialise it in various forms. The creator of the data set would own the IP in the data set to the exclusion of the donor of the HBM and Botes, Olckers & Labuschaigne, (2021) suggest that data sharing agreements should thus include a requirement to the effect that genomic data not be deidentified.

3.2.4.3 Publicly-funded research

The Intellectual Property Rights from Publicly Funded Research and Development Act 51 of 2008, is intended to ensure intellectual property from publicly-funded research is protected and commercialised for the benefit of the people of South Africa (RSA, 2008) be it social, economic, military or some other benefit.

3.2.5 Summary of legal issues relating to the use of HBM in research

Chapter 3 analysed the legislative requirements internationally and locally in terms of the ownership of HBM.

Internationally the matter of ownership is not clear cut. To date, the matter has been decided by the courts on a case-by-case basis. It is generally recognised, that once HBM has been removed, the right to possess and use HBM passes to the recipient.

Additional property rights may be gained where material and data is further processed. In South Africa, Intellectual property from publicly funded research must be used for the benefit of the people of South Africa.

South Africa is the first country to enforce the use of a MTA based on the National SA MTA template for the transfer of HBM and all biobanks must have the oversight of an NHREC-approved HREC. All research protocols and the MTA must be reviewed by a HREC.

Informed consent is a legal requirement for participation in health research and for the donation of HBM.

According to the Regulations to the South African NHA (RSA, 2012),

- HBM may only be removed for specific purposes including health research
- any person who acquires […] tissue […] for health research in terms of the NHA, acquires exclusive rights in respect of the use thereof if removed for the purpose of health research.

The National SA MTA template (RSA, 2018) states that ownership does not pass to the recipient/biobank. The research participant retains the right to direct its use or destruction/withdrawal from the study. The biobank becomes the custodian of the HBM with an obligation to ensure that the research participant's informed consent requirements are respected. HBM can only be transferred subject to an approved protocol and informed consent from the participant. The biobank remains the custodian.

The "DoH Ethics in Health Research: Principles, Processes and Structures" is an important document providing guidance for health research including research on HBM.

CHAPTER 4: PROTECTION OF RESEARCH PARTICIPANTS BY THE MATERIAL TRANSFER AGREEMENT

4.1 Introduction

The principles of autonomy in the granting of consent and of distributive justice in the sharing of the benefits of research are fundamental to ensuring the rights of research participants. Research participant privacy must be protected and personal data kept confidential. The MTA, an agreement between the biobank and research institutions receiving samples transferred from the "provider" biobank, is the vehicle which transfers responsibility in this respect. A biobank may only supply approved institutions with the HBM and only for use in studies approved by an approved HREC and according to a specific protocol.

In respect of ownership, the South African National SA MTA template (RSA, 2018) states that, "the research participant remains the owner of the material until such materials are destroyed". The National Health Act (2003) *Regulations regarding the general control of human bodies, tissue, blood, blood products and gametes* (RSA, 2012). Regulation 26 states that, provided the HBM is used for the purposes for which it has been donated, the recipient acquires exclusive rights to it (RSA, 2012: Regulation 26). The recipient in this case is the biobank and the "purpose" or permitted use should be documented in the informed consent agreement.

The National SA *MTA template*, requires detailed informed consent to be signed and benefit sharing arrangements to be in place.

Figure 4.1, below contextualises the relationships between stakeholders, agreements and the flows of HBM and data in biobank research. It maps out key areas of responsibility and allows for an analysis of areas of vulnerability of research participants in the context of South African legislation.

