ETHICAL ISSUES ASSOCIATED WITH USING HUMAN BIOLOGICAL MATERIAL IN COLLABORATIVE RESEARCH WITH DEVELOPED COUNTRIES:

A CASE STUDY

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DECLARATION

I Mahomed Aslam Sathar declare that this research report entitled

Ethical Issues Associated with Using Human Biological Material in Collaborative Research with Developed Countries: A Case Study

As submitted in partial fulfilment of the requirements for the degree of MSc Med (Bioethics and Health Law) is my own unaided work except where I have explicitly indicated otherwise. I have followed the required convention in referencing the thoughts and ideas of others. It has not been submitted before any degree of examination at this or any other university.

Signature **day of** **month** **year**

DEDICATION

This dissertation is dedicated to:

My son Muhammad Ismaeel,

My daughter Cheryl Natasha

My grandsons Humzah and Uzayr and

The Vulnerable and Voiceless Majority in Africa

ABSTRACT

Although Human Biological Materials (HBMs) are invaluable resources in biomedical research, they have not been without controversy in collaborative research between developed and developing countries. The normative arm of the study compared the key ethical issues in the laws, regulations and guideline documents of developed and developing countries with regard to the use, collection, storage, export and benefit-sharing of HBMs in collaborative research with developed countries. The empirical arm of the study examined how investigators and a Research Ethics Committee (REC) at a South African institution addressed these ethical issues, implemented national and international frameworks with regard to the use of HBMs.

The majority of sponsors (59.6%, 90/151) in the study were from the USA compared to other developed countries (p=0.0001) with the bulk (65.84%) of the funds (R517.19 million) allocated for HIV research. HBMs for storage was obtained largely from adults (80.8%, 122/151) compared to children (12.6%, 19/151) [p <0.0001]. Whilst the principle investigators (PIs) of all 151 protocols informed the REC of their intent to store HBMs, only 87.4% (132/151) of PIs informed research participants (P <0.0001). In 47.7% (72/151) and 71.5 % (57/151) of protocols research participants were informed of the location and duration of storage, respectively, compared to 86% (130/151) and 19.25% (29/151) informing the REC (p < 0.0001), respectively. In 98% (149/151) of protocols informed consent (IC) was obtained from research participants with 76.8% (116/151) of protocols soliciting broad consent compared to specific consent (21.2%, 32/151) [p < 0.0001]. In the remaining 2% (3/151) of protocols IC for storage was not obtained. In 69.5% (105/151) of protocols confidentiality was

maintained by a code and in 9.35% (14/151) of protocols HBMs was anonymised [$p < 0.0001$].

Significantly more protocols informed the REC (90/151, 59.6%) than the research participants (67/151, 44.4%) that HBMs will be exported ($p= 0.011$). Separate consent forms were not available for 60.9% (92/151) of protocols as per the requirement REC's standard operating procedures (SOP). In 74% (51/69) of protocols the rationale for export was to access specialised laboratories (74%, 51/69) that were not available locally. Export permits were not available for 73.2% (109/151) of protocols. Where export permits were available, there were more exports to the USA (31/42, 73.8%) than to Europe (26.2%, 11/42) [$p < 0.0001$]. In the majority of protocols research participants were not informed of benefit sharing from any discoveries (129/151, 85.4%) or commercialisation (123/151, 81.5%) of products derived from their HBMs. Material Transfer Agreements (MTAs) were not available for 94.7% (143/151) protocols. Whilst 122/151(80.8%) protocols disclosed the amount of funds available from the sponsors for the research to the REC, not a single PI made such disclosures to the research participants ($p < 0.0001$).

The varied definitions of what constitutes HBMs, the different terminologies used to describe identifiability, confidentiality, the different models of informed consent and different standards of ownership in the various national and international frameworks are characterised by a maze of definitions, laws, regulations and guidelines that are confusing, conflicting and defy generalisation. International and national laws, regulations and guidelines are fragmented and lack harmonisation. Most developing countries are in favour of severe restrictions on the use of their HBMs in collaborative

research with developed countries. The protocols in the empirical study did not adequately address the inter-related ethical issues of export, storage, IC, commercialisation and benefit sharing derived from HBMs that are currently the subject of intense debate and controversy and central to the access to HBMs in collaborative research with developed countries. Because the empirical study is limited by the use of a convenient sample, the results cannot be generalised to other RECs in South Africa. Nevertheless, the data gives some credibility to the anecdotal evidence that HBMs are leaving the country unaccounted for without export permits and MTAs in place. Given the long delays in harmonizing and publishing new regulations and changes, outdated regulations and regulatory frameworks create opportunities for the proliferation of undesirable and unethical practices. Omissions in the RSA regulatory and ethical frameworks with regard to HBMs and Tissue Biobanking are concerning and require urgent action.

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Page

TABLE OF CONTENTS

Page

LIST OF FIGURES

Page

LIST OF TABLES

LIST OF DEFINITION

Human Biological Materials (HBMs) includes any material obtained from a human being including but not limited to organs and parts of organs, cells and tissue, blood, plasma, serum, genetic material, polar bodies, blastomeres, embryos and gametes (sperm and ova), proteins, waste (urine, faeces, sweat, hair, epithelial scales, nail clippings, placenta), cell lines from human tissue, microbial isolates, saliva, breast milk, vaginal washings and other body fluids.

LIST OF LEGISLATION

DEVELOPED COUNTRIES

Australia

National Health and Medical Research Council Act of 1992

National Health and Medical Research Regulations of 2006

Europe

Convention of Ovideo 1997. Articles 21-22, ETS No 164

Directive 2004/23/EC of the European Parliament and the Council of 31 March 2004.

EU Data Protection Directive 95/46/EC of the European Parliament and the Council.

United Kingdom

Human Tissue Act (United Kingdom) of 2004.

Human Tissue Act (Scotland) of 2006

United States of America

FDA and Department of Health and Human Science's (DHHS) Office for the Protection of Human Research Protection (OHRP), regulation 45 CFR46

DEVELOPING COUNTRIES IN AFRICA

Nigeria

National Health Bill of 2011.

Zimbabwe

Government Notice Act of 1974

Research Act of 1986

Tanzania

National Institution of Medical Research, Act of Parliament No 23 of 1979.

Amendment of NIMR Act of 1997, Tanzania Government Gazette, No 675

Kenya

Science and Technology Act of 2001

Malawi

Presidential Decree on 30th March 1974, Malawian Government Gazette, June 11, 1976, General notice No 398

Constitution of Malawi Article 19(5) of 1994

BRICS

Republic of South Africa

Constitution of the Republic of South Africa, 1996

South African Human Tissue Act 65 of 1983

Intellectual Property Rights from Publicly Financed Research and Development Act 51 of 2008

National Health Act No 61 of 2003

National Health Act No 61 of 2003. Draft Regulations relating to the use of Human Biological Material 20110401 – Regulation. Government Gazette, RSA Regulation 263 No 34159 of 01-Apr-2011

National Health Act No 61 of 2003. Draft Regulations relating to the import and export of human tissue, blood, blood products, cultured cells, stem cells, embryos, zygotes and gametes. Government Gazette, RSA. Regulation 266 No 34159 of 01-Apr-2011

National Health Act No 61 of 2003. Draft Regulations relating to Tissue Banks. Government Gazette, RSA. Regulation 267 No 34159 of 01-Apr-2011

National Health Act No 61 of 2003. Draft Regulations regarding the use of human DNA, RNA, cultured cells, stem cells, blasotmeres, polar bodies, embryos, embryonic tissue and small tissue biopsies and diagnostic testing, health research and therapeutics. Regulation 7 of 2007. Annexure A1. Published 5th/29th January 2007

LIST OF ABBREVIATIONS

AiBST	African Institute of Biomedical Science and Technology
AHEC	Australian Health Ethics Committee
AIDS	Acquired Immunodeficiency Syndrome
ARC	Australian Research Council
AVCC	Australian Vice Chancellor's Committee
BR	Belmont Report
BREC	Biomedical Research Ethics Committee
BRICS	Brazil Russia India China South Africa
CEP (REC)	Comite de Etica em Oesquisa
CIHR	Canadian Institute of Health Research
CIOMS	Council for International Organisation of Medical Sciences
CNS	Consello Nacional de Saude (National Health Council)
COE	Council of Europe
COMREC	College of Medicine Research and Ethics Committee
CONEP	Comissao Nacional de Ethica em Pesquisa (National Commission for Research Ethics)
COSTECH	Commission of Science and Technology
CoV	Convention of Ovideo
DHHS	Department of Health and Human Sciences
DNA	Deoxyribonucleic acid
DoH	Department of Health
EC	European Council
EGE	European Group of Ethics in Science and Technology

EP	Export Permit
EU	European Union
FDA	US Food and Drug Administration
FWA	Federal Wide Assurance
GRAD	Genomic Research in the African Diaspora
HBM	Human Biological Material
HIV	Human Immunodeficiency Virus
HMSC	Health Ministry Screening Committee
HPCSA	Health Professional Council of South Africa
HRDC	Health Research and Development Committee
HREC	Human Research Ethics Committee
HTA	Human Tissue Authority
HUGO	Human Genome Organisation
ICHRP	The International Compilation of Human Research Protections
ICMRC	Indian Council of Medical Research
IFC	Indo-Foreign Cell
IHD	Department of International Health
IPTTO	Intellectual Property and Technological Transfer Office
IPR	Intellectual Property Right
IRB	Institutional Review Board
ISBER	International Society for Biologic and Environmental Repositories
MCAZ	Medicines Control Authority of Zimbabwe
MCC	Medicines Control Council
MOH	Ministry of Health
MRC	Medical Research Council

MRCZ	Medical Research Council of Zimbabwe
MSF	Medicines San Frontiers
MTA	Material Transfer Agreement
NBAC	National Bioethics Advisory Commission
NC	Nuremberg Code
NCB	Nuffield Council of Bioethics
NCI	National Cancer Institute
NCST	National Council of Science and Technology
NCST	National Commission of Science and Technology
NEC	National Ethics Committee
NHA	National Health Act
NHMRC	National Health and Medical Research Council
NHRECN	National Health Research Ethics Committee of Nigeria
NHRECT	National Health Research Ethics Committee of Tanzania
NHSRC	National Health Sciences Research Committee
NIH	National Institute of Health
NIMR	National Institute of Medical Research
NNHB	Nigerian National Health Bill
NRCM	National Research Council of Malawi
NSERC	National Sciences & Engineering Research Council of Canada
OBBR	Office of Biorepositories and Biospecimen Research
OHRP	Office for Human Research Protections
OHSR	Office of Human Subject Research
PI	Principal Investigator
PPPO	Public-Private Partnership Organisation

PRE	Interagency Advisory Panel on Research
RADA	Research and Development Agreement
RCP	Royal College of Physicians
REC	Research Ethics Committee
R&D	Research and Development
RSA	Republic of South Africa
SACGHS	Secretary's Advisory Committee on Genetics, Health and Society
SADOH	South African Department of Health
SAGCP	Guidelines for Good Clinical Practice in the Conduct of Clinical Trials in South Africa
SAHTA	South African Human Tissue Act
SANHREC	South African National Health Research Ethics Council
SAMRC	South African Medical Research Council
SHTAct	Scottish Human Tissue Act
SSHRC	Social Sciences & Humanities Research Council of Canada
TANHERF	Tanzanian National Health Research Forum
TB	Tuberculosis
TCPS	Tri-Council Policy Statement
TFDA	Tanzanian Food and Drug Authority
UK HTAct	United Kingdom Human Tissue Act
UK	United Kingdom
UKMRC	United Kingdom Medical Research Council
UNCST	Ugandan National Council of Science and Technology
UNESCO	United Nations Education and Cultural Organisation
UNIAIDS	Joint United Nations Programme on HIV/AIDS

UNICEF	United Nations International Children's Emergency Fund (United Nations Children Fund)
USA	United States of America
WHO	World Health Organisation
WMA	World Medical Association
UKZN	University of KwaZulu Natal

CHAPTER 1

INTRODUCTION TO THE PROBLEM

1.1 Introduction

Biomedical research like the world economy has entered the era of globalization and increasingly clinical trials are being conducted in developing and emerging regions (e.g. Eastern Europe, Latin America, Asia, Middle East and Africa) of the world (Theirs *et al.* 2008). The latter defines nations whose economies are in the process of rapid growth and industrialization but are considered to be in a transitional phase between developing and developed world status (ibid). It has become increasingly difficult to undertake biomedical research in developed countries because of strict regulations, elaborate safety and compensation requirements and small homogenous populations (Nundy *et al*. 2005). Consequently, under these conditions, the recruitment of research participants into clinical trials are slow and expensive (ibid). Ijsselmuiden and Faden (1992) and Temmerman (1992) (cited in Wilmshurst 1997) provide several reasons cited by pharmaceutical companies for sponsoring clinical trials in developing and emerging regions of the world, including Africa, some of which are:

- The ability to reduce operational costs
- Lower risk of litigation
- Recruiting a large number of trial participants who are prepared to give unquestionable consent timeously
- Less stringent ethical review
- Under-reporting of side effects because of lower consumer awareness,
- The desire of personal advancement by participants and

- The rapid pace of growth of market size and infrastructure.

Additional explanations include:

- Research capacity and regulatory authority (Theirs *et al.* 2008; Dhai 2005),
- Harmonisation of clinical practice and research (ibid) and
- The establishment of contract research organizations that are focused on global clinical trials (Tucker and Makgoba 2008).

South Africa, with its first world research infrastructure and its rapidly expanding HIV/AIDS and TB epidemic is ideal for clinical research and is increasingly viewed as the "gateway" for launching clinical trials northwards into the rest of Africa (Cambrill 2005 cited in Dhai 2005). In 2003, South Africa was rated as the 4th top recipient of international grants from the National Institute of Health (NIH), USA (Cambrill 2005 cited in Dhai 2005). In April 2007, South Africa was ranked 21st globally and 8th behind seven other emerging regions and the only African country to be listed in the rankings regarding actively recruiting trial sites (Theirs *et al.* 2008). Whilst there has been a tremendous increase in biomedical research and funding from developed nations to address the leading causes of morbidity and mortality, Africa, including South Africa, has lagged behind in building its scientific capacity (Tucker and Makgoba 2008).

In the context of this report the acronym HBMs is used to include any material obtained from a human being including but not limited to organs and parts of organs, cells and tissue, blood, plasma, serum, genetic material, polar bodies, blastomeres, embryos and gametes (sperm and ova), proteins, waste (urine, faeces, sweat, hair, epithelial scales,

nail clippings, placenta), cell lines from human tissue, microbial isolates, saliva, breast milk, vaginal washings and other body fluids.

There are many reasons to participate in collaborative research and for exporting HBMs from developing to developed countries that can provide benefits (Upshur *et al*. 2007). Analysis of HBMs is lucrative (ibid). Economic benefits, discoveries and patents are derived from them (ibid). Nevertheless, serious concerns have been raised of a new colonialism, the commodification and traffic of human identity and the exploitation of vulnerable communities by exporting HBMs Out of Africa with an accompanied worsening of inequities in healthcare and economic disparities between developed and developing nations (de Haas 2011, Tucker and Makgoba 2008, Upshur *et al*. 2007).

1.2 Controversies in the use of Human Biological Materials (HBMs) in Research

There have been several controversies involving the use of HBMs in collaborative research between developing and developed countries that have raised a host of ethical issues. Some examples include:

- Kenyan scientists accused their foreign collaborators of patenting discoveries without due acknowledgement and for alleging fraud and theft of research material (Andanda 2004 and Butler 2004 cited in Andanda, 2008).
- Ugandan scientists reported that millions of dollars due to the exportation of 80% of HBMs, whose fate were unknown, were lost in terms of foreign exchange from their country (Nakkazi n.d.cited in Upshur *et al.* 2007).

- The Indonesian government refused to share samples of H5N1 virus with the World Health Organisation (WHO) in developing a vaccine unless they were given guarantees that their samples would not be used for the vaccines unaffordable to the developing countries (Emerson *et al*. 2011).
- Malawian bioethicists referred to researchers from developed countries as "parachute, tourist and mosquito researchers who use developing countries, especially Africa, its institutions and researchers simply as specimen collection centers and collection technicians", respectively (Ndebele 2007).
- Indian scientists accused foreign researchers of violating national guidelines in the export of HBMs from India (Mudur 2002).
- Tongans rejected the offer of a foreign based company to conduct research because individual consent failed to reflect community values (Dickenson 2005 cited by Upshur *et al*. 2007).
- Members of the Canada's Nuu-chah-nulth tribe demanded the return of their HBMs because their donated bloods were used for un-specified research (Dalton 2004).
- Members of the Havasupai American Indian tribe in Arizona were outraged to find out that HBMs they donated for a diabetes genetics study was used for what they considered as potentially stigmatising studies of schizophrenia, inbreeding and population migration without Tribal and individual consent that violated their cultural and religious beliefs (Mello & Wolf 2010, Dalton 2004).
- Conference attendees representing regional working groups from Africa, Asia and the US expressed concerns about the export of HBMs from African, Asian and South American countries to the USA (MacQueen and Alleman 2008).

Some attendees questioned if their respective Ministers of Health were aware that HBMs were being exported (ibid).