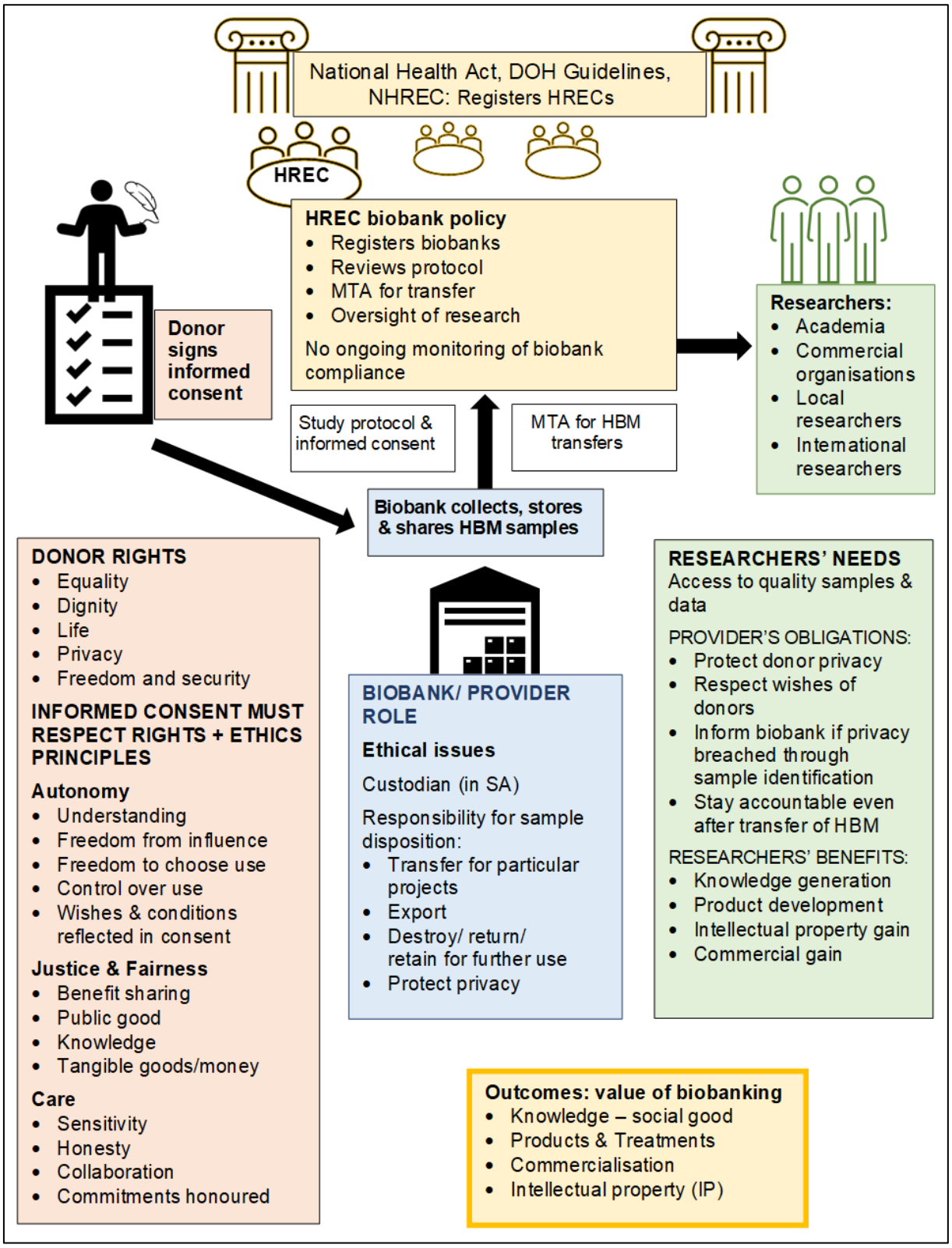


Figure 4.1: Relationships between stakeholders and the flows of HBM and data in biobank research

4.2 Evaluation of the WITS MTA in protecting research participants regarding ownership of HBM

The objective of this study was to critically evaluate the extent to which the WITS MTA (WITS HREC, 2015a) protects research participants from the perspective of ownership of HBM. The South African National SA MTA template (RSA, 2018) published in terms of the NHA (2003), has however become the subject of this analysis as it has legal standing, is very similar and is more recent. The reasons for the similarity between the two MTA templates and the minor differences between the National SA MTA template and the WITS MTA are documented in Section 3.2.3

4.3 Analysis of the National SA MTA template

The table below explores each of the relevant points in the National SA MTA template (RSA, 2018) and the extent to which they protect research participants. The sections of the National SA MTA template (RSA, 2018) are referenced in brackets in the first column.

Table 4.1: Analysis of provisions in the National SA MTA template pertaining to aspects of ownership and control over HBM

National SA MTA template principles	Comments
Ownership remains with the research participant. (3.3)	The inclusion of this S3.3 in the National SA MTA fills the gap in the legislative framework with respect to the role of the biobank as “custodian” of the HBM and makes it clear that ownership does not pass to the biobank. Whether or not it has the effect of creating ownership by the research participant in the HBM is not clear but it does clarify the position of the biobank as “guardian” of the HBM and of the rights of the study participant to have their informed consent respected in research. Exclusive rights to the use the HBM removed for research purposes, vest with the biobank

Table 4.1: Analysis of provisions in the National SA MTA template pertaining to aspects of ownership and control over HBM (continued)

National SA MTA template principles	Comments
The National SA MTA template applies to projects registered with an approved HREC.	NHREC approved HRECs have legal standing and must apply the NHA and DoH Ethical Guidelines (RSA DoH, 2015) to research by approved biobanks.
Agreement must be given by the recipient of transferred material to abide by laws and policies (3.2; 3.4; 3.5) and with legislation and the informed consent document.	The informed consent should relate to a specific project protocol.
The provider remains the custodian of the material even after transfer (3.3)	This places accountability on the provider (biobank) for compliance with the informed consent and study protocol. It appears that this responsibility cannot be transferred to the recipient. There is no provision in the National SA MTA template for commitment of the recipient to ensuring research participant requirements are known to and respected by researchers. The addition of such a binding clause could reinforce research participant rights.
The provider must obtain export permits (4.1)	Onus is on the provider/biobank to ensure legalities are complied with.
Requirement for the provider to inform HREC and the research participant if materials become identifiable. Similarly, the recipient must inform the provider. (4.2)	This is intended to protect the research participant's privacy.

Table 4.1: Analysis of provisions in the National SA MTA template pertaining to aspects of ownership and control over HBM (continued)

National SA MTA template principles	Comments
The provider must obtain informed consent from the research participant where reasonably possible and approval from the HREC for any further use of the material. (4.3)	The ethical and legal principles presented in this research are consistently aligned on the primary requirement for informed consent from the research participant. The National SA MTA template requirement for informed consent is however qualified with the statement “where reasonably possible” with no context for what should be considered as “reasonably possible”. The DoH Ethical Guidelines (RSA DoH, 2015) would apply in the context of secondary use. In this instance, it recommends that, if broad consent has not been given for the secondary use of samples, expedited HREC review is required taking into consideration the nature of the informed consent (3.3.7.l). New consent would be required if the scope was different unless the samples can be properly anonymised and results would not be a risk to anyone. If samples can be linked to the donor, HREC must decide on a case-by-case basis. In the case of consent that covers future use, the research participant’s rights become a challenge to comply with, particularly where samples are anonymised and transfer has taken place.
The recipient is bound by HREC approved protocol (5.1) The recipient must maintain confidentiality of material (5.2).	The National SA MTA template does not specifically bind recipients to comply with protocol requirements. A statement should explicitly extend this provision to subsequent recipients of the HBM Information for the research participant in the informed consent on how the HBM use will be controlled is important. The MTA is not shared with the research participant. This means that they will not be familiar with

how the informed consent should be enforced, confidentiality maintained or understand the transfer process of HBM or the implications and the obligations of other recipients and researchers to the biobank, and thus to the research participant.

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Table 4.1: Analysis of provisions in the National SA MTA template pertaining to aspects of ownership and control over HBM (continued)

National SA MTA template Principles	Comments
Only parties listed in the MTA may receive samples from a recipient (5.3).	Parties listed in the Annexure A should be HREC approved. This needs to be stated in the National SA MTA template. The MTA should provide guidance for onward transmission of samples.
Benefit sharing: The MTA only requires that it be negotiated and documented (7.1).	The DoH Ethical Guidelines (RSA DoH, 2015) state that the principles of distributive justice should inform benefit sharing (2.1).
No guidelines are provided for HREC or parties to assess agreements.	It is of concern that the WITS MTA (WITS HREC, 2015a) refers only to the benefits as received by the recipient/researcher and does not consider the research participant. The National SA MTA template (RSA, 2018) also refers to possible research participant benefits.
On discontinuation of the study the recipient must immediately discontinue use of the material and destroy it, return it to the provider or other as approved by HREC (9.4).	The National SA MTA template should also reference the informed consent for the research participants requirements..