- Medicines San Frontiers (MSF), an international humanitarian aid organisation, expressed concerns that "other organisations" take HBMs that they (MSF*)* have collected from patients treated by MSF for further use without explicit consent (Schopper *et al*. 2009**:**4). In addition, MSF claims that the results from these additional studies have never been provided to them and patients are not being informed about the fate of their HBMs (ibid).

Some examples of controversies with regard to HBMs from the Republic of South Africa (RSA):

- The director of a large research unit at a South African Medical School removed heart valves from the bodies of poor Blacks lying in the local police mortuary without consent and shipped them (human heart valves) abroad (Scheper-Hughes 2001).
- A South African National Tissue Bank transferred hundreds of Achilles tendons abroad, removed without consent from the bodies of victims of township violence (ibid).
- South African "informants" expressed concerns that although the South African Human Tissue Act 65 of 1983 (SAHTA 1983) [to be replaced by the National Health Act 61 of 2003, Chapter 8] requires a permit to export HBMs from the country, HBMs *a*nd information, might be leaving the country at a regular pace, undocumented and unaccounted for at a national level (Hardy *et al*. 2008:S20).

There has been substantial funding from public sector research funding bodies in the developed world for the establishment of first world state of the art research facilities in developing countries, including RSA. Some examples of funding bodies include:

- The National Institute of Health (NIH) in the USA
- The United Kingdom Medical Research Council (UKMRC)
- The European Union (EU).
- Wealthy private donors and charitable organization from developed countries (Hardy *et al.* 2008, Tucker and Makgoba 2008) also contribute to such development.

Whilst these organisations may appear to be altruistic and philanthropic, they are increasingly being viewed as instruments "perpetuating traditional and prevailing imperialist paradigm" (Tucker and Makgoba 2008) to research vulnerable populations. Researchers from developed countries are perceived as 'moving in and stripping the developing world of its raw materials (HBMs and data), without benefiting patients or acknowledging the contribution of local scientists" (Clarke and Egan 2008). The latter is exemplified by the paucity of authors from developing countries in scientific publications emanating from such collaborations (Emmanuel *et al*. 2004). In addition, African scientists and researchers from developing countries are not represented as equal partners and leaders in the Health-related Public-Private Partnership Organisations (PPPO), all of which are located in developed countries e.g. USA and Europe (Tucker and Makgoba 2008).

Recently, scientists, ethicists and professional bodies have expressed serious concerns about international ethical norms, especially in light of the US Food and Drug Administration (FDA) ruling "that clinical trials performed outside the US no longer

have to conform to the Declaration of Helsinki" (Goodyear *et al*. 2009). The authors (ibid) citing several sources in their editorial comment that the ruling by the FDA creates "the impression that it (FDA) is more interested in facilitating research than respecting the rights of people who are subjects (participants), entrenching different standards for different parts of the world (ethical pluralism), establishing the USA's right to unique policies (exceptionalism) and one country imposing standards on others (moral imperialism)."

The objectives of this research report using both empirical and normative components are:

- To establish whether local and national ethical guidelines and frameworks with regard to the use, storage and distribution of HBMs are informed by national and international guidelines.
- To undertake a comparative review of the laws, regulations and guidelines of selected developed and African developing countries and BRICS region regarding the use of HBMs for research. BRICS is a grouping acronym that refers to the countries of Brazil, Russia, India, China and South Africa whose economies are considered to be the five largest emerging economies of the world.
- To explore and describe the ethical issues associated with the use, storage (including Biobanks) and distribution of HBMs in research.
- To undertake a retrospective audit of research protocol submissions to a tertiary institution's Research Ethics Committee (REC) as a case study in order to determine whether these ethical guidelines and frameworks regarding the use, storage, reuse and export of HBMs are implemented and adhered to.

This chapter (Chapter 1) sets the backdrop to the problem and outlines the various concerns and controversies that have been associated with the use of HBMs. Chapter 2 comprises a review and a comparative analysis of some laws, regulations and guideline documents of developed and developing African countries and BRICS regions with regard to the use of HMBs. Chapter 3 reflects on important ethical issues pertaining to the use of HBMs. Chapter 4 is the empirical component of the research report. It consists of a retrospective cross-sectional descriptive audit of research protocols submitted to a tertiary institution's REC for ethics approval. This audit assesses researchers' adherence to and the REC's implementation of ethical guidelines with regard to use, distribution, storage and export of HBMs obtained during the course of collaborative research with developed countries. Chapter 5 analyses and discusses the findings of the research and Chapter 6 concludes the report and makes recommendations for the use of HBMs in research.

CHAPTER 2

LAWS, REGULATIONS AND GUIDELINES ON THE COLLECTION, STORAGE, USE AND EXPORT OF HBMs IN RESEARCH

2.1 Introduction

The ethical principles that regulate the conduct of research with human participants have evolved from the Nuremberg Code (1947) and have since included the Belmont Report (1979), the Council for International Organisation of Medical Sciences (CIOMS) created in 1993 and updated in 2002 [CIOMS 2002], the United Nations Education and Cultural Organisation (UNESCO) created in 1945 [UNESCO 2006), the Declaration of Helsinki adapted by the World Medical Association (WMA) in 1964 and updated in 2008 (2008), amongst others. These guidelines and declarations have had a significant influence in the development of national bioethics policies, laws and guidelines. The International Compilation of Human Research Protections (ICHRP) [ICHRP 2011] lists over 1000 laws, regulations and guidelines that govern human participant research in 101 countries. This document lists the various key organizations globally and locally in each listed country according to region.

The guiding policies in developing and emerging regions of the world draw reference to and embrace international codes and guidelines that are influenced by debates between Europe and the USA [Baeyens *et al*. n.d]. Because this study was constrained by space, only the laws, regulations and national guidelines of the selected developed and developing countries in Africa and the BRICS member countries were included where they were available in English. Australia, Canada, United States of America (USA) and the United Kingdom (UK) were selected from the developed countries,

because they have well established governance of research. The BRICS member countries included, India, Brazil and RSA. Kenya, Malawi, Nigeria Tanzania, Uganda and Zimbabwe were selected from the developing countries in Africa. In this research report Tables 1 to 3 have been adapted from ICHRP (2011) which lists each of selected country's respective laws, regulations and guidelines applicable to HMBs when they were available. This chapter considers the laws, regulations and guideline documents of developed and developing countries in Africa and the BRICS regions with regard the use of HBMs and briefly discusses biobanks.

2.2 Developed Countries

In Australia, the National Statement on Ethical Conduct in Research Involving Humans The National Statement (NHMRC 2007a) and The Australian Code for the Responsible Conduct of Research, The Code (NHMRC 2007b) provides guidelines for research involving humans (Table 2.1). The National Statement and The Code were developed jointly by the National Health and Medical Research Council (NHMRC), the Australian Research Council (ARC), the Australian Health Ethics Committee (AHEC) and the Australian Vice-Chancellors' Committee (AVCC) [Table 2.1]. These organizations collectively share the responsibility to promote ethically good human research in Australia.

In Canada, three federal research agencies, the Canadian Institute of Health Research (CIHR), National Sciences and Engineering Research Council of Canada (NSERC) and Social Sciences and Humanities Research Council of Canada (SSHRC) jointly created the Interagency Advisory Panel on Research (PRE) as part of a collaborative effort (Table 2.1). PRE's Tri-Council Policy Statement (TCPS) guides all human subject

research in Canada. The first edition of the TCPS (1998) has recently been substantially revised and replaced by the second edition (TCPS 2 2010).

In the USA, federal law complies with the FDA and Department of Health and Human Science's (DHHS) Office for Human Research Protection (OHRP), regulation 45 CFR46 (a to c) [Table 2.1]. The latter section is referred to as the Common Rule. Oversight of these federal regulations is delegated to the OHRP which monitors compliance with federal regulations. Institutions that comply with and adhere to federal regulations are awarded Federal Wide Assurances (FWA). All institutions, including those in developing countries who secure and conduct NIH funded research on humans must have their RECs audited and accredited by OHRP and obtain FWAs. FWAs are part of OHRP's quality assurance process and an institution's commitment to adherence to written policies and procedures. FWAs influence an institution's ability to secure NIH funding. The frameworks governing the conduct of human subject's research in the USA differ among the 50 states, (Hakimian *et al.* n.d). The OHRP (2008, 1997) issued its guidance on the use of HBMs and repositories (Table 1) whilst the National Bioethics Advisory Committee (NBAC) [2001a, b] has made several recommendations to these guidelines (Table 2.1).

In Europe the legal protection of human participants in clinical trial research is addressed via the Council of Europe (CoE 2006) Bioethics Division and the European Group of Ethics in Science and Technology (EGE) [EGE 2004]. The use and transfer of data associated with tissues is regulated by the EU Data Protection Directive 95/46/EC of the European Parliament and the Council (EU 1995). The CoE draws reference to the Convention on Human Rights and Biomedicine (also referred to as the Convention of Oviedo [CoV]), Articles 21-22, ETS No 164 (CoV 1997). The article reflects the

principles of the EC directive 2004/23/EC (EC 2004) on setting standards and safety for the donation, procurement, testing, storage, and distribution of human tissues and cells.

In the UK, the Nuffield Council of Bioethics (NCB) is independent of the UK government and is funded jointly by the Nuffield Foundation, UK Medical Research Council (UKMRC) and the Wellcome Trust (Table 2.1). Its comprehensive report (NCB 1995) deals with the ethical and associated legal questions raised by the medical and scientific uses of HBMs. The Human Tissue Act in the UK (UKHTAct) [UKHTAct 2004] came into force on 1st September 2006, having been passed as law in 2004. The UKHTAct (2004) applies in full in England, Wales and Northern Ireland, but not in full in Scotland where separate legislation has been enacted. The Scottish Human Tissue Act (SHTAct 2006) only applies to tissue from the deceased. The UKHTAct (2004) established the Human Tissue Authority (HTA) as the oversight body corporate. The HTA produced several codes of conduct (HTA 2009a). The remit of the HTA is to ensure that regulated activities in the use of whole body donation and the taking, storage and use of human organs and tissues for education, training and research from living and deceased persons are carried out in a lawful and ethical manner.

Table 2.1. Key Organisations, Laws, Regulations and Guidelines for Research with HBMs in Developed Countries (adapted from ICHRP 2009)

Country	Key Organisations	Guidelines, Laws Regulations	References
Australia	NHMRC,AHEC ARC, AVCC	National Health and Medical Research Council Act 1992.National Health and Medical Research Regulations 2006	ICHRP (2011:69)
		The National Statement.	NHMRC (2007a).
		The Code	(NHMRC 2007b)
Canada	CIHR,NSERC, SSHRC,PRE	Tri-Council Policy Statement	TCPS 2 (2010) TCPS (1998)
United States	FDA,DHHS,OHRP OHSR,NBAC, NIH	Issues to consider in research use of stored data on Tissues. Guidance on Research involving coded private information on biological specimens. 45 CFR 46 (a to c)	OHRP (2008,1997), NBAC (2001a, b), NIH (2004)
United Kingdom	UKMRC,NCB Wellcome Trust, HTA	Human Tissue Act HTA codes of Practices	UKHTAct (2004), NCB (2003, 1995), HTA (2009a)

2.3 Developing Countries in Africa

In most but not in all instances the laws, regulations and guidelines of developing African countries were available (Table 2.2).Where they were available they have been referenced (Table 2.2) and commented on in the text.

In Kenya the legal framework of science and technology is provided by the Science and

Technology Act of 1979 (Table 2.2). In Kenya the National Council for Science and Technology (NCST) is responsible for coordinating all human subject research and makes final decisions about protocol applications (Table 2.2). Two other national bodies involved in ethical review are the Kenyan HIV/AIDS Vaccine Subcommittee and the Pharmacy and Poisons Board both of which are affiliated with the Ministry of Health.

In Malawi the National Commission of Science and Technology (NCST) formerly known as the National Research Council of Malawi (NRCM) develops national regulations and guidelines for health-related research (Table 2.2). The National Health Sciences Research Committee (NHSRC) and the University of Malawi College of Medicine Research and Ethics Committee (COMREC) are the only government-approved health research and ethics committees in Malawi (Table 2.2). Both NHSRC and COMREC report to and are monitored by NCST. All human subjects studies conducted within the country must be reviewed by one of these two committees on behalf of NCST.

After 8 years of inaction and procrastination the Nigerian National Health Bill (NNHB) was passed (Anon 2011). Part IV of the Bill makes provision for the establishment of National Health RECs for research or experimentation with human participants (NNHB 2011). In Nigeria, the National Health Research Ethics Committee of Nigeria (NHRECN) sets the norms and standards for conducting research on humans and animals, including clinical trials (Table 2.2). NHRECN advises the Federal Ministry of Health on ethical issues on human subject research, determines guidelines for the functioning of RECs and registers and audits all RECs in Nigeria. NHRECN has been awarded FWAs by the OHRP.

In Tanzania, the National Institute for Medical Research Act of Parliament No 23 of 1979, provides for the establishment of a national institute for medical research for the promotion of medical research (Table 2.2). The National Institute of Medical Research (NIMR) and the Commission of Science and Technology (COSTECH) grants research and ethical clearance and the latter issues research permits for human subject research in Tanzania (Table 2.2). The Tanzanian National Health Research Forum (TANHERF) serves as a link between health authorities and health researchers (Table 2.2). The National Health Research Ethics Committee of Tanzania (NHRECT) prepares national guidelines for human subject research and accredits and monitors Tanzanian RECs. Clinical trials conducted in Tanzania must also be registered with the Tanzanian Food and Drug Authority [TFDA].

In Uganda the Ugandan National Council of Science and Technology (UNCST), a semi-autonomous government agency advises, develops, implement policies and strategies for integrating Science, Technology, Research development and ethical conduct of research on human subjects (Table 2.2). In Zimbabwe the Research Act of 1986, Chapter 10:22 provides for the establishment of the. Medical Research Council of Zimbabwe (MRCZ) to regulate the conduct of health research in Zimbabwe (Table 2.2). Clinical trials are regulated by the Medicines Control Authority of Zimbabwe (MCAZ), which is a statutory body responsible for the registration of drugs, biologics and medical devices (Table 2.2). MRCZ serves as the National Ethics Committee (NEC) and provides health researchers and institutions with independent ethical advice on human subject research. The MRCZ is supported by the Government of Zimbabwe through the Ministry of Health and Child Welfare. MRCZ have been awarded FWAs by OHRP.

Table 2.2. Key Organisations, Laws, Regulations and Guidelines governing Research with HBMs in Developing Countries in Africa (adapted from ICHRP 2009)

Country	Key Organisations	Guidelines, Laws Regulations	References
Nigeria	NHREC	National Health Bill 2011, National Code of Health Research Ethics	ICHRP (2011:97) NHRECN (2007)
Zimbabwe	MRCZ,MCAZ	Government Notice Act (1974) and Research Act (1986).	ICHRP (2011:100)
		Conducting Health Research in Zimbabwe: What researchers need to know. Ethical guidelines for collection of Blood samples for research (1999)	MRCZ (2004)
Uganda	UNCST	National Guidelines for Research involving Humans as Research Participants	UNCST (2007)
Tanzania	TNHRF, NIMR COSTECH,NHRECT TFDA	National Institution of Medical Research, Act of Parliament No 23 of 1979.Amendment of NIMR Act 1997, Tanzania Government Gazette, No 675	ICHRP (2011:99)
		Guidelines on Ethics for Health Research in Tanzania	NHRECT(2001)
Kenya	NCST	Science and Technology Act (2001)	ICHRP (2011:96)
		Guidelines for ethical Conduct of Biomedical Research involving Human Subjects in Kenya. Kenyan National Guidelines for Research and Development of HIV/AIDS Vaccine (2005)	NCST (2004)
Malawi	NRCM, NHSRC COMREC	Presidential Decree on 30th March 1974, Malawian Government Gazette, June 11, 1976, General notice No 398 and Constitution of Malawi Article 19(5) (1994)	ICHRP (2011:97)
		Procedures and Guidelines for the conduct of Research in Malawi. Policies and guidelines for the access and collection of genetic resources in Malawi	NRCM (2003,2002)

2.4 BRICS Regions

South Africa's national ethics regulations are governed by the National Health Act No 61 of 2003, Chapter 9 (Table 2.3).The South African National Health Research Ethics Council (SANHREC) under the auspices of the Department of Health (SADOH), registers and audits South Africa's many RECs, as well as sets norms and standards for human subject's research. SANHREC is separate from the National Health Research Committee (SANHRC)**,** which focuses on setting research priorities and a research agenda for RSA. South Africa's DOH has promulgated two sets of guidelines, which complement each other (Table 2.3).The Health Professional Council of South Africa (HPCSA) is a statutory body and the Medical Research Council in South Africa (SAMRC), an autonomous body, each independently published multiple volumes on ethics guidelines on various topics (Table 2.3). Before a clinical trial can be approved by an REC, it must be registered with the South African National Clinical Trials Registry at the National Department of Health (Dhai and Cleaton-Jones 2011) and be in compliance with the Medicines Control Council (MCC) requirements. The MCC is a statutory national regulatory authority. In South Africa approximately 8 of 34 local Research Ethics Committees (REC) have been granted FWAs by the OHRP (Moodley and Myer 2007: 1).