Table 4.1: Analysis of provisions in the National SA MTA template pertaining to aspects of ownership and control over HBM (continued)

National SA MTA template principles	Comments
The provider must obtain informed consent from the research participant and submit this to HREC with protocol and MTA (10.1). A form for secondary consent may be needed (10.3). The research participant must be kept appraised of the study's progress as required by informed consent (10.4).	The extent to which the research participant is protected here will be determined by the informed consent obtained and specifically, by the information given and the understanding gained in the informed consent process.
There is no guidance on benefit sharing arrangements.	Research participants should be fully informed of potential benefits and the extent to which they and their communities may benefit. The principle of distributive justice must be applied in benefit sharing arrangements.

Source: Based on RSA, 2018; RSA DoH, 2015; WITS HREC, 2015a.

The National SA MTA template (RSA, 2018) addresses most key ethical and legal requirements for the governance of the transfer of HBM in biobanking. It places appropriate responsibilities on the provider and the subsequent recipients of material, respecting research participant rights and requirements related to the collected material and in this way, protects the research participant. The Wits MTA (WITS HREC, 2015a) suggests there should be consideration for benefit sharing with research participants.

Further, the MTA attempts to address the ownership and custodianship of HBM in biobanking to ensure alignment of rights and responsibilities of parties to an MTA in the absence of legal clarity on ownership.

4.4 Gaps in the National SA MTA template and recommendations

This analysis has identified only minor gaps in the National SA MTA template (RSA, 2018) with respect to ownership and research participant rights, which could leave research participants vulnerable as they do not have direct control of their material. Recommendations include the following:

- Details of the informed consent process should be included in the study protocol and must be complied with by the biobank and researchers.
- The biobank control over the sample, as far as the National SA MTA is concerned, appears to end with the subsequent transfer of materials to entities identified in Annexure A of the National SA MTA template (RSA, 2018). Accountability for compliance with the MTA, research protocol and informed consent should be expressly transferred in writing with the transfer of material. Details inserted into the protocol of how samples can be traced would be of value. The HREC should also be informed of such steps.
- The Annexure B of the National SA MTA template (RSA, 2018) lacks guidance for effective governance of benefit sharing arrangements. Whilst there is no legal requirement for sharing benefits with research participants, there are ethical obligations to inform the research participant of potential benefits and to indicate what benefit the research participant may receive. Typically, this would relate to the social good. It is recommended that the Annexure B should provide for the identification of potential benefits from the study and be explicit on what benefit will be received by research participants. The study protocol could also be the vehicle for this information.
- Generic governance standards for biobanks should be established in respect of the informed consent process. Benefit sharing arrangements in study protocols should provide for compliance of biobanks and research institutes with these standards and research participant directives and protocols.

4.5 Gaps in the legislative provisions and the MTA regarding informed consent and recommendations

The study-information needs of a potential subject, as well as the methods used to deliver information, must be carefully considered in the granting of informed consent to participate in a study. Where a subject is capable of giving informed consent and,

after ensuring that a potential subject has understood the information, the informed consent must be given freely and preferably be given in writing (WMA, 2013).

Beauchamp and Childress (1994) contended that one can only have personal autonomy if there is freedom from both controlling interferences by others and from limitations such as inadequate understanding that prevents meaningful choices. This is particularly relevant in the case of informed consent as research participants are likely to not have the technical insights to interpret all of the information supplied. It is argued that two conditions are essential to autonomy, namely: (a) liberty (independence from controlling influences), and (b) agency (capacity for intentional action).

For an action to be autonomous, only a substantial degree of understanding and freedom from constraint would be acceptable rather than complete understanding and absence of influence. Substantial autonomy is achievable in decisions in patient research and appropriate criteria of substantial autonomy should be addressed in each research context. The context of biobanking is a highly specialised niche of health research with a level of complexity added by the need to account in the consent for the future use of samples.

A contradiction of terms in biobank documentation is the use of the word “donor” to denote the person from whom HBM has been taken. The question of whether material is expressly donated is not raised in the literature. According to Beauchamp and Childress (1994), the act of donation cannot be inferred but is required to be specific. This is not mentioned anywhere in the informed consent processes reviewed.

4.6 Summary of evaluation of National SA MTA template

The National SA MTA template is a valuable tool for the protection of research participants and HBM storage in biobank research. It provides for most ethical and legal requirements for the protection of research subjects and provides for an enforceable framework for the transfer of samples and accountability for the requirements of research participant informed consent.

CHAPTER 5: DISCUSSION, RECOMMENDATIONS AND CONCLUSIONS

In this chapter the ethical theory of act utilitarianism is proposed and defended as the appropriate ethical framework for biobank governance. The study considers matters related to the ownership of HBM. It concludes with recommendations for improving the National SA MTA template and for further research.

5.1 Discussion of ethical principles and human rights considerations in biobanking

> *Ownership [is] the legal relation between a person (individual, group, corporation, or government) and an object. (…) Because the objects of property and the protected relations are different in every culture and vary according to law, custom, and economic system and the relative social status of those who enjoy its privileges, it is difficult to find a least common denominator of "ownership"* (Encyclopaedia Britannica, 2021).

Nonetheless, whilst the context and details will vary, ownership conveys rights to the person in respect of the object, in this case the body or tissue of the potential research participant.

The subject of whether a living person owns their own body and can, independently, decide what to do with it, has been a subject of much debate through the ages. Examples of such situations include debates around assisted suicide, surrogate parenthood, abortion laws and the donation of body parts. Biobanking of HBM is no exception.

It is not the purpose of this analysis to debate the question of ownership of a living human's body, but rather to examine the question of ownership of HBM once it has been removed from the body and to determine whether ownership ought to remain with the research participant. This study has demonstrated that the legal position is not clear. For purposes of this analysis, the researcher took the position that the participant does own their HBM before it is excised.

This study has shown that legislation, both locally and internationally, does not provide clarity on the ownership of HBM or the rights of a research participant in their HBM. International and local guidelines on biobanking go no further than suggesting that ownership issues should be considered and discussed with research participants. This

lack of clarity has led to the subject of ownership being largely ignored by investigators, biobanks and even research ethics committee protocols. The literature confirms that the subject is seldom adequately addressed in informed consent processes and agreements. Bioethical considerations are therefore of significant value in biobank governance.

In the following sub-sections, these ethical principles are analysed in the context of biobanking.

- beneficence in considerations of the societal good and informed consent;
- non-maleficence in assessing the risks to research participants;

5.1.1 The principle of beneficence in considerations of the societal good and informed consent

The principle of beneficence, doing good for others or promoting others' well-being or interests, has relevance to the informed consent process. The principle of beneficence may take priority over other principles, such as the principles of autonomy and distributive justice. In the biobanking process, there are times when a research participant cannot be contacted to authorise the use of HBM for additional studies. The importance of the health research in this case may take precedence, in which case a research ethics committee would be called upon to assess the benefits and risks of the study and make the decision.

For a research participant to be autonomous in the informed consent process, the information provided by the investigator must be sufficient and understandable to assist the participant in deciding to participate in research. In providing useful information to the research participant, the investigator is complying with the principle of beneficence. The contribution to society of health research is reflective of beneficence.

5.1.2 The principle of non-maleficence in assessing the risks to research participants

The principle of non-maleficence recognises the duty not to do harm. In the context of biobanking it is relevant, amongst others, to do as little harm as possible in decisions related to the rights of a research subject, in providing adequate and understandable information when informing consent and respecting participant rights.

5.2 An Act Utilitarian approach to Biobanking

The researcher has argued the importance of ethical principles in biobanking governance and that the public interest in research should prevail. Research participants should be protected, and the interests of stakeholders ought to be balanced equitably. If an equitable balance cannot be achieved, we need to be able to ethically justify the removal of HBM from research participants for research, including for possibly undefined future research.

The societal benefit from biobanking is the principal goal. A biobanking governance framework must therefore consider the risks and benefits of the direct role players in the context of the benefits to society. In the absence of certainty on ownership of HBM, ethical principles should guide biobank governance.