In Brazil the Comissao Nacional de Ethica em Pesquisa (National Commission for Research Ethics) [CONEP] is responsible for assessing ethical issues arising from all research involving human subjects in Brazil (Garrafa & ten Have 2010, Diniz *et al*.1999) [Table 3]. In 1966, Consello Nacional de Saude (National Health Council) [CNS] and the Ministry of Health of Brazil published Resolution 196 (Novaes *et al*. 2009). Resolution 196 (CNS 1996), is the standard guidelines for regulating research involving human participants in Brazil. But with rapid scientific and technological

developments, CNS 196 was limited and did not address all the ethical issues that CONEP encountered. Additional guidelines/laws /resolutions that are complementary to resolution 196 were promulgated to deal with specific issues (Table 2.3). The resolutions applicable to HBMs include:

- CNS 292/99 defined a memoranda of cooperation with foreign research
- CNS 304/00 applies to research with indigenous peoples
- CNS 340/04 is applicable to research in human genetics
- CNS 347/05 informs researchers regard storage or use of HBMs and
- CNS 370/07 deals with registration and accreditation of RECs/Comite de Etica em Pesquisa (CEP) in CONEP and registration renewal [Novaes *et al*. 2009].

The majority of the documents are in Portuguese and reference is made only to those documents that were available in English and relevant to this research report.

In India, the Indian Council of Medical Research (ICMR), an autonomous agency within the Indian Ministry of Health, is the apex body in India for the formulation, coordination and promotion of biomedical research under the Department of Health Research, Ministry of Health and Family Welfare, Government of India (Table 2.3). The ICMR provides guidance and co-ordinates collaborations in biomedical research between India and other foreign agencies through its Indo-Foreign Cell (IFC). Applications for research projects involving foreign collaborations are submitted to the Division of International Health (IHD) of ICMR for approval through the Health Ministry Screening Committee (HMSC) of which ICMR is the secretariat.

Table 2.3. Key Organisations, Laws, Regulations and Guidelines governing Research with HBMs in the BRICS Regions (adapted from ICHRP 2009)

Country	Key Organisations	Guidelines, Laws Regulations	References
South Africa	DOH,NHREC SAMRC,HPCSA MCC	Constitution of RSA Article 12(2) (1996), NHA No 61, Chapter 8, S53-68 (2003), Ethics in Health Research: Principles, structures and Processes.	NHA (2007,2004) SAHTA (1983) SADOH (2004a)
		HPCSA Booklets 6,7 SAMRC Booklets 1,2 Guidelines for Good Clinical Practice in the Conduct of Clinical Trials in Human Participants in South Africa	HPCSA (2008a, b) SAMRC (2002 a, b), SAGCP (2006)
Brazil	CNS, MS, CONEP , CEP	CNS:Decree 98 830; Collection by foreigners of data and scientific materials in Brazil (1990) Portugese	ICHRP (2011:89)
		Standard Guidelines and Regulatory Research Involving Human Beings. Resolutions CNS 196/96;251/97;292/99; 301/00;303/00; 304/00;340/04; 346/05;347/05; 370/07	CNS (2005,2000,1999,1997, 1996)
India	ICMR,IFC,IHD,HMSC	Ethical Guidelines for Biomedical Research on human Participants	ICMR (2006)
		Guidelines for exchange of HBMs for biomedical research	ICHRP (2011:73)

2.5 Definitions of HBMs

In general, human tissue is most often referred to in the context of solid tissue, as originating from a solid organ. However, tissue can also be defined broadly to include collections of cells and intracellular substances from bodily fluids such as blood, saliva, semen and waste materials viz. urine, faeces and nail clippings. Given the complexity of the subject matter and the limited definition of what constitutes human tissue, it is not surprising that the materials obtained from humans have variously been described as human tissue, human biological materials, biospecimens, bodily materials, human tissue, separated biological material, separated bodily materials and separated human tissue. The definitions in each of the respective documents (when provided) in the developed and developing African countries and BRICS member countries are provided in Tables 2.4 to2.6.

2.5.1 Developed Countries

In the UKHTAct (2004) the term "tissue" is used to refer to "any, and all, constituent part(s) of the human body formed by cells." (Table 2.4). The Act further divides human tissue into "relevant and bodily material"(Table 2.4). It categorises potentially "relevant material" into four categories in determining whether a sample is "relevant material." The four categories include: "specifically identified relevant material, processed material, bodily waste products (including excretions and secretions) and cell deposits and tissue sections on microscope slides" (Table 2.4). To supplement the Act's broader policy framework on "relevant material," a list has been produced to provide guidance on whether specific materials fall within the definition of "relevant material" under the Act. The fundamental principle according to the Act is that if a sample is known to contain even a single cell that has come from a human body, then the sample should be

classified as “relevant material.” The Act’s wording reflects that a single cell can be researched.

In the USA, the policy and guideline documents of the OHRP (2008, 1997) and the NBAC (1999) makes reference to and uses interchangeably the terms “biological materials, human biological specimens, human tissue materials and biological specimens” without providing any definitions (Table 2.4). The National Cancer Institute (NCI) of the NIH makes reference to “biospecimens or specimens” and provides a comprehensive definition (Table 2.4). Information sheets 14 (section 11) and 17 (section 2a) of the Office of Human Subjects Research (OHSR) at the NIH makes reference to “human specimens/samples” and “human biological material,” respectively (OHSR, n.d.). In these information sheets the definition of “human biological material” excludes blood whilst the open ended definition of “human specimens” includes blood and genetic material (ibid) [Table 2.4]. The Canadian TCPS 2 (2010) and The Australian Code (NHMRC, 2007b) makes reference to “biological materials” (Table 4). the latter, without providing a definition. The Australian National Statement (NHMRC 2007a) makes reference to “tissue” with a general reference to “blood and other body fluids” without defining human tissue *per se* (Table 2.4).

Table 2.4. Definitions of HMBs in Developed Countries

Developed Countries	Definitions	References
UK	**Tissue:** any and all constituent parts of the human body formed by cells	UKHTACT (2004)
	Bodily Material is material that has come from a human body (living or deceased) and consists of or includes human cells. this includes hair and nails, and does not specifically exclude gametes. extracted DNA and or RNA (where no whole cells remain) is not classed as bodily material	
	Relevant Material includes any tissue that consists of or contains human cells but not cell lines or hair and nails from living people or human gametes and embryos	
	Bodily Waste Products (including excretions and secretions) HTA considers bodily waste should normally be regarded as relevant material	
	Cell Deposits and Tissue Sections on Microscope Slides are considered to constitute relevant material. this is because such deposits or sections are likely to contain whole cells or are intended to be representative of whole cells	
CANADA	**HBMs** includes tissues, organs, blood, plasma, skin, serum, DNA, proteins, cells, hair, nail clippings, urine, saliva, and other body fluids	TCPS 2 (2010)
AUSTRALIA	**Tissue:** blood and other body fluids.	NHMRC (2007a)
	B**iological Materials:** no definition	NHMRC (2007b)
USA	**Biological Materials, Human Biological Specimens (specimens), Human Tissue Materials, Biological Materials:** no definition	OHRP(2008, 1997)
	Human Specimens/Samples: includes blood and other body fluids, tissues, DNA and other direct derivatives from human tissue.	OHSR (n.d)
	HBMs: all tissues and fluids obtained from living individuals with the exception of blood	OHSR (n.d.)
	Biospecimen/Specimen. a quantity of tissue, blood, urine, or other biologically derived materials used for diagnosis and analysis. A single biopsy including multiple paraffin blocks or frozen specimens, subcellular structures (DNA), cells, tissue (bone, muscle, connective tissue, and skin), organs, gametes (sperm and ova), embryos, fetal tissue. and waste (urine, faeces, sweat, hair and nail clippings, shed epithelial cells, and placenta)	NC1(2007a)

2.5.2 Developing Countries in Africa

The Kenyan (NCST 2005) and Tanzanian (NHRECT 2001) national guidelines make references to "human tissue" with a general reference to "blood, urine saliva, tissue, other body fluids and organs" without defining human tissue *per se* (Table 2.5). In Malawi, the framework (NRCM 2003) refers to "genetic resources" with reference to "agricultural/forestry/ fisheries/parks and wildlife resources" and not human tissues (Table 2.5). The Nigerian national guidelines makes reference to "samples and biological materials" that includes "herbs and plants" in its Material Transfer Agreement (MTA) without defining what constitutes "samples" or "biological materials"(Table 2.5). The Ugandan national guideline (UNCST 2007) is the only document that makes reference to HBMs, provides a definition and includes "microorganisms" in its definition (Table 2.5).

Table 2.5. Definition of HBMs in Developing African Countries

Developing African Countries	Definitions	References
Uganda	**HBMs** Any substance obtained from a human research participant including, but not limited to: blood, urine, stool, saliva, hair, nail clippings, skin, and microorganisms and other associated bio-products obtained from human research participants	UNCST (2007)
Kenya	**Human Tissue:** blood, urine, saliva, tissue. Other body fluids and organs	NCST (2005)
Tanzania	**Human Tissue:** blood, urine, saliva, tissue. Other body fluids and organs	NHRECT(2007)
Malawi	**Genetic Resources:** agriculture/forestry/fisheries/parks and wild life resources	NRCM (2003)
Nigeria	**Samples and Biological Materials:** no definition	NHRECN (2007)

2.5.3 BRICS Regions

Of the BRICS countries only India (ICMR 2006) provides a comprehensive definition of HBMs (Table 2.6). In South Africa, the Human Tissue Act of 1983 (SAHTA) and the South African national guidelines (SADOH 2004a) makes reference to and defines the constituents of "human tissue", whilst Draft regulation 7 of 2004 of the South African National Health Act no 61 of 2003 [NHA 2007] and NHA (2011a-c) makes reference to "biological materials" (Table 2.6). Several regulations relating to Chapter 8 of the NHA have been published for comment and review (NHA 2011). However, Chapter 8 has not as yet been promulgated and hence the SAHTA (1983) still applies. In Brazil, Resolution 196/96 (CNS 1996) makes reference to "scientific material, tissue, organs, other parts of the human body and biological materials" without providing a definition of what constitutes these materials (Table 2.6). The decrees accompanying Resolution 196/96 (CNS 1996) viz. Decree No 98.830 of 15th January 1990 on the collection of scientific material and data by foreigners in Brazil, Decree No 8.489 of November 1992 and Decree No 879 of July 1993 on the removal of tissues, organs or other parts of the human body for humanitarian and scientific purposes are in Portuguese and therefore not discussed in this report.

Table 2.6 Definitions of HBMs in the BRICS Regions

Country	Definition	Reference
South Africa	**HBMs** Any material from a human being including blood, cells, tissues, DNA, RNA, polar bodies, blastomeres, embryos and gametes	NHA (2007)
	Human Tissue includes any flesh, bone, gland, organ, skin, bone marrow or body fluid, but excludes blood or gamete (NHA, 2004);	SAHTA (1983) NHA (2004)
	Human Tissue includes substances, structure and texture of which the human body or any part or organ of it is composed, that is removed or separated from living human being, and includes blood, blood components and waste products	SADOH (2004a)
India	**HBMs** Include organs and parts of organs, cells and tissue, sub-cellular and cell products; Blood, gametes(sperm and ova), embryos and fetal tissues, waste (urine, faeces, sweat, hair, epithelial scales, nail clippings, placenta), cell lines from human tissue	ICMR (2006)
Brazil	**Scientific materials, tissues, organs, other parts of the human body, biological materials:** no definition	CNS(1996)

2.6 Export Permit (EP), Material Transfer Agreement (MTA) and Intellectual Property Rights (IPR) in Collaborative Research

Emmanuel *et al* (2004) published a set of benchmark principles that called for collaborative partnerships with national and/or international research institutions as necessary for the justification of research in the developing world. These benchmarks are broadly relevant to the use of HBMs in addressing the issues of Export Permits (EP), Material Transfer Agreements (MTAs) and Intellectual Property Rights (IPRs) in collaborative research.

2.6.1 Developed Countries

Canadian (TCPS 2 2010, TCPS 1998), Australian (NHMRC 2007a), UK (NCB 2003, 1995), UKMRC (2001) and US (NBAC 2001a,b,) guideline documents and frameworks draw the attention of their respective researchers entering into collaborative research with developing countries to take cognisance of and abide by both international and national guidelines of the collaborating country. In general, the documents recommend that researchers sponsored by developed countries must consider community engagement as an ethical requirement for research involving human participants in developing countries (Tindana, *et al*. 2007). These guidelines refer to countries or communities with limited resources whose populations are vulnerable to exploitation by wealthier countries undertaking research there. The guidelines recommend that the research must be responsive to the health needs of the study population. In addition, the guideline documents also inform their respective researchers that HBMs must be treated with respect and dignity taking into

consideration the cultural and religious implications associated with HBMs; that researchers consider the equitable distribution of benefits, if any, available to participants when the study/research ends; build local capacity; must be culturally sensitive and enter into collaborative partnerships with their respective communities and its indigenous populations.

TCPS2 (2010) and NHMRC (2007a, b) draws the attention of Canadian and Australian researchers, respectively, to compliance of the laws, regulations, guidelines and agreements (MTA and IPR) in collaborative enterprises (Table 2.7). Each of the 50 states of the USA have laws regulating the conduct of research using HBMs and associated data (Baeyens *et al.* n.d, Hakimian *et al.* n.d). The emphasis of NBAC (2001a) is focused on the ethical conduct of Phase 111 clinical trials in developing countries and draws the researcher's attention to article 15 of UNESCO's declaration [see reference UNESCO 2006 for article 15]. Whilst US regulatory guideline documents including those of the NBAC (2001a) makes provision for MTA and IPR for it and other countries in the developed world, it is silent on the requirements of MTA and IPR with developing countries. (Table 2.7).

In the UK, the HTA has produced 9 codes of practices that provide practical guidance on human tissue legislation (HTA 2009a). Amongst its many remits, the HTA has powers of inspection, entry, search, and seizure. The HTA issues, revokes, reviews, and suspends licenses and provide guidance on removal, storage, use, disposal, import and export of relevant material for research or human application (Table 2.7). The actual import and export of relevant material is not considered a licensable activity under the UKHTAct (2004). However, the HTA recommends that, whenever possible, the import and export of tissues be conducted via the HTA licensing regime under the supervision

of a “Designated Individual (DI)” named on the license (HTA 2009b). The DI acts as the “gatekeeper” for any imported tissue and ensures that a “Service level agreement (SLG)” or MTA is in place with the end user (ibid). Breach of license requirements can lead to severe penalties, ranging from fines through to imprisonment of up to three years (ibid). In Scotland there is no equivalent of the HTA nor are licenses required for storage and use of human tissue (SHTAct 2006).

2.6.2 Developing Countries in Africa

With a few exceptions, the national guidelines of most African countries stipulate that transfer and export of HBMs in collaborative research must be negotiated through an MTA and or an IPR between the host and recipient institutes that define how HBMs can be legitimately used in collaborative research (Table 2.7). In Nigeria, the NHRECN (2007) draws reference to an MTA specifically to IPR and patents and not to the use of HBMs in international collaborative research. The document informs that investigators should not enter into an MTA or confidentiality agreements without the prior consent of the MRC, as these agreements potentially have a bearing on the ability of the MRC to commercialise IPR. In Uganda, UNCST (2007) details the contents of the MTA in collaborative research and the conditions of publications and authorship. The guidelines inform that with the exception of quality control, HBMs should only be transferred abroad if in-country capacity is lacking or non existence. In addition the guidelines (ibid) require that all publications arising from the research must be submitted to the REC of the local institute with UNCST reserving the right to review the manuscript for publication. It encourages researchers to share their finding with communities on whom the research was done (ibid).

In Kenya, NCST (2004) *per se* does not address the key issues with regard the use and storage of HBMs in collaborative research with developed countries. However, Kenya's National guidelines for Research and Development of HIV/AIDS Vaccines requires that an MTA is signed between the collaborating parties when HBMs are being exported (Andanda 2008:173 citing the Kenya National guidelines for Research and Development of HIV/AIDS Vaccines, March 2005) [Table 2.7]. In order to address issues of IPR and commercialisation, the guidelines inform that research using such material can only commence once the Research and Development Agreement (RADA) has been agreed upon and signed (Andanda 2008:173)[Table 2.7]. The national guideline of Malawi (NRCM 2003) is silent on the use of HBMs in collaborative research with developed countries (Muula and Mfutso-Bengo 2007). However, it allows for the export of genetic material (DNA) from Malawi because of the lack of adequate expertise and infrastructure to undertake genetic analysis in Malawi (ibid) [Table 2.7]. To prevent the exploitation of Malawi's genetic resources and not to discourage collaborative research with developed countries, the NRCM's guidelines, on genetic resources (not necessarily human genetic material) of Malawi (NRCM 2002) requires an MTA with collaborating institutions (Table 7). The Tanzanian national guidelines recommend an MTA between local researchers and their foreign collaborators (NHRECT 2001) [Table 2.7]. The national guidelines of Zimbabwe (MRCZ 2004) is silent on the requirement of an MTA and an IPR to define how HBMs can be legitimately used in collaborative research. However, its guidelines on the collection of blood (MRCZ 1999) stipulate that blood samples or its products cannot leave Zimbabwe without the permission of MRCZ (Table 2.7). Where blood is intended for use for commercial purposes or for export, this must be explicitly stated in the protocol for review (ibid).

2.6.3 BRICS Regions

In India, apart from the technical details required when submitting an Indo-foreign collaborative research proposal, the national guidelines (ICMR 2006) draw attention to the requirement of an MTA (Table 2.7). These guidelines enshrine the definition, modalities and mechanism for transfer of HBMs for biomedical research as well as regulate the exchange of biological material for commercial purpose. It categorically states that if the material transfer is envisaged as a part of a collaborative project, the proposal must be routed through the appropriate authorities for evaluation and clearance. When there are claims and potential for commercial exploitation (development of vaccines, diagnostics, therapeutics, drugs etc) the guidelines require mutual agreements on IPR (Table 2.7).

In Brazil, according to Resolution 196 (CNS 1996) the responsibility/duty of CONEP with regard to research with human subjects is to promote ethical standards and guidelines for specific areas of research that include collaboration with foreign researchers, storage, use and export of HBMs and research with the indigenous populations (Table 2.7). To this end CNS promulgated resolutions 347(CNS 2005), 304 (CNS 2000) and 292 (CNS 1999). Resolution 347 deals with issues related to storage of HBMs and the use of such material stored for future research. It contains regulatory information about maintenance of research samples in repositories, ownership, confidentiality, consent and the conditions and duration of storage. Resolution 304 seeks to affirm the rights of indigenous peoples with regard to developing theoretical and practical research involving human life, the territories, cultures and natural resources of indigenous peoples of Brazil. It also recognizes the right of participation of indigenous people in decisions that affect them. Resolution 292 informs the researcher

and institutions that he/she/it should be well aware of the legal norms and regulations on exporting HBMs abroad and those that protect industrial property and/or technology transfers, emphasising, as the case may be, the agreements established, as well as the legal norms on sending HBMs abroad (Table 2.7).

In South Africa, neither Chapter 8 of the NHA Act no.61 of 2003 nor the SA Department of Health's ethical guidelines (SADOH 2004a) informs researchers of the requirement of an MTA or an IPR for the transfer of HBMs in international collaborative research. Section 68 of the NHA makes provisions for the Minister to make regulations regarding the import and export of tissues, the acquisition and storage of tissue or any other matter relating to regulating the control and use of HBMs. Both SAHTA (1983, ch 3 s25) and draft regulations of section 68 of the NHA (Act no. 61 of 2003) [NHA 2011b] consider it illegal to export biological materials without an export permit (Table 2.7). In addition, the draft regulations allow a maximum of 5000mls of plasma for export in a single shipment from a single authorized organisation, institution or person. Section 68 and the draft regulations do not specifically stipulate that an MTA or an IPR are prerequisites for the export of HBMs obtained from South African participants in international collaborative research. The NHA places the responsibility upon institutions that conduct research using HBMs to develop policies regulating the conduct and ethical approval of such research. Sections 13.3 of the HPCSA guidelines (2008a) state that an MTA must be in place with the REC prior to exporting HBMs and data whilst section 9 of the guidelines (HPCSA 2008b) informs researchers to share benefits derived from discoveries and patents with the indigenous population (Table 2.4). Although section 17 of the Publicly Financed Research and Development Act no 51 of 2008 (IPRAct 2010) regarding *inter alia* intellectual property rights, patents and benefits when using the country's resources (Table 2.4) do not make reference

specifically to HBMs, its wording can be applicable to HBMs. The Act (ibid) is intended to ensure that patents which emanates from publicly financed Research and Development (R&D) is protected and commercialised for the benefit of South Africans. Sections 6 and 7 of the Act (ibid) requires that all South African institutions are obliged to have an Intellectual Property and Technological Transfer Office (IPTTO) on site that will negotiate MTAs between collaborating partners in research. It will be interesting to see how many foreign collaborators will comply to the regulations with research funded by developed world sponsors.

Chapter 8 (sections 53-68) of the NHA 61 of 2003 contains provisions relating to the control of use of blood, blood products, tissue and gametes in humans. Section 68 of the Act (ibid) makes provision for the Minister to make regulations relating to tissue, cells, organs, blood, blood products and gametes. To date only Section 53 of Chapter 8 of the Act (ibid) has been promulgated. The Act that is currently in force that pertains to Section 56 of the NHA is the SAHTA (1983). According to the SAHTA (ibid), “any tissue, blood or gamete removed or withdrawn from the body of a living person shall, subject to the regulations, only be used for medical and dental purposes.” In the case of tissues this includes “transplantation, production of a therapeutic, diagnostic and prophylactic substance, blood transfusion and in the case of gamete, for artificial insemination.” There is nothing in the SAHTA (ibid) that either makes reference to the use of HBMs from living persons for research/scientific investigations or defines what medical means in this context. The Act states that the only instance tissue may be used for research is when a person “donates” his/her specific tissue/s for that purpose upon his/her death either through a will, a signed document with two witnesses or orally in the presence of two witnesses. In addition the deceased’s spouse, major child, parent, guardian, major brother or sister may “donate” the deceased’s tissues after his/her death

to any institution for purposes of research. According to the Act (ibid) to use HBMs of a living person for any purpose other than that stipulated in the SAHTA (ibid) is a criminal offence. The position of Section 56 of the NHA is similar to the interpretation of the SAHTA (ibid). In its national ethics guidelines, the SADOH (2004a) simply reiterates that the use of human tissue must be governed by regulations prescribed by the NHA and encourages institutes to develop policies that would regulate the ethical conduct of research using HBMs. At the time of writing this report, Chapter 8 was not promulgated. Until chapter 8 is promulgated, the SAHTA (ibid) still applies. In their 1993 handbook the SAMRC expressed its doubts that scientific investigations and experimentations can be defined as medical (SAMRC 1993).

At a Human Tissue Symposium held in Durban (McQuoid-Mason 2011) several groups discussed general aspects of the medico-legal, ethical implications and the impending legislative debate on the use of human tissue from both the living and dead, organ donation and retention. It also dealt with the use of HBMs in clinical practice, teaching and research, treatment of human remains and indigenous African interpretation of the ‘spirit’ (Amadlozi). The symposium proposed revisions to Chapter 8 of the NHA (2004) in relation to the general use of HBMs (McQuoid-Mason 2011). There was general agreement that the provisions of the SAHTA (1993) and NHA were inadequate (McQuoid-Mason 2011).

Table 2.7. EP, MTA and IPR requirements for use of HMBs in collaborative research between Developed, Developing countries in Africa and BRICS Regions

Country	EP	MTA	IPR
Developed			
USA	√		
Canada	√	√	√
UK	√	√	
Australia	√	√	√
BRICS			
India	√	√	√
Brasil	√	√	√
RSA	√	√	√
Developing Countries in Africa			
Uganda	√	√	√
Nigeria	√	√	√
Zimbabwe	√	√	√
Malawi	√	√	√
Tanzania	√	√	√
Kenya	√	√	√

2.7 Biobanks

Repositories range from small collections of samples in domestic freezers in academic or hospital settings to large-scale national or private biobanks (Zika *et al.*, 2010; National Cancer Institute (NC1) 2007a; Watts 2007; Thomsen 2004; Austin *et al.* 2003 and Godard *et al.*, 2003).

2.7.1 Definitions

Numerous studies of genetic epidemiology and post-genomics research rely increasingly on the use of biobanks (ibid). There are variations in the definitions of biobanks. Some literature refers explicitly to biobanks, others include a gene bank, a population biobank, a database of gene donors or several kinds of biobanks (diagnostic/research) (ibid). There is a distinction between the physical biological samples themselves, which together constitute a collection, and the database made up of the information derived from these samples (ibid). Advocates of Genetic Exceptionalism perceive genetic data to be distinct from personal and or other medical data (ibid). There is an ongoing debate as to whether there should be special and separate legislation for genetic data or genebanks used in genetics or whether both banks and genetic data should be regulated by existing laws. A clear definition of the type of biobank used in the context of genetic epidemiology or post-genomics projects is a key element for implementing proper ethical management.

2.7.2 Types of Biobanks

Between 1998-2002, 70 or more biobank projects were set up (Watts 2007, Austin *et al*, 2003). Currently, there is an estimated 126 biobanks in 23 European countries, alone (Zika *et al*. 2010). Zika *et al* (2010) reports that the conservative estimate number of collection of HBMs by biobanks in the USA in 1999 was a staggering 307 million specimens. This accumulation occurs at a rate of more than 20 million samples per year (Zika *et al*. 2010). Given the frantic race towards scientific developments and improvement of health and increased collaborations with developing countries, one can

only imagine today's actual numbers in the USA alone. GRAD (Genomic Research in the African Diaspora) has established biobank to collect genetic material from 25 000 African Americans and other people of African descent to study the impact of genetic and environmental variations on disease patterns and drug response [Kaiser. 2003]. Biobanks have become a global phenomenon, and are considered as one of ten ideas changing the world right now (Park 2009). There are many different types (Rothstein and Knoppers 2005, Majumder 2005) and models of biobanks, depending on the type of HBMs that are stored and the environment in which they are collected (Watts 2007, Maschke 2005, Thomsen 2004). Biobanks may also be divided into public vs. private, disease specific vs. general and prospective vs. archival (Winickoff 2008, Thomsen 2004, Austin *et al.* 2003, Winickoff and Winickoff 2003). The well known biobank projects are those in Iceland, United Kingdom, Estonia, Latvia, Sweden, Singapore, and Canada (Watts 2007, Maschke 2005, and Thomsen 2004). In some cases the biobank is directly linked to the national health care system with the view to improve the health of the community, to advance research agendas and to stimulate the economy (Thomsen 2004, Maschke 2005). In others the biobank literally serves as a repository of HBMs and genetic materials, patient data and medical history information, that is available as a resource to qualified investigators and researchers with approved protocols who request HBMs for their study (ibid). The more ambitious UK Biobank became operational in 2006 with the intent to recruit 50 000 volunteers and some predict that it will probably be regarded as the gold standard in biobanking across the world (Winickoff 2007: 441)

Depending on the type of HBM, there are various methods of collection, processing and storing. The quality and integrity of the HBMs affect the results of the analysis

performed on these biosamples. Unless specified by contract, law or accepted guidelines, biobanks establish their own policies that best suits their profile (Zika *et al*. 2010). Several regulatory bodies have generated guidelines and regulations related to the operation and governance of biobanks including the collection, long-term storage, retrieval and distribution of HBMs for future use and their accompanying data. In the developed world, the International Society for Biological and Environmental Repositories (ISBER) [ISBER 2008], Department of Health and Human Services (DHHS), USA, Secretary's Advisory Committee on Genetics, Health and Society (SACGHS) [SACGHS 2007], the NIH (NIH 2006), the NCI (NCI 2007a) guidelines describe 'best practices" principles of state-of-the-science HBMs resource and laboratory procedures as a guide to biobank activities with the view to harmonization of such policies.

In Africa there are two African biobank initiatives, one in Zimbabwe, (Matimba *et al*. 2008) and the other in The Gambia (Sirugo *et al*. 2004). The African Institute of Biomedical Science and Technology (AiBST) in Zimbabwe contains 1,488 HBMs from several ethnic sub-Saharan African populations groups, including South Africa (Matimba *et al*. 2008). In the early 2000's, The Gambian Biobank contained approximately 57 000 biosamples from West Africans (Sirugo *et al.* 2004). The National Biotechnology Strategy Report commissioned by the South African government recommended that the development of South Africa's health biotechnologies programme will require the establishment and support of a national biobank. (cited in Hardy *et al*. 2008a). The former Minister of Health, Dr Tshabalala-Msimang at the time proposed that matters relating to stem cell harvesting, banking and research should be under the complete control of governments and not private individuals or the private sector, emphasising that the Ministers of Health should have

the authority over the research, storage and approval of cell banks (SADOH 2005). In 2009 the South African Department of Justice tabled amendments to the Criminal Law (Forensic Procedures) Amendment Bill (B2-2009) that would see the establishment of a national DNA biobank as a criminal intelligence tool. Although the Department of Health national guidelines makes reference to "Human Tissue Respositories"(SADOH 2004b: s8.7 p40), currently no robust policies or ethical guidelines have been promulgated that define the establishment, governance, goals and structure of a national biobank or a national DNA database in South Africa.

2.8 Conclusion

Most of the ethical debates regarding the use of HBMs take place between European and North American countries. This in turn influences the national guidelines and laws of developing countries and BRICS regions. "European and North American standards differ not only in their definition of terminologies but the whole regulatory framework (Elger and Caplan 2006:3-4) which makes harmonization ever more difficult" (ibid:2). This lack of harmonization is reflected in the guideline documents of African countries.

Biobanks are unsettling relationships between genes, tissues, medical records and persons (individual and collectives) and are increasingly being restructured by new "rights of control, access, exclusion and property", both material and intellectual (Winickoff 2008: 440). Accompanying the boom of biobanks are the numerous and divergent regulations and guidelines with differing norms and terms which have created not only controversies but serious barriers to an international harmonised framework (Elger & Caplan 2006). The ethical issues associated with biobanks are "not new but old unresolved problems of confidentiality, consent, benefit-sharing, commodification and ownership of HBMs presented in new ways" (Winickoff 2008:440).

In chapter 3 the ethical challenges associated with the use, storage and distribution of HBMs will be examined. Issues of commodification, benefit sharing and the perceptions of research participants who avail their HBMs for biomedical research will be described.

CHAPTER 3

ETHICAL ISSUES IN RESEARCH INVOLVING THE USE OF HBMs

3.1 Introduction

Regulations and guidelines governing the collection, storage and use of HBMs in current and future research are inconsistent and have resulted in a number of ethical concerns with widespread disagreement about the definition of identifiability, ownership of HBMs and the type of Informed Consent (IC) needed for research with stored HBMs (Kapp 2006, Woolf and Lo 2004). What makes it even more complex is that HBMs obtained from communities with diverse cultural practices from developing countries and exported to developed countries in collaborative research are subjected to standards that that conflict with local culture (McIntosh *et al*. 2008, Upshur *et al*. 2007).

3.2 Identifiability of HBMs

The extent to which HBMs used in research can be linked with the identity of its source is important in assessing the potential risks and possible benefits to the research participant. HBMs are identifiable if they alone or when combined with other information available to the investigator can reasonably identify the research participant. The definition of “identifiability” of HBMs in research is based primarily on European and American standards (Elger and Caplan 2006). Various international frameworks viz. World Medical Association (WMA), CIOMS, OHRP, NBAC, COE, European Society of Human genetics, Consortium on Pharmocogenetics (cited in

Knoppers and Saginur 2005) catergorise HBMs and its associated data using a non-exhaustive list of terminologies that are confusing and contradictory (Elger and Caplan 2006, Knoppers 2005a and Knoppers and Saginur 2005), so much so, that it has been described as a "Tower of Babel" (Knoppers 2005b:7, Knoppers & Saginur 2005:925-926). Most European frameworks (CoE 2006) use five levels of identifiablity (identifiable, coded, linked anonymous, non-identifiable and unlinked anonymous). In the USA the OHRP uses terminology recommended by the NBAC. Both the ICMR (2006) and NBAC (2001b, 1999) distinguish between samples that are stored in repositories (identified and unidentified, in bold) and samples that are collected for research (identified, coded, unidentified and unlinked)[Table 3.1]. The South African (SADOH 2004a:s7.1 p33) and Australian (NHMRC 2007a) national guidelines define 3 categories of identifiability) [Table 3.1]. Whilst the Kenyan (NCST 2005) and Tanzanian (NHRECT 2007) guidelines make reference to encoded and anonymised HBMs, respectively, none of the frameworks of the developing countries in Africa, including Kenya and Tanzania, provide for nor define the levels of identifiability for HBMs.

Table 3.1 Terminologies used in various frameworks to define Identifiability of HBMs

CoE(2006)	**TCPS2 (2010)**	**ICMR (2006)**	**NBAC (1999)**	**NHMRC (2007a)**	**SADOH (2004a)**
identifiable	identifiable	identified	identified	Identifiable	identified
coded	anonymised	coded	coded	Re-identifiable	potentially Identifiable
linked anonymous	deidentified	unidentified	unidentified	Non-identifiable	de-identified
Non-identifiable	anonymous	unlinked	unlinked		
unlinked anonymous	identified	**identified**	**identified**		
		unidentified	**unidentified**		

Anonymous (unidentified, de-identified not re-identifiable) refers to HBMs and its associated data that were originally collected without identifiers or identifiers have been permanently removed and are impossible to link with their sources (Elger and Caplan 2006, Knoppers and Saginur 2005, Cambon-Thomsen 2004). It is a term appropriate for archaeological samples (Elger and Caplan 2006:4). The term anonymised refers to HBMs that were originally identified but stripped either irreversibly (unlinked anonymised) or reversibly (linked anonymised) (Elger and Caplan 2006, Knoppers and Saginur 2005, Cambon-Thomsen 2004). In the latter, identification is possible through a code but the code is not accessible to researchers (ibid). HBMs that are coded can be linked, are identifiable, are potentially identifiable or re-identifiable and have the same characteristics as reversibly (linked) anonymised samples (Elger and Caplan 2006). However, researchers have access to the code. Identified HBMs have identifiers (name, date of birth, address, postal codes, social security number) attached to them that allows the researchers to identify the source (Elger and Caplan 2006, Cambon-Thomsen 2004). How the different terms of identifiability are used depends on which side of the Atlantic one finds oneself (Elger and Caplan 2006:4).

Knoppers and Saginur (2005:925) citing the Ethics Committee of the Human Genome Organisation (HUGO) warns that irreversibly stripping HBMs of identifiers reduces the scientific value of the research material.The authors (ibid) did not explain why or how. *Although anonymising (irreversibly) HBMs allows researchers to use HBMs without obtaining IC*, it also means that *the data (including genetic) generated from HBMs can not be linked or matched to the medical records (phenotype) of the research participants or their relatives. The significance of the diagnostic and or prognostic*

value of the findings that may be important in determining the risks and benefits(including those derived from discoveries, patents and commercialisation) can neither be evaluated nor communicated to the research participants to enhance the research (italics is the authors own interpretation). Knoppers and Saginur (2005), proposed that the terminology governing identifiability be limited to two categories viz: "coded (single or double and identifiable only through breaking the unique or the two unique codes given the sample) and anonymised (i.e. originally identified or coded/ identified/ traceable/pseudonymised) that while including clinical or demographic data is now stripped of possible identifiers." Elgar and Caplan (2006:4) on the other hand, in providing arguments in favour or against, propose enlarging the definition of non-identifiable.

OHRP's 45 CFR part 46 (2008) in enlarging the definition of non-identifiable/coded HBMs provides guidance as to when research involving HBMs is considered non human research. OHRP (2008) considers HBMs not to be identifiable when HBMs cannot be linked through a system of codes provided the holder/s of the code, e.g. IRBs/RECs, Biobanks, Data management centres, by agreement do not release the code to the investigator/s under any circumstances. The code is not released until the research participant is deceased or if the law prohibits or allows its release. These guidelines according to OHRP (2008) applies to both archived HBMs and those collected/to be collected for future research unrelated to the original/current research. Unlike RSA's national guidelines (SADOH 2004a), OHRP uses regulatory language that is ambiguous and it provides researchers a means to avoid strict regulations and allows any type of future research without IC or IRB/REC approval.

There are two types of HBMs that are stored in repositories/biobanks, viz. Residual/ abandoned tissue/medical care and research samples (van Veen 2006, Knoppers 2005b). The former are collected from patients either during the course of treatment or in the course of a diagnostic procedure (ibid). It can be used for research under specific conditions and represents the majority of samples presently held/archived in repositories (ibid). There is disagreement in the literature as to whether different ethical framework should be constructed for the use of these HBMs for research as there are differing opinions over whether the use of such tissue for research constitutes human subject research. Van Veen (2006) argues that the two distinct types of HBMs require distinct regulatory frameworks. Maschke (2006) on the other hand disagrees and informs that in the USA regulatory frameworks do not make a distinction between the two types of tissue. Maschke (2006) argued that in the US, residual samples have long been used for research purposes without explicit consent.

3.3 Informed Consent

IC has been the central tenet to research ethics since the Nuremberg Trials. It is imperative that research participants are informed of all pertinent information regarding the study. The IC process encompasses four elements viz, disclosure, understanding capacity and voluntariness (McQuoid-Mason and Dhai 2011:71-74). Protecting the research participants' autonomy shows respect for the individual. IC allows individuals to exercise their fundamental right to self-determination and to decide whether and how their HBMs will be used in research. Defining IC requirements for the collection, storage and use of HBMs and related information for research remains one of the most controversial issues in the international debate (Helgesson *et al*. 2007, Elger and Chaplan 2006, Thomsen 2004). The root of the problem is the "differing international

and national guidelines governed by a patchwork of ethical and legal provisions" (Maschke 2005) that have influenced IC requirements [Table 3.2]. The ethical and legal implications as pertaining to IC and HBMs in biobanks vary by the nature of the governance model of the bank (Maschke 2005; Cambo-Thomsen 2004). Several features of biobanks themselves have generated intense debate about IC and it has become one of the most controversial issues in biobanking (Hoffman 2009, Helgessen *et al.*2007, Knoppers 2005a b).

Table 3.2. Consent requirements for research with stored HBMs by International Organisations and Biobanks (adapted from Salveterra *et al*. 2008 and Cambon- Thomsen 2004)

Organisations/Biobanks	Type of IC
Organisations	
WHO	Specific/Partially restricted/Broad
CIOMS	Specific
UNESCO	Partially restricted
HUGO	Broad
COE	Specific
NBAC	Multi-layered
Biobanks	
Canada (CARTaGENE)	Multi-layered
Estonia(EstonianGenome Project Foundation)	Broad
Iceland(DeCode Genetics)	Broad
UK (UK Biobank Limited)	Broad
Sweden	Specific
Singapore	Specific
Japan(University of Tokyo)	Broad

3.3.1 Types of IC

According to some commentators research participants must be re -contacted to give IC for the use of their stored HBMs for each new research project (Annas *et al* cited in Elger and Caplan 2006: 2). However, several problems have been cited with this approach (Helgesson *et al*. 2007, Hansson *et al.* 2006) viz, that:

- It can be costly
- It jeopardises the amount and quality of the research that can be done
- It introduces selection bias because participants may be lost to future projects either because they can not be contacted, they have relocated, demised, or do not respond to the repeated request for re consent
- Research participants do not wish to receive extensive information (Hoeyer cited in Thomsen 2004: 869)
- IC is perceived as "a contract to protect the researcher (Ducoumau cited in Thomsen 2004:869).
- Research participants develop "consent fatigue" (Knoppers cited in Thomsen, 2004:869)

Generally, international and regional regulations agree that IC should be free and explicit and that it should be waived under specific conditions (Knoppers 2005a, b, Clayton 2005). However, the amount of information given to the research participant differs widely across a range of consent models each with its own advantages and disadvantages (Mello and Wolf 2010, Hofmann 2009, Salvaterra *et al.* 2008, Da Rocha and Seoane 2008, Helgesson *et al*. 2007, Hansson *et a*l. 2006, Maschke 2005 and Cambon-Thomson 2004) [Table 3.3].

Table 3.3. Definitions of IC Models (Mello and Wolf 2010, Hofmann 2008 and Salvaterra *et al*. 2008, Hansson *et al*. 2006, Cambon-Thomsen 2004)

IC Models	Definition
Broad/General/Generic	Allows the use of HBMs in current and all unspecified future research at any time.
Blanket/Open	Unlimited/no restriction on the range of options.
Partially Restricted	Allows the use of HBMs in current and in future research directly or indirectly associated with the current research.
Multi-layered/Tiered	Research participants are provided with a menu of options to choose from..
Specific/"True"	Allows use of HBMs only in the current research. Research participants are re-contacted to consent for each new use of their HBMs that is outside the scope of the original consent.
Hypothetical	Consent under the presumption that the participant would have consented were they able to.
Implied/inferred	Consent is not directly stated but suggested from an action.
Initial	Designed to provide comprehensive explanation so potential participants can decide whether to enroll in a given study.
On-going .	Is intended to keep participants aware of information relevant to their continued participation.
Passive/tacit/silent	Consent is suggested without reacting or resisting. or silence may be interpreted as an approval.
Presumed	Research participants are informed that their HBMs will be used for future research unless they expressly deny permission. It presumes that individuals (in general) would have consented to the research if they were able to consent at the time of future use.
Future/Deferred	Postponing the IC procedure to after commencing with the research.
Re-consent	It provides research participants with all the information they need to decide whether to continue to participate given significant changes/findings of the research.

3.3.2 IC requirements for research with HBMs in Developed and Developing countries in Africa and the BRICS Regions

CIOMS (2002) informs and requires researchers in collaborative enterprises with developing countries to respect customs, such as obtaining IC from "a community leader, a council of elders or another designated authority." Various national and international guidelines require researchers to establish "community partnerships, have "respect for the community" and obtain "community consent". The various national and international guidelines also inform that unless expressly denied, community consent should not be substituted for individual consent (Peziosi *et al*. 1997 and Barry 1988 cited in Newton and Appiah-Poku 2007). In many cultures, including African culture, community permission (collective IC or Group IC) to conduct biomedical or clinical research is considered an important ethical requirement (Tindana *et al*. 2006, Dallo *et al*.2005). Emanuel *et al* (2004) in his set of benchmark principles, recommends that when conducting research in developing countries, which in addition to respecting the community's values, culture, traditions and social practices, researchers must consider the cultural appropriateness of IC. Whilst the iterations are not specific to IC and HBMs, the principles expressed here could be extrapolated to include IC for the use of HBMs.

There have been continuing philosophical debates about the appropriateness of applying the guidelines of IC formats of industrialized, highly individualist countries like the USA and or Europe to all human participants in cross-cultural settings including communitarian societies especially in Africa (Agulanna 2010, Crigger *et al*. 2001). Table 3.4 reflects the various models of IC required for research with HBMs in

the frameworks of those developed and developing countries in Africa and the BRICS regions referred to for the purposes of this report.

The imposition of consent requirements of Western cultures on communitarian societies like those in Sub-Saharan Africa is viewed as "cultural imperialism (Gabadegesin cited in Agulanna 2010). Agulanna (2010) views the charge of "cultural imperialism" *as being* unjustified and over-exaggerated. Andoh (2009) contends that community consent is an "unethical process, that it should be subverted and effective mechanisms to raise the individual's comprehension and capacity instituted to allow research participants in Africa to make informed decisions to participate or not to participate in research." Crigger *et al* (2001) on the other hand advocates a "balanced view" and suggest that "cultural practices should be accommodated into a universal ethical framework." The Constitution of the Republic of South African, 1996, considered to be one of the most progressive and liberal in the world, is the only national constitution globally which has IC in research entrenched in it (Dhai and Cleaton–Jones 2011. 166). The HIV/AIDS pandemic in RSA has demonstrated that the majority of research participants viz Black Africans, are more than capable of making autonomous informed decisions to participate in research without compromising community values, even though some still may be subservient to authority (Dhai 2005). IJsselmuiden and Faden (1992) are of the view that many of the arguments regarding IC are based on "outdated anthropological literature that do not reflect the rapid cultural and geo-political changes that accompany urbanisation, population migrations, warfare, globilisation" and new found democracy. e.g. in South Africa. The authors (ibid) are of the view that illiteracy argument used to justify the difficulties encountered by culturally diverse populations in Africa in comprehending the IC process is rooted in

"Eurocentric racist's philosophies" (ibid). Research participants in developing countries may not understand the language of the researcher or the research, but they are literate in their own language to understand and evaluate the risks and benefits of the research (ibid).

Table 3.4 Consent requirement for research with stored HBMs in developed and developing African countries and the BRICS regions

Country	Type of IC	References
Developed		
USA	Multi-layered	NBAC (1999)
UK	Generic/Broad	HTA(2009c), UKHTAct (2004),NCB (1995)
Australia	Specific/Partially restricted/Broad	NHMRC (2007a)
Canada	Specific/multi-layered #	TCPS2 (2010)
BRICS		
Brazil	Specific	CNS 2005
India	Specific	ICMR (2006)
RSA	Specific	SADOH(2004a), HPCSA(2008b)
Developing African Countries		
Kenya	*	NCST (2005)
Malawi	*	NRCM (2003)
Nigeria	*	HREC (2007)
Tanzania	Specific	NHREC (2001)
Uganda	Broad #	UNCST (2007)
Zimbabwe	Broad #	MRCZ (2004)

*Although the IC is elaborate the guidelines do not define the conditions of IC for storage and future uses of HBMs.
Separate consent form for storage of HBMs

3.3.3 Broadening IC

There have been continuous debates on the evolving nature of IC for research regarding the storage and use of HBMs (van Diest and Savulescu 2002, Knoppers and Laberge 1995 cited in Kapp 2006). Much of the debate takes place between Europe (Mello and Wolf 2010, Hofmann 2009, Salvaterra *et al*. 2008, Da Rocha and Seoane 2008, Helgesson *et al.* 2007, Hansson *et al.* 2006, Maschke 2005 and Cambon-Thomson, 2004) and the USA (Lwoff 2008, Salvaterra *et al*. 2008**,** Kapp 2006, Elger and Caplan 2006, Knoppers, 2005). The recommended solutions offered by proponents in Europe and the USA have been referred to as either an "European or American solution", respectively by Elger and Caplan (2006).

According to the proponents (Helgesson *et al*. 2007, Hansson *et al.* 2006, Helgesson and Johnson, 2005) of the "European solution" (Elger and Caplan 2006:3), obtaining broad consent is ethically acceptable for future unspecified research with stored HBMs provided :

- Personal information is protected by a system of codes and secrecy laws
- It is consistent with current practice
- Every new research is approved by a competent REC
- Research participants have the right to withdraw (opt-out) their HBMs at any time requesting their destruction and
- The research is low risk.

Although Hansson *et al* (2006) argue in favour of broad consent they "do not suggest a policy where anything goes" and argue against blanket consent, because in the case of the latter, "important HBMs could be consumed for technical, commercial and even

political applications (e.g. criminal investigations, paternity testing, immigration) that may jeopardise public trust in medical research."(ibid) The recent Havasupai Indian Tribe case showed that general/broad consent can lead to problems when research participants can not contemplate future risks of unspecified research (Mello and Wolf 2010). The case also questioned what constitutes adequate IC and raised issues of ownership of HBMs.

The arguments (Arnason 2004 cited in Hansson *et al*. 2006: 266) against broad consent state:

- that broad consent is not truly IC but rather a general authorisation
- it deprives research participant the right to self determination in favour of research interests
- one can not assess the risks and benefits to research participants in open-ended studies and that asking for specific consent shows respect for the participant.

Hofmann (2009) in challenging the premises on which Hansson *et al* (2006) base their arguments in favour of broad consent argue that "personal information can not be protected by a system of codes and secrecy laws, because it presupposes that the information is identifiable by someone." Even de-identified or anonymised HBMs can be identified (McGuire 2006 cited in Hofmann 2009). Because HBMs stored in biobanks are distributed to many researchers world-wide through collaborations (Hofmann 2009), it is difficult to prevent future uses and to withdraw HBMs (ibid). A precondition for withdrawal of HBMs is that research participants would need to know that they are enrolled in a new or future study which has to be approved by an REC (Hansson *et al*. 2006). Hofmann (2009) argues that to provide detailed information to

the participants of a new study is no different than obtaining IC for a new study or broadening an existing study.

The most controversial argument is that of Hansson *et al* (2006) who view IC as "restricting participants' autonomy" and consider broad consent for future research as "respecting autonomy the most" in the use of stored HBMs. Hofmann (2009:127) argues that Hansson *et al* (2006) "confuses autonomy with liberty" that their autonomy argument breaches the standard aims of consent, viz. "protection, deliberation and understanding." Hofmann (2009:127) further argues that Hansson *et al's* (2006) benefit argument (technology optimism) is based on the "hopeful principle" which is as "flawed as the precautionary principle" than on "well founded research trends or sound arguments." Even though the arguments for broad consent are flawed (Hansson *et al.* 2006), Hofmann (2009) favours the "Authorisation Model" (Caulfield *et al*. 2003) of IC for the use stored HBMs for future research but cautions that broad consent should not be abandoned at the risk of not undertaking meaningful research because of "cumbersome and rigid IC requirements." He advocates that new models of IC that preserves autonomy, that are less restrictive and not as "permissive" as blanket or broad consent must be amended by law should it differ from existing consent principles (Da Rocha and Seoane 2008; Helgesson *et a.l* 2007, Caulfield *et al*. 2003).

NBAC (2001a) recommends waiver of IC, if the research involves no more than minimal risk, if it does not affect adversely the rights and welfare of the research participants, if obtain obtaining IC would not be practical or possible and where possible, participants will be provided with additional information. However, NBAC (2001a) also recommends that in spite of the waiver, obtaining IC shows respect for the

autonomy of the individual. OHRP (2008) on the other hand, by broadening the definition of non-identifiable, considers research with non-identifiable HBMs as non-human research, requiring neither IC nor a review of the research protocol by an REC. OHRP (2008) further states that the IC for storing identifiable HBMs must include a clear description of the specific types of research to be conducted. However, it is argued that research participants have a right to control the uses to which their HBMs are used regardless of the risks they pose (Mello and Wolf, 2010:2).

Proponents of the "American solution" (Elger and Caplan 2006) support multi-layered/tiered consent (Mello and Wofle 2010, Salvaterra *et al*. 2008). Accoring to Mello and Wolf (2010: 3) multilayered consent :

- Provides the research participants with a menu of options to choose from
- Provides the research participant with reasonable degree of control over the use of their HBMs
- Avoids re-contacting research participants.
- Protects autonomy
- Considers the individual and the communities perspectives of the use of HBMs (Mello and Wolf 2010; Salvaterra *et al*. 2008).

The disadvantages of multilayered consent (Mello and Wolf 2010: 3) are that:

- It retains the disadvantages of specific consent (viz. highly burdensome and costly, loss of research opportunities and data if re- contact is impractical or participant refuses to consent and repeated consent can be burdensome)
- *It retains the disadvantages of* general consent (*viz*. limited control over use of HMBs, loss of data if participants consent to some and not all future research, consent is less informative and does not provide an opportunity for participants

to reconsider their willingness to participate in light of new scientific development)

- The consent form is too complex
- Data may be lost if participants refuse to participate.

3.3.4 Culture and IC regarding the use of HBMs in Research

There has been controversy with regard to the collection of HBMs in a wide range of cultural settings (de Haas 2011, MacQueen and Alleman 2008). There have been concerns that HBMs may be used for satanic rituals, that confidential information may be disclosed, that HBMs from disempowered and vulnerable populations in the South will be used to develop drugs to treat more affluent societies in the North and to enrich pharmaceutical companies with no benefits accruing to those who provide HBMs (ibid). In some cultural settings HBM has social worth. It helps to connect to another individual (spirit, soul or ancestors) or a place (ibid). HBMS also creates identity or personhood and plays an important role in healing (Jenkins and Sugarman, 2005:18).

Regulations that allow the use of HBMs that would otherwise have been discarded as "biohazardous waste" may be used in biomedical research for public good, exported abroad without IC and regard for cultural and religious implications or stripped of identifiers and stored with the intent to undertake research (de Haas 2011, Jenkins and Sugarman 2005). Under current U.S. federal regulations, the use of "waste" HBMs in research is allowed and exempt from REC oversight, if the HBMs are truly anonymous and considered non-human(Title 45, U.S. Code of Federal Regulations; 46.101[b][4]). Prospective collection of waste samples is not exempt from review, but may be reviewed by an expedited mechanism (45 CFR 46.110) and often qualify for waiver of

consent (45 CFR 46.116[d]). The dual consideration of HBMs on the one hand as being worthless to be discarded as waste and on the other as being a valuable resource to others in the creation of scientific knowledge, pursuit of academic qualifications and grant applications, highlights the complex nature of cultural interpretation of HBMs.

There are individuals and groups of people both in developed and developing countries who regard all body parts and HBMs as sacred, entitled to respectful burial and in some cases specific body parts (such as the placenta and umbilical cord) are accorded special significance and may have rituals or traditions associated with them (de Haas 2011, MacQueen and Alleman 2008, van Bogaert and Ogunbanjo 2008, Jenkins and Sugarman 2005). The use in research of "waste" tissues from such people without their consent may not be acceptable and may be considered a cultural outrage. A savvy investigator could avoid obtaining IC by delaying the submission of the protocol for review until after the required number of HBMs have been collected and stripped of all identifiers. Thus the tedious and expensive task of obtaining IC is avoided and the protocol is subject to expedited review of a retrospective sample collection that would have otherwise been discarded as waste.

3.3.5 Perspectives of research participants on IC, the collection, storage, use and export of HBMs in collaborative research between Developing and Developed countries

A systematic review of 30 empirical studies (27 from developed countries viz. UK, USA, France, Sweden and Japan and 3 from developing countries viz. Uganda, India and Singapore) over 10 years (1995-2005) assessed the views of more than 33 000

individuals (patients, research participants and the general public) regarding IC for research on their HBMs [Wendler 2006]. The author (ibid) concluded that most individuals were willing to "donate" their residual HBMs with a one-time general consent, provided the research had the approval of an IRB/REC. Seven of 30 studies (ibid) were based on the views of US non-Hispanic whites and one on Ugandans. These empirical studies in the US either excluded Latin and Native Americans (ibid) or included only 1-8% of minorities' viz. African American, Hispanic, Asian American, Native American and other groups (Chen *et al*. 2005). Nevertheless, these limited studies hinted that 75% of African Americans would allow unlimited future research with their HBMs compared to 88% of Whites and other minority groups [Chen *et al*. 2005] and 85% of Ugandans [Wendler *et al*. 2005]. In a larger study, Pentz *et al* (2006) reported that although 95% of Whites and African Americans agreed to provide their HBMs for future research, African Americans were less likely to consent to one time general consent to use their HBMs for diabetes (92%) and Alzheimer's (72%) research compared to Whites (95% and 85%), respectively . However, a small percentage of African Americans (15-16%) compared to Whites (8-9%) preferred a checklist approach to IC for each research project (ibid).

The above empirical studies are in contrast to recent studies from the Middle East (Abou-Zeid *et al*. 2010; Al-Qadire *et al*. 2010). Eighty per cent (80%) of Egyptians agreed to provide blood for research with only 54% supporting one time general consent (Abou-Zeid *et al*. 2010). The study revealed that 44.3% of Egyptians would prefer to provide blood for unspecified future research and 39.9% felt that all future research should be restricted to the current study (ibid). Sixty-six per cent (66%) of Egyptians would allow their HBMs to be used for future genetic research (ibid). The

same authors (ibid:7) citing several studies state that public willingness to provide HBMs for future genetic research varied from 42% to 90% between American, Swedish, British, Singaporean and Japanese participants. Forty-nine per cent (49%) of Saudis felt that it was the norm to conduct research with residual HBMs without IC, 37% required general or proposal-specific consent, 30% felt research could be allowed without REC approval (Al-Qadire *et al*. 2010:3) and 14% thought that their residual samples should be used only for medical care (ibid:3).

Murphy *et al.* (2009) reported that US residents expressed a range of IC preferences towards the creation of a national genome databank, proposed by the NIH and other federal agencies. The authors (ibid) reported that 48% preferred blanket IC, 42% specific IC and 10% tiered IC. African Americans (38%) and Hispanics (40%) had less preference for blanket IC compared to 51% of Whites, with 81% of African Americans and Hispanics preferring specific consent for each research proposals compared to 73% of Whites (ibid). In addition, US citizens expressed an overwhelming desire for a "contract" between researchers and themselves that offered participants greater protection than the IRB and they had some recourse to litigation if researchers violated the agreement (ibid). The lower rate of willingness may be associated with issues of confidentiality, trust, and stigmatization and of genetic information of family, ethnic and racial groups being accessible to insurance companies and other unspecified sources (ibid). A qualitative anthropological study in Malawi showed that poor IC, lack of cultural sensitivity, failure to follow traditional custom and lack of benefit sharing were among several reasons identified that influenced Malawians not to participate in biomedical research (Mfutso-Bengo *et al*. 2008).

Ninety-five per cent (95%) of White and African Americans would allow their HBMs to be used for future research locally whilst 92% of White and 85% of African Americans would authorize the use of their HBMs for research elsewhere within the USA (Pentz *et al*. 2006:736). Ninety-four per cent (94%) of Ugandans would allow export of their HBMs to Tanzania and Kenya (Wendler *et al*. 2005) whilst 62% of Egyptians would allow export to other Middle Eastern countries. In addition, 95% of Ugandans will allow export of their HBMs to the USA and Europe (ibid) compared to 84% of white Americans and 76% of African Americans who would allow export of their HBMs to Europe (Pentz *et al*. 2006). In contrast, 41.8% and 37.2% of Egyptians will allow export of their HBMs to Europe and the USA, respectively (Abou-Zeid *et al*. 2010) .

In a survey of Egyptian researchers and policy makers 81% of respondents agreed that HBMs obtained from Egyptians must be kept in the country, 76% agreeing that HBMs should be exported only when research facilities are unavailable and 80% agreed that a portion of the HBMs must be accessible to local scientists (Zhang *et al*. 2010:4). Factors that might account for Egyptians being unwilling to export samples to western countries may revolve around issues of trust, confidentiality, commodification, religious values and lack of oversight on types of future research (Abou-Zeid, *et al*. 2010:4)' P*olitical factorsl i.e. American foreign policy in the Middle* could possibly be an additional reason not to export HBMs to the USA (the authors personl view in italics). The majority of Egyptians agree that MTAs must reflect that foreign collaborators will share royalties from discoveries, patents and IPR that arise from research using HMBs obtained from Egyptians with local scientists (87.1%), the population and country(69.4%); that Egyptians have access to products derived from

the use of their HBMs (89.2%)(Zhang *et al*. 2010:3); .In addition, most Egyptians agree that local scientists must be consulted, have decision making power, a power to veto and be involved in protocol development in collaborations with developed countries when using their HBMs for future research (ibid:4). With regard to authorship on publications arising from research using HBMs, 78.5% of Egyptian agree that MTAs should reflect that local scientists be credited with authorship on all publications 54.3% agreeing to authorship on the first publication arising from the use of HBMs they provide to research (ibid:5). Surprisingly only 48.4% of Egyptians agree that MTAs should reflect that local scientists be given authorships if they provide sufficient intellectual input into the (ibid: 5). However, 90.9% agreed that MTAs must also reflect that local scientists are given the opportunity to provide intellectual input to justify their authorship (ibid:5). Similarly, Zhang *et al*. (2010) when comparing the views of researchers, REC members, HBMs collectors and policy makers from developed (Japan and Korea) and developing (India and China) Asian countries reported that the latter expressed strong sentiments that the rights of local scientists and research participants must be recognized and protected through more comprehensive and inclusive MTAs. In addition, that more severe restrictions should be imposed on the use of HBMs in collaborative research with developing countries (ibid).

In the UK, the NCB (2010) launched a public consultation exercise seeking peoples' opinion on a number of issues concerning the use of human bodies and its materials in medicine and research. Although this study was completed, the report and its recommendations were not available at the time of writing this report on the NCB website.

3.4 Ownership and Benefit sharing using HBMs in ethical research

The ownership, custodianship and commodification of the human body and HBMs has been the source of tension and the subject of philosophical debates (Quigley 2007, Bjorkman and Hansson 2006, Gordana 2005, Dickenson 2002 and Resnik 1998) controversies and recommendations (Andanda 2008, Dressler 2007, Charo 2006, Hakimian & Korn 2002). Much of the debate has taken place from the perspective of the western legal, ethical, philosophical and religious traditions that ignores the traditional cultural values placed on HBMs by communities in developing countries. Furthermore, populations in developing countries including minorities in developed countries have complained about exploitation of their HBMs that brings no return of benefits to their communities in collaborative research with more affluent developed countries (refer to Chapters 1.2 , 3.3.4 and 3.3.5 above). The lack of respect and cultural sensitivity, failure to accommodate and follow traditional customary law and the lack of benefit sharing were among several reasons identified that influence the willingness of communities in developing countries to participate in collaborative research with developed countries (ibid).

In landmark cases in the UK (case of R vs. Kelly cited in Andanda 2008) and the USA (cases of John Moore vs. Regents of the University of California, Greenberg *et al* vs. Miami Children's Hospital and Washington University and Catalona cited in Hakimian and Korn 2004:2502-2503), respectively, the courts with reference to their national case laws, state health and safety laws with regard to the use of HBMs in research, ruled that research participants who "donate" their HBMs for research, make an irrevocable gift (ibid). The courts implied that research participants waived their rights

to their HBMs in accordance with properly obtained IC (ibid). The court's rulings in these cases were based solely on issues of ownership and property rights. The ruling ignored relationships of trust and respect between investigators and research participants, the right of research participants to opt out from the study, to withdraw their HBMs and request its destruction without prejudice. Importantly the rulings ignored the research participants right to self-determination and autonomy. Recently, in the Havasuapi case the US Appeal Court ruled that researchers from the University of Arizona return HBMs to the Havasuapi Native Americans (Mello and Wolfe 2010). Thus in this case, the court not only respected the traditional customs of Havasuapi Native Americans but also recognised their right of custody and ownership of their HBMs and their right to self determination and autonomy. This issue is yet to be tested in the South African Court.

The Nuffield council on Bioethics proposed that HBMs removed from patients during the course of their treatment should be considered "abandoned" thus denying tissue providers rights over their removed tissues (NCB 1995:67-68)**.** The FDA (1998) states that the use of the term "donation" is prohibited because it implies "abandonment" of property rights even though the IC may state that HBMs will be used for research purposes. FDA regulation 21 CFR 50. 20 (ibid) and OHRP (1996) prohibits the use of any "exculpatory" language in the IC document in which research participants are made to waive or relinquish any legal or property rights over their HBMs. The NCI's (2007b) Office of Biorepositories and Biospecimen Research (OBBR) recommends the use of the term "custodianship" rather than "ownership" in the context of HBMs and Biobanks. Custodianship implies that the HMBs are held in trust or protective care by a third party (Custodian). The custodian protects and preserves the entity (HBMs), facilitates the conduct of scientifically and ethically sound research by *bone fide*

researchers according to the wishes of the providers of HBM. Ownership, on the other hand, gives the possessor of the entity (HBMs) absolute control to do as he/she pleases with impunity and without accountability to anyone. Under such circumstances benefits accrue only to proprietors of HBMs.

3.5 Conclusion

The guidelines of most developed countries consider it an ethical imperative that researchers who undertake their research in developing countries where resources are limited and whose communities are vulnerable to exploitation, encourages their researchers to give-back and to consider the equitable distribution of benefits that is consistent with social justice, solidarity and equity. In addition, IC is important for the future and secondary uses of stored HBMs. Although IC allows individuals to exercise their fundamental right to self-determination, the Havasupai settlement questioned if the exclusive reliance on IC or the various models of IC proposed to manage HBMs in developed countries are in fact appropriate for developing countries, and vulnerable populations. Confusing and conflicting standards of ownership and control of HBMs confound the efforts of researchers and RECs to ensure that research is conduced ethically.

There is broad agreement with positions taken by developing countries in the current debate, favouring severe restrictions on the use of their HBMs by developed countries. The unwillingness of disempowered vulnerable populations in both developed and developing countries to share their HBMs with researchers from developing countries revolves around issues of trust, confidentiality, ownership and the lack of benefit sharing derived from research performed on their HBMs. This return of benefits can be

achieved in various ways viz. a percentage of benefits could be contributed to health sector organisations or donated to humanitarians or educational programmes, provide free access to medical treatment, build local capacity and enter into agreements of joint ownership of relevant IPR

As international collaborative research with South Africa increases, no empirical study to-date has either solicited the perceptions of South African researchers, research participants, members of RECs and policy makers or assessed researchers' adherence to and the REC's implementation of ethical guidelines with regard to use, distribution, storage and export of HBMs obtained during the course of collaborative research with developed countries. Chapter 4 is the empirical component of this research report which consists of a retrospective cross-sectional descriptive audit of research protocols submitted to a tertiary institution's REC for ethics approval. The research examines and explores some of the ethical issues that have been raised and discussed in the previous chapters.

CHAPTER 4

ACCESS TO HBMs IN COLLABORATIVE RESEARCH WITH DEVELOPED COUNTRIES CONDUCTED IN SOUTH AFRICA. A CASE STUDY

4.1 Introduction

Access to HBMs from developing countries in collaborative research with developed countries has not been without controversy. There have been accusations of fraud and theft (Andanda 2004 and Butler 2004 cited by Andanda, 2008), loss of foreign exchange due to uncontrolled export (Nakkazi cited by Upshur *et al.* 2007), inappropriate or lack of benefit-sharing (Zhang *et al.* 2010) with profits accruing mostly to universities, researchers, bioscience and pharmaceutical companies (Hayden cited by Emerson *et al*. 2011:2), a paucity of authors from developing countries in scientific publications emanating from such collaborations (Clarke and Egan 2008, Emmanuel *et al*. 2004), non representations of African scientists and researchers as equal partners and leaders in PPPOs (Tucker and Makgoba 2008) and the perception that African institutions and its researchers are specimen collection centers and collection technicians, respectively (Ndebele 2007). South Africa has not been immune to the controversies associated with HBMs. South African researchers have expressed concerns that HBMs might be leaving the country at a regular pace, undocumented and unaccounted for at a national level (Hardy *et al*. 2008), in some cases without consent and information about the fate of HBMs (Schopper *et al*. 2009). There have been substantial, impressive contributions to develop first world state of the art research facilities in South Africa, funded largely by traditional public-sector research funding bodies as well as wealthier private donors and charitable organizations from developed

countries (Tucker and Makgoba 2008). Whilst these organisations may appear to be philanthropic, they are increasingly being viewed as instruments "perpetuating traditional and prevailing imperialist paradigm" to research in vulnerable populations (ibid) with local researchers acting as African proxies to provide HBMs to their more illustrious and wealthier funders and collaborators from developed countries (Ndebele 2007).

Although RECs in South Africa are guided by international guidelines and frameworks it is possible that some may be uninformed about the ethical and regulatory requirements regarding the use, collection, storage, transfer and benefit-sharing of HBMs in collaborative research with developed countries (authors own opinion). An extensive literature search has revealed that no such empirical study to-date has been published from South Africa. The aims of the empirical arm of the research report were:

1. To undertake a retrospective audit of the research protocols submitted to the institution's REC for ethical approval
2. To examine if researchers at the institution addressed and complied with the ethical issues associated with the use, collection, storage, transfer and benefit-sharing of HBMs in collaborative research between South Africa and developed countries and
3. To examine if the REC implemented and applied the laws, regulations and national and/or international guidelines and frameworks with regard to the use, collection, storage, transfer and benefit-sharing of HBMs in collaborative research between South Africa and developed countries.

4.2 Materials and Methods

4.2.1 Study Design

The study was a retrospective cross-sectional descriptive audit of research protocols submitted over a 6 year period from January 2004 to December 2009 for review to the institution's REC. The REC is registered with the NHREC of South Africa and has an FWA from the OHRP.

4.2.2 Study Methodology

As a member of the Biomedical Research Ethics Committee (BREC) since 2004 to-date, the author of this report has been privy to the information having signed a confidentiality agreement both as a member of BREC and as principal investigator (PI) of this study. Research protocols were screened with the aim to seek disclosures made by the PIs to the REC in the formal application and disclosures made to the research participant in the general information and IC documents. Specific attention was paid to disclosures made with regard to storage, duration and location of storage, future uses of stored specimens, type of consent, confidentiality, export permits and MTAs. The information was also sought elsewhere viz. in investigators brochures, in the correspondence between the REC and the PI, to ascertain if there were suggestions or hints that HBMs were to be stored and or exported.

4.2.3 Inclusion and Exclusion criteria

Included into the data analysis were all protocol submissions funded by a developed world sponsor viz. Research Institutes, Funding agencies, private funders, charitable organizations, Biotech and Pharmaceutical companies, that required the use , storage

and export of HBMs. Also included were studies sponsored by developing world sponsors that required the export of HBMs to collaborators in developed countries. Excluded were retrospective case studies, retrospective studies with archived HBMs and protocols that were of minimal risk submitted for postgraduate studies and that did not require the export of HBMs.

4.2.4 Ethics Approval

The study was approved by the Biomedical Research Ethics Committee (BREC) of the University of KwaZulu-Natal (UKZN) [BE090/09] and the Human Research Ethics Committee (HREC) of the University of the Witwatersrand (M090567), South Africa.

4.2.5 Data Collection and Statistical Analysis

Data from eligible protocols and documents were screened and transcribed onto a data capture sheet and an MS excel spreadsheet, anonymised and imported onto an electronic data base, for qualitative coding and analysis. Data was imported into SPSS version 15.0 (SPSS Inc., Chicago, Ill, USA) and analysed using descriptive statistics. Frequency tables and graphs were used to summarise categorical variables, while mean, standard deviation and range were used to summarise quantitative analysis. The Chi-squared test was used to determine the significance of any differences. Differences were considered significant when p valued < 0.05.

4.3 Results

4.3.1 Disclosures made to the REC in the Formal Application

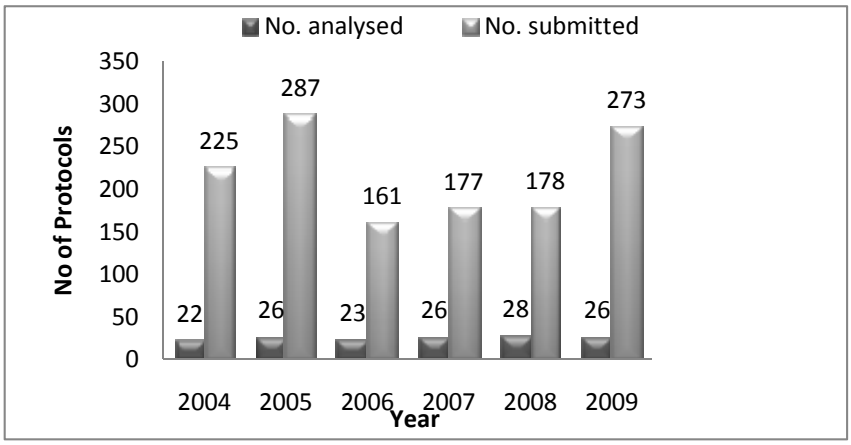

Fig.4.1. Number of protocols submitted over a six period

Between 2004 and 2009 a total of 1305 protocols were submitted for ethics approval to the institution's REC. All protocols were screened by the author. One hundred and fifty one (151) of 1305 (11.57%) protocols fulfilled the study's inclusion criteria and were subject to detailed analysis (Fig.4.1). One hundred and forty-two of 151 (94.1%) sponsors of the various research protocols were from developed countries, six (4%) from developing countries and in 3(1.9%) protocols the sponsors were not disclosed. The majority of sponsors [59.6% (90/151)] were from the USA compared to other countries ($p = 0.0001$). In the latter, 16.6% (25/151) were from Europe, 11.9% (18/151) from the UK, 3.97% (6/151) included combinations of sponsors from either USA/UK/EU (Fig. 4.2). In the remaining 9 protocols, 8 (5.3%) sponsors were from RSA and one from Australia (0.7%). In 2% (3/151) of protocols the sponsors were not disclosed.

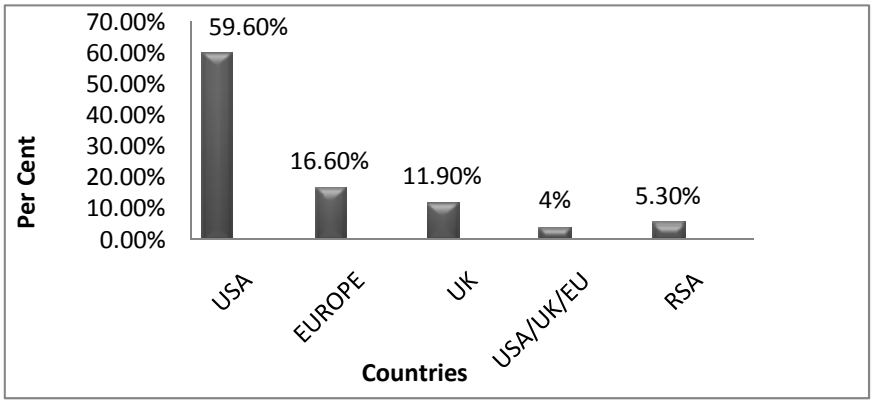

Fig. 4.2. Funders of research from developed and developing countries

Financial disclosures with regard the amount of funding that was available for the various research projects were made in 122/151(80.8%) protocols. The total amount of funding over the 6 period was R785.55 million ranging from R10 000 to R70 million (R6.4 ± R14.4: R0.7million). From 2004 (R40.64million) there was an approximate 3 fold increase per year in the amount of funding with a decline in 2008 (R61.75million) followed by a seven fold increase in 2009 (R280.11 million) [Fig. 4.3]. The majority of the funds (65.84%) [R517.19million) were for HIV research. The majority, 78.80% (119/151) of studies were sponsored for HIV and TB research. Fifty-one percent (77/151) of protocols were related to studies on HIV (drug trials, vaccine, microbicide and basic science studies) compared to 19.2% (29/151) on TB (drug trials and basic science), 8.6% (13/151) on TB and HIV co-infection and12.6% (19/151) of protocols were clinical drug trials not related to either TB and or HIV (p=0816) . The remaining 8.6% (13/151) were basic science studies [Fig.4.4].

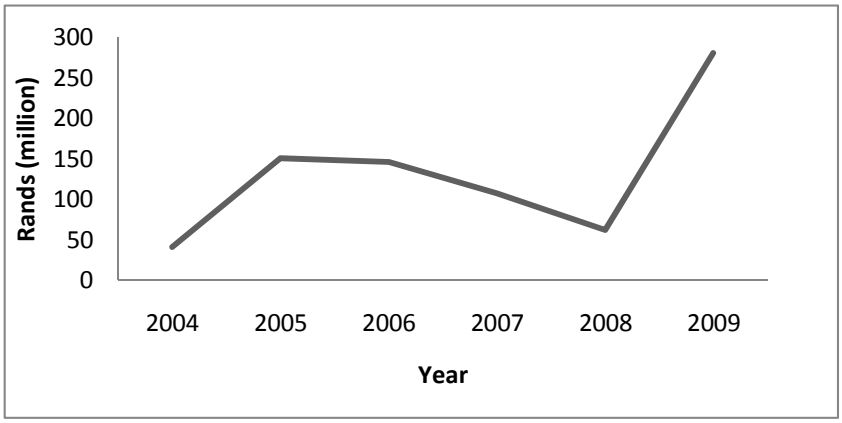

Fig.4.3.Amount of funding over a 6 year period

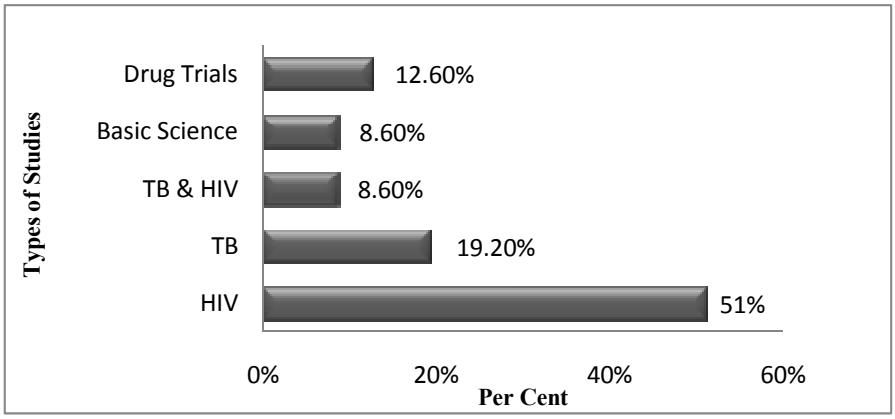

Fig.4.4 Types of studies reviewed by the REC

In 80.8% (122/151) of protocols HBMs for storage were obtained from adults compared to 12.6% from children (19/151) [p <0.0001]. In an additional 6.6% (10/151) of protocols HBMs were obtained mothers and their infants. Thirty-two percent (48/151) of storage sites were located locally, 12% (18/151) of sites were located internationally and 7% (11/151) nationally [Fig.4.4]. In 14% (21/151) of protocols, the storage sites were not disclosed. In the remaining 35% (53/151) HBMs were being stored in any combination of local, national and international sites (Fig. 4.5).

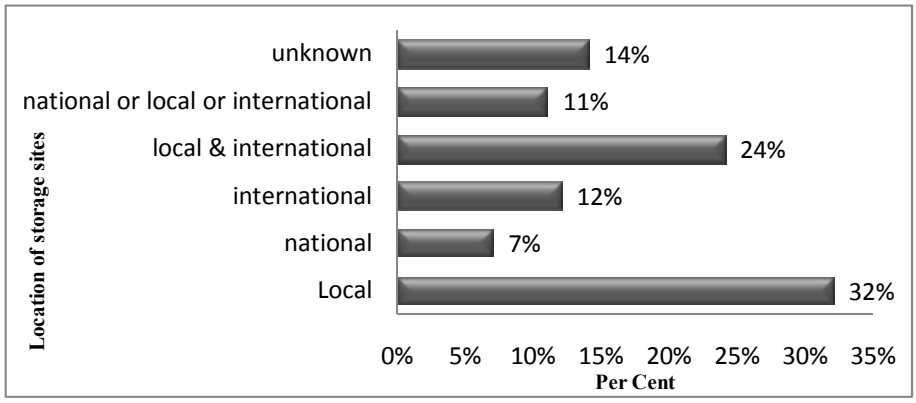

Fig.4.5. Locations of storage sites for HBMs

One hundred and thirteen of 115 (78.4%) storage facilities included research (17.2%, 26/151,) or tertiary institutions (11.3%17/151), commercial laboratories that provided both storage and diagnostic services (13.9%;21/151), biobanks (3.3%, 5/151), hospitals (0.7%, 1/151) and the sponsors of the research (6.6%, 10/151).Thirty-three of 151 protocols (21.9%) did not disclose the type of storage facility (Fig. 4.6). In 80.8% (122/151) of protocols the duration of storage was not disclosed. In the remaining 19.2% (29/151) of protocols the duration of storage ranged from 5 months to > 20yrs (7.9± 5.6 yrs, median 9 yrs).

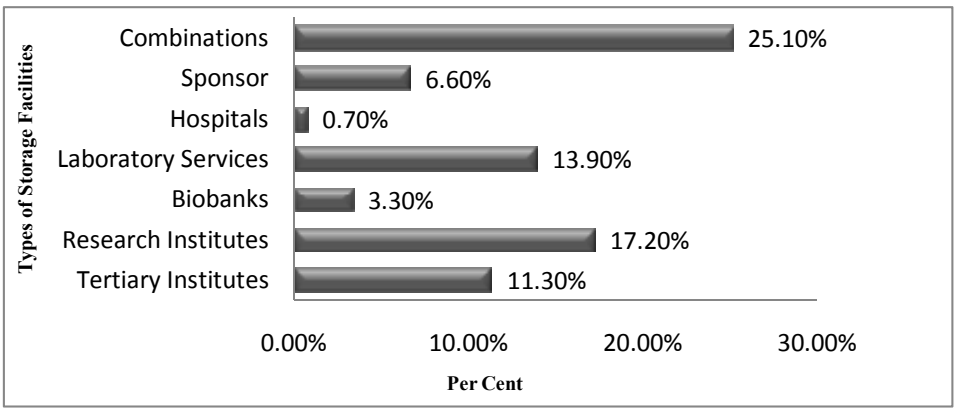

Fig.4.6. Types of storage facilities for HBMs

Compared to 103 of 151(68.2%) protocols the rationale for storing HBMs was not disclosed in 31.8% (48/151) of protocols ($p<0.0001$). In 22.5% (34/151) of protocols the REC was informed that HBMs were being stored for current research, for future research in 18.5% (28/151) and both current and future research in 27.2% (41/151) of protocols ($p=0.473$). In 69/151 protocols (45.7%) that were storing HBMs for future research, in 17.4% (12/69) of protocols the type of future research was specified, in 53.6% (37/69) it was non-specific whilst in 29% (20/69) it was not specified at all.

In 73.2% (109/151) of protocols no export permits were on file at the completion of the audit. In 31/42 (73.8%) protocols the permits were for export to the USA and in the remaining 26.2% (11/42) export was to Europe ($p < 0.0001$). In 13.2 % (20/151) of the REC was informed that HBMs were not for export whilst in 41.2% (62/151) of protocols there were no disclosures to export ($p <0.0001$). The rationale for export in the remaining 69/151(45.69%) protocols were to specialised laboratories in 51/69 (73.9%), for quality assurance purposes in 4/69 (5.8%), access to unspecified secondary users in 5/69 (7.2%), to specialised storage facilities in 2/69 (3.0%) and the lack of local expertise in 7/69 ((10%) [Fig.7]. MTAs were not available for 94.7% (143/151) of the protocols. Of the 5.3% (8/151) protocols that provided MTAs, 75% (6/8) were between local researchers and collaborators from the USA and 25% (2/8) with those from Europe. The trend in the submission of MTAs and export permits in collaborative research with developed countries over the six year period has not changed (Fig.4.8).

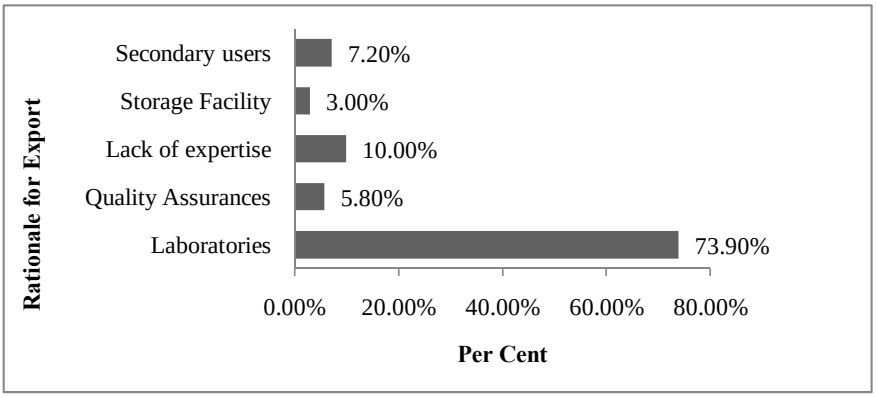

Fig.4.7. Rationale for exporting HBMs

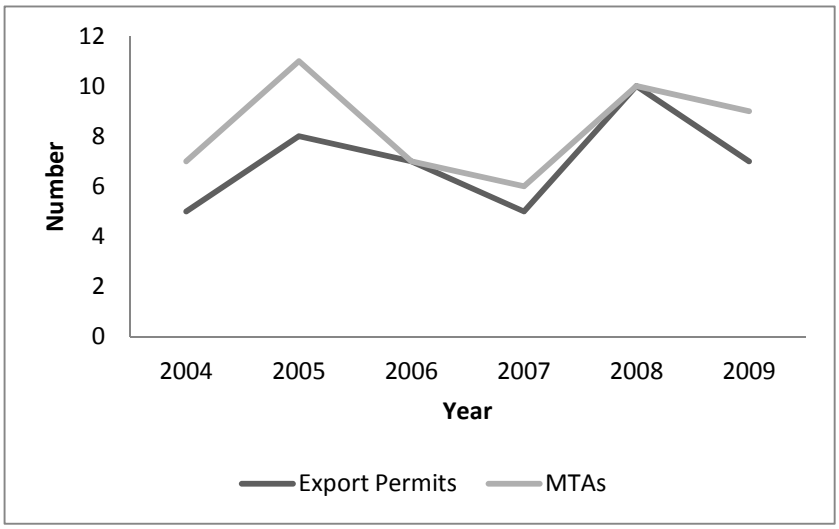

Fig.4.8. Number of Export permits and MTAs submitted over a six year period

4.3.2 Disclosures made to Research Participants in the Information and consent documents

Whilst the PIs of all 151 (100%) protocols informed the REC of the intent to store HBMs, only 132 of 151 (87.4%) protocols informed research participants ($p < 0.0001$). In 81.5% (123/151) of protocols research participants were informed of the different types of HBMs being stored (Table 4.1). In 44.4% (67/151) of protocols research

participants were informed of the intent to export and of the location (47.7%, 72/151) of storage of their HBMs (Table 4.1) compared 59.6% (90/151)[p=0.011] and 86%(130/151)[p<0.0001] protocols that informed the REC, respectively. In 71.5% (57/151) of protocols research participants were informed of the duration of storage (Table 4.1) compared to 19.2% (29/151) that informed the REC (P<0.0001). Only 39.1% (59/151) of protocols discussed with research participants their option to withdraw their HBMs from storage (Table 4.1). Issues of ownership of HBMs were discussed in only 8.6% (13/151) of protocols of which 5.3% (8/13) informed research participants that their HBMs were either the property of the sponsors of the research or both sponsors and the investigators (3.3%, 5/13) of the research (Table 4.1). In 43% (68/151) of protocols research participants were informed of the fate of their samples at the completion of the research and or duration of storage (Table 4.1). In 64 of 151 (42.4%) of protocols participants were informed that their HBMs will be destroyed, returned (2/151, 1.3%) or considered donated (2/151, 1.3%) to the sponsors or investigators of the research (Table 4.1).

In 21.2% (32/151) protocols research participants were informed of secondary use of their stored HBMs and of the possibility of re-contact (21.9%, 33/151) if the results of the research were considered to have an influence on their diagnosis and treatment (Table 4.1). Seventy-two (47.7%) and 98 of 151 (64.9%) protocols informed that genetic and other tests (immunology, microbial genetics, biochemistry, study related, pharmacokinetic, diagnostic etc.) will be performed on the stored HBMs, respectively (Table 4.1). Of the genetic tests, 65.28% (47/72) of protocols informed that the tests were related to the current protocol whilst in 34.7% (25/72) of protocols the genetic tests were not specific ($p < 0.0005$)(Table 4.1). Fifty-seven of 151 (37.7%) protocols

informed research participants that all future research undertaken with their HBMs would be reviewed by the REC (45.6%, 26/57) that approved the initial study, by RECs of sponsors (16/57, 28.07%) or other unspecified RECs (15/57, 26.3%) (Table 4.1). In the majority of protocols research participants were not informed of benefit sharing from any discoveries (129/151, 85.4%), or commercialisation (123/151, 81.5%) of products derived from their HBMs (Table 4.1). Whilst 122/151(80.8%) protocols disclosed the amount of funds available from the sponsors for the research to the REC, not a single PI made such disclosures to the research participants ($p< 0.0001$) (Table 4.1).

Table 4.1. Disclosures to research participants in the information and consent documents

	%(n) n=151
STORAGE	87.4(132)
Types of HBMs	81.5(123)
Residual	31.8(48)
Additional	16.6(25)
Additional & Residual	17.2(26)
Not specified	21.9(33)
Duration	71.5(57)
Location	47.7(72)
Fate of HBMs	43(68)
Destroyed	42.4(64)
Returned	1.3(2)
Donated	1.3(2)
Opt out	39.1(59)
Ownership	8.6(13)
Funders/Sponsors	5.3(8)
Funders & PI	3.3(5)
Genetic Tests	47.7(72)
Study Related	31.1(47)
Specified	2.6(4)
Not specific	13.9(21)
Other Tests	64.9(98)
Review of New Protocols	37.7(57)
Local REC	45.6(26)
Sponsor REC	28.6(16)
Other REC	25.3(15)
Export	44.4(67)
Re-contact Results	21.9(33)
Other Users	21.2(32)
Financial Disclosure	0
Benefit Sharing	
Discovery	14.6(22)
Commercialisation	18,5(28)

The PIs of 98% of protocols (149/151) obtained IC from research participants for the storage of HBMs. Most protocols (76.8%, 116/151) solicited broad consent compared to specific consent (21.2% 32/151) [$p < 0.0001$]. In 2.0% (3/151) of protocols, no IC was obtained (Table 4.2). Forty-five per cent (68/151) of protocols provided research participants with the option to withdraw their consent for storage (Table 4.2). Only 17.2% (26/151) of investigators sought the consent of research participants to make HBMs available to other users. The PIs of 79% (119/151) of protocols discussed how confidentiality of HMBs would be maintained with research participants. In the majority (69.5%, 105/151), confidentiality was maintained by the use of a code and by being anonymised in 9.35% (14/151) [$p < 0.0001$] (Table 4.2). In the remaining 21.2% (32/151) of protocols confidentiality was not specified (Table 4.2). Separate consent forms for the storage of HMBs and for genetic testing were available for only 39.1% (59/151) and 9.9% (15/151) of protocols, respectively (Table 4.2).

Table 4.2. Types of Consent and Confidentiality of stored HBMS

Consent and Confidentiality	%(n) (n=151)
Consent	98(149)
Broad	76.8(116)
Specific	21.2(32)
No consent	2.0(3)
Opt Out	45(68)
Other Users	17.2(26)
Confidentiality	78.5(119)
Coded	69.5 (105)
Anonymous	9.0 (14)
Not Specified	21.5(32)
Separate Consent	
Storage of HBMs	39.1(59)
Genetic Tests	9.9(15)
Paediatric	0(0)

4.4 Discussion

The REC reviewed an average of 218 protocols per year over the 6 year period from 2004 to 2009. There was a three fold increase in the amount of funding for research sponsored by developed countries from 2004 with a sudden drop in 2008. In the latter, the decrease in funding in 2008 from developed countries coincided with the Great Global Financial and Economic Crash of 2008 (Altman 2009). The majority of studies were funded by sponsors from the USA (59.6%, 90/151). Majority of the funds (65.84%, R517.19million) were allocated for research to address one of the country's national health priorities, the HIV/AIDS epidemic (51%, 77/155). The significantly (p

<0.0001) lesser amounts of HBMs obtained and stored from children (12.6%, 19/151) compared to adults (80.8%, 122/151) for research purposes over the 6 year period indicates that less emphasis is placed on paediatric research

Similar to empirical studies in Kenya (Langat 2005) and the USA (Wolf *et al.* 2010), almost all investigators in the current study informed and obtained consent (98%, 149/151) from research participants to store their different types of HBMs for current and future research. More than 50% of protocols informed research participants that their stored HBMs will be used for other studies (74.9%, 113/151), discussed the duration of storage (71.5%, 57/151) and issues of anonymity and confidentiality (78.5%, 119/151). Less than 50% of protocols informed research participants of the future uses, genetic tests (47.7%, 72/151), other users (21.2%,32/151), location (47.7%,72/151), fate (43%,68/151), intent to export (44.4%,67/151) and review of new research protocols (37.7%,57/151) using their stored HBMs. In addition, less than 50% of protocols discussed the option to re-contact research participants to disclose research results (21.9%, 33/151), the option to withdraw HBMs from storage (39.1%,59/151) and the option to withdraw consent(45%,68/151) for storage of their HBMs.

In a Kenyan empirical study (Langat 2005), the majority of investigators (89.2%) did not see the need to request the permission of the RECs nor seek the IC of research participants (91.2%) to store (for future research) and export (87.7% vs 92.8%, respectively) HBMs (Langat 2005). In the current study the majority of investigators informed the REC (100%) and research participants (87.4%, 132/151) regarding storage of their HBMs and sought the research participants' IC (98%, 149/151) to store HBMs. While significantly more protocols informed the REC (59.6%, 90/151) than the research participants(44.4%,67/151) that HBMs were being exported (p< 0.0001),

60.9% (92/151) of protocols did not provide separate consent forms for storage as required by the REC's standard operating procedures (SOP).

In the Kenyan study (Langat 2005) more protocols required storage of HBMs in local (9.2%) than in foreign institutes (5.2%). Similarly in the current study, 32% (48/151) of storage sites were exclusively located locally and 12 % (18/151) internationally. An additional 35% (53/151) were a combination of local, national and international storage sites. In spite of the fact that the South African Human Tissue Act (SAHTA 1993) requires that researchers obtain a permit from the South African Ministry of Health to export HBMs, in this study export permits were not available for 73.2% (109/151) of protocols for HBMs exported in collaborative research with developed countries and this trend does not appear to have changed for the 6 years from 2004 to 2009. In those instances where export permits were available, the majority of export permits were for export to the USA (73.8%, 31/42) and Europe (26.2%, 11/42). Although the Kenyan study did not document and analyse quantitatively the reasons for export (Langat 2005), the rationale for export in the current study were either for quality assurance purposes (5.8%, 4/69), access to unspecified secondary users (7.2%, 5/69), specialised storage (3.0%, 2/69), lack of local expertise (10%,7/69) and to specialised laboratories (74%, 51/69).

It has been recommended that sharing of benefits derived from the use of HBMs are best addressed through MTAs between collaborating countries and researchers and that it is best implemented by RECs in their respective collaborating institutions and countries (Zhang *et al*. 2010, Andanda 2008, OBBR 2007, Muula and Mffutso-Bengo 2007, Emmanuel *et al*, 2004). In this study less than 20% of protocols discussed benefit

sharing with research participants regarding discoveries (14.6%, 22/151) and commercialisation (18.5%, 28/151). Only 8.6% (13/151) of protocols discussed ownership of HBMs with research participants. Neither the SAHTA (1983), the proposed Chapter 8 of the South African NHA Act no.61 of 2003 nor the South African national ethics guidelines (SADOH 2004a) inform researchers of the requirement of an MTA in international collaborative research. However, the SAMRC (2002a) and HPCSA (HPCSA 2008a,b) guidelines informs and advices researchers to draw up MTAs prior to engaging in collaborative research. In the current study MTAs were not available for 94.7% (143/151) of protocols sponsored by developed countries using, storing and exporting HBMs in collaborative research.

IC is a fundamental component in research ethics which allows research participants to exercise their fundamental rights to self-determination. Whilst most protocols were reviewed and approved by the REC and personal information was protected by a code in the majority (69.5%, 105/151), less than 40% (39.1%, 59/151) of protocols discussed with research participant their option to withdraw (opt-out) their samples from storage and only 42.4% (64/151) were informed that the samples would be destroyed. In the current study the majority (76.8%, 116/151) of protocols sponsored by developed countries solicited broad consent, 21.2% (32/151) obtained specific consent and no consent was obtained in 2% (3) of protocols.

Federal regulations (FDA 1998) and OHRP (1996) in the US prohibits the use of any exculpatory language in the IC document in which research participants are made to waive or relinquish any legal or property rights over their HBMs even though the IC may state that HBMs will be used for research purposes. However, using exculpatory

language similar to those in the American study (Wolfe *et al.* 2010: 12), some protocols in the current research informed research participants that their HBMs belonged either to the sponsors or the investigators of the research without accruing benefits (see examples below):

"Any information derived directly or indirectly from exploratory research, as well as any patents, diagnostic tests, medications, or biological products developed directly or indirectly as a result of this exploratory research, are the sole property of the sponsoring company (and its successors, licensees, and assigns) and may be used for commercial purposes. You have no right to this property or to any share of the profits that may be earned directly or indirectly as a result of the exploratory research. However in signing this form and donating blood samples for exploratory research, you do not give up any rights that you would otherwise have as a participant in research."

"In the future, some of the research may help develop new products, such as tests and drugs. If this would happen and these tests or drugs make money, there are no plans to share that money with the people who gave the specimens."

The South African national ethical guidelines requires researchers on application for ethical approval of their protocols to disclose "the sources and extent of funding to the research participant" and to 'publicly acknowledge all sponsorships of research" (SADOH 2004a, sections 2.11 and 7.10). Not a single researcher in the current study made any disclosures to research participants regarding the amount of funding secured for the research from developed world sponsors.

4.5 Conclusion

HBMs are invaluable resources in biomedical research and its associated data provide critical resources for basic scientific discoveries, in supporting emerging technologies, in the discovery of predictors of disease and in the development of new therapies. This is the first empirical study conducted in South Africa that explored the ethical issues

regard the use, storage, export and benefit-sharing of HBMs in collaborative research with developed countries. The research provides empirical evidence that South Africa's first world research infrastructure and its rapidly expanding HIV/AIDS and TB epidemics not only attracts large sums of funding and research collaborations from and with developed countries, but that the cross border flow of HBMs may have increased without export permits, MTA and IPR agreements in place.

Whilst researchers informed the REC and obtained the research participants IC to store their HBMs, the majority of the protocols did not adequately address the inter-related ethical issues and challenges of export, storage, informed consent, commercialisation, distribution and benefit sharing derived from HBMs that are the subject of intense debate and controversy and central to the access to HBMs in collaborative research with developed countries. The impression created is that developed countries are more interested in "mining" vulnerable populations in developed countries of their "natural resources" viz. HBMs, entrenching and imposing their own standards and ignoring the call of developing countries to impose stricter regulations in collaborative research using HBMs.

The empirical arm of the research has several limitations. Firstly it was based on a convenience sample of a single REC in South Africa. Secondly, the findings of this study may be biased towards a specific REC and may neither reflect nor be generalisable to other RECs in the country. Thirdly, all the information was obtained from written documents in which investigators informed the REC what they intended doing. They do not inform the REC what was done in practice. Neither was there any monitoring of the use of HBMs in the collaborative studies by the REC. Finally, the

study did not solicit the opinions, preferences and perceptions of research participants, researchers and or members of RECs on the ethical issues associated with HBMs.

CHAPTER 5

ANALYSIS AND DISCUSSION

The guiding policies regarding HBMs in developing and emerging regions of the world are influenced by international laws, regulations and guidelines. The latter are determined by debates between Europe and the USA which take place in the context of the western legal, ethical, philosophical and religious traditions where traditional cultural values placed on HBMs by communities in developing countries may not necessarily be considered. The varied definitions of what constitutes HBMs, the different terms used to describe identifiability and confidentiality, the different models of IC, the use of ambiguous regulatory language is not only confusing, but also makes comparisons of laws , regulations and guidelines of the different countries difficult and defies generalization (Helgesson *et al*. 2007: 973). Clearly, there is lack of harmonisation and consensus regarding the laws and regulations that should govern the use of HBMs in research.

Whilst the majority of Ugandans (95%) are keen to export their HBMs to the USA and Europe (Wendler *et al.* 2005), Ugandan scientists on the other hand have complained that millions of dollars due to the exportation of 80% of HBMs, “whose fate were unknown, were lost in terms of foreign exchange from their country” (Nakkazi cited by Upshur *et al.* 2007). Malawians showed that poor IC, lack of cultural sensitivity, failure to follow traditional custom and lack of benefit sharing were among several reasons identified that influenced Malawians not to participate in biomedical research (Mfutso-Bengo *et al*. 2008). The majority of Egyptians are less favourable to exporting their HBMs to both the USA (62.6%) and Europe (51.2%) [Abou Zaidi *et al.* 2010). Factors

that might account for Egyptians unwillingness to export samples to western countries may revolve around issues of "trust, confidentiality, commodification, religious values, lack of oversight on types of future research" (Abou-Zeid, *et al*. 2010:4) or may even be *political i.e. the pursuing American foreign policy in the Middle East* (author's opinion in italics). In the current research for the majority of protocols (73.2%, 109/151) there was neither evidence of export permits being obtained for HBMs that were to be exported to developed countries nor any indication that this trend has changed since 2004 to 2009. Clearly the legislative requirements as per the SAHTA (1983) are being ignored by the researchers, are not being enforced by the lawmakers and by the REC where the project was done. No empirical study to-date have solicited the perceptions of South African research participants regard the export of their HBMs.

Most developed countries, especially Europe and the USA including the WHO secretariat, take the position "that MTAs should not contain legally binding benefit sharing arrangements and restrictions on IP rights and that reference should be made only to guidelines"(Zhang *et al* 2010.7). This is understandable, because guideline documents are not legally binding. The position of most developing countries is that "MTAs should contain legally binding benefit arrangements and should not allow recipients of HBMs to pursue IP rights on products developed using the HBMs" (ibid). None of these proposals have been followed up by the WHO secretariat (ibid)**.** Therefore, it's not surprising that in the current study MTAs were not available for 94.7% (143/151) of protocols sponsored by developed countries. Whilst the guideline documents of most developed countries inform their researchers of the need for MTAs in collaborative research, they are in the main used for collaborations intra-nationally and between developed countries. With the exception of RSA's national ethics guideline document (SADOH 2004a), the frameworks of most developing countries in

Africa and the BRICS regions require MTAs to be in place before engaging in collaborative research with developed countries (see Table 2.7). The recently promulgated IPRAct (2010) in South Africa does not make specific reference to HBMs but the Act is intended to ensure that patents which emanate from publicly financed R&D is protected and commercialised for the benefit of South Africans. It would be interesting to see if foreign collaborators would adhere to the Act.

Debates continue to rage about the appropriateness of applying IC formats of developed countries to the collection, storage and use of HBMs, to research participants from cross-cultural settings and communitarian societies, like those in Africa (Agulanna 2010). Europe favours broad consent provided specific conditions are met (Helgesson *et al*. 2007, Hansson *et al.* 2006, Elger and Caplan 2006, Helgesson and Johnson, 2005) whilst US favors multilayered/tiered consent (Mello and Wofle