This analysis of the application of the ethical principles to biobanking highlights that, even where legal and ethical principles are strictly adhered to, a research participant is not likely to be truly autonomous in providing consent for future use of HBM or be able to be assured that protection of privacy can be guaranteed.

The substantial overarching benefits of health research are all determining. However, the researcher argues that the potential risk to research participants, especially if biobanks and researchers do not comply with legal and ethical norms and the informed consent document, is material with only indirect personal benefits. The benefit for biobanks and researchers could on the other hand be substantial with limited HBM-related risks.

Consideration should be given to achieving an equitable balance of risks and benefits for all stakeholders. If it cannot be achieved, then we need to be able to justify the removal of HBM for research, especially for undefined future research.

Kant's principled autonomy suggests a different approach which takes account not only of the principle of autonomy but introduces the concept of obligations that precede the granting of all rights. Such an approach does not emphasise only the importance of independence in decision making but introduces the concept of balance between the rights of an individual and the obligations of that individual. In the context of informed consent for the transfer of HBM this would introduce the dynamic that whilst the research participant should be free to make decisions without coercion, there is also a need for regard to be had by the research participant to the potential benefit to health research from which the public and the research participant could benefit (Ursin,2009).

A purely deontological approach to bioethics in biobanking would not be appropriate. The deontologist would find that biobanks and researchers use research participants as a means to research and would thus find biobanking to be immoral, not recognising or acknowledging value in societal good as the beneficial outcome of biobanking.

The researcher has advocated that in the case of a community where societal values are based on collective ownership, it may be appropriate to consider a communitarian approach to inform the research, consent process and arrangements for the sharing of the benefits and that the autonomy of individuals could be compromised.

Considering the varied and potentially conflicting interests of biobank stakeholders and the valued contribution to health research, act utilitarianism is an applicable ethical theory in the context of which biobanking decisions should be made. An act utilitarian approach will determine a course of action that "creates the greatest happiness for the greatest number" (Dhai & McQuiod-Mason, 2010). This approach should, in an impartial and objective manner, take account of the rights and interests of the research subjects, biobanks, researchers and the societal good. It should focus on the best possible outcome (in this case the facilitation of health research and the protection of research participants) and seek to balance as far as possible the risks and benefits for each.

The researcher has identified and shown how and where ethical principles ought to be applied in biobank research. This is particularly relevant given the lack of certainty around HBM ownership. These principles ought to be applied according to act utilitarian ethical theory to facilitate health research, to ensure as far as possible the autonomy of research participants and protection of their rights to privacy. The principles of care and communitarianism are relevant in certain instances and the principles of beneficence and non-maleficence should be consistently applied throughout. The equitable distribution of benefits needs to be considered including the nature and amount of information and results arising from the research.

The consideration of bioethical principles in this manner should result in the greatest benefit for all.

5.3 Considerations related to ownership of HBM

Who owns the HBM? Ownership of an object can be transferred to another in a contractual arrangement. The transfer of HBM in biobanking from research participant to biobank and then to other recipients and researchers is governed by the informed

consent and the MTA. If the informed consent does not otherwise address ownership, the ownership of the HBM is not transferred with the transfer of the HBM.

A research participant may not be paid for HBM. Therefore, HBM cannot be sold to a biobank. The only other way that ownership could transfer is if the HBM is donated. The act of excision of HBM from a living human is “loosely” referred to as a “donation”. However, the act of donation is also not generally explicit in informed consent documents. The mere signing of an informed consent must not be assumed to imply donation (Beauchamp & Childress, 1994). Only explicit agreement on donation would effectively transfer ownership rights in the HBM to the biobank.

Therefore, unless ownership rights are specifically transferred by the research participant to the biobank, the research participant would by default remain the owner of the HBM if indeed ownership existed before removal thereof. The implication would be that the control over the HBM, until destroyed, would remain with the research participant.

In order to be in a position to continue to facilitate research, biobanks need to retain the confidence and trust of the public, participants, researchers and communities.

How does ownership of HBM impact rights in biobanking? If ownership of HBM were to transfer to the biobank, certainty would increase but ownership rights should be exercised in a fair manner and ethical principles applied. The following would apply:

- The biobank would assume all rights over the HBM.
- The biobank would have an obligation to ethically use and protect the HBM.
- Internal ethics and governance to legal and ethical principles would be imperative.
- The biobank would not need to refer back to the participant or research ethics committees for further authorisation to use the HBM.

If ownership remains with the participant, the following would apply:

- The biobank would assume a custodian role for the HBM.
- The informed consent ought to convey the requirements of the participant.
- Informed consent is not however always exhaustive or embracing of best practice principles.
- The biobank and researchers would be obliged to comply with best practice for informed consent.

- The recipient would have residual rights in the HBM and could:
  - withdraw or cancel the transfer arrangements;
  - potentially influence/direct research work; and
  - have the right to determine what HBM is used for and have to be contacted for additional studies.
- The participant would have the right to direct the transfer of the HBM.

Such a situation would create a practical conundrum in that a biobank would then be at the behest of multiple owners of HBM and the biobanking process would be rendered ungovernable, prejudicing research and the overall goals of biobanking.

However, it is important to note, that it is not the ownership of the HBM *per se* that alone protects participants, but rather also the governance of biobanks according to bioethical principals and theories.

5.4 Recommendation on whether ownership of HBM ought to remain with research participants

Considering the analysis above, the interests of health research are best served where the control of HBM vests with the biobank and bioethical principles are in place to protect the research participant. If absolute control remains with the research participant, biobanks could face practical issues and research could be at risk of being hindered and the benefits to society may not be realised. Therefore, the researcher recommends that, a balance needs to be found between facilitation of research and research participant protection. The ownership of HBM therefore ought to remain with the research participant with control passing to the biobank.

In the absence of clarity on ownership a more suitable model would be the concept of biobanks in entrustment or custodianship-like arrangement to store and control the use of HBM. This would provide for the greatest benefit to all research stakeholders.

5.5 Recommendations for improving the National SA MTA template

The gaps identified in the previous chapter, in S4.4, are potential points of vulnerability for research participants. Biobanks ought to have policies and checks and balances in place to ensure that participants' rights are respected. These precautions should include:

- Standards for oversight over informed consent processes.

- Ensuring that the information for research participants is complete and understandable to the extent that they can make an informed decision to participate.
- Transparency of potential benefits from research and benefit sharing.

Best practice guidelines for those involved in preparing and assessing research protocols and in the granting of informed consent and decisions on benefit sharing would be of value. Notwithstanding these shortcomings, the South African biobank "donor" is protected to an extent comparable with global standards.

5.6 Recommendations for further research

An effective legal and ethical framework exists in South Africa for setting and implementing standards in biobank governance. In the absence of clarity or certainty on ownership rights in HBM, the application and incorporation into existing policy of bioethical principles and theory, should protect subjects.

There was no evidence in South African literature of checks and balances on compliance of HREC approved biobanks with the DoH guidelines or of the monitoring of biobanks to ensure compliance. Without appropriate mechanisms in place to ensure that ethical and legal requirements are being enforced, research participants could be vulnerable to exploitation.

5.7 Conclusions

The following points are concluded from this bioethical analysis of the ownership of HBM in South Africa:

- South African biobanking legislation and guidelines align with global best practice.
- South Africa is reported to currently be the only country enforcing the use of a common MTA which attempts to provide clarity to the ownership issue. However, the "ownership" of the HBM attributed to research participant has not been conclusively resolved.
- Recommendations were made on bioethical principles which ought to be in place to protect research participants in the context of ownership of HBM in South Africa.
- It was argued that ownership of HBM ought to remain with the participant but that control should transfer to the biobank which would act as custodian.

- The review of the literature and analysis of the National SA MTA template (RSA, 2018) confirm that, the National SA MTA template (RSA, 2018) provides adequately for the protection of research participants.
- An act utilitarian approach to biobank governance is recommended to be an appropriate governance framework to protect research participants.

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ANNEXURE A: PLAGIARISM REPORT

A Turnitin Plagiarism report dated 5th February 2021 is submitted as a separate document.

ANNEXURE B: ETHICS WAIVER

No ethics waiver is required as there are no human or animal participants involved in in the research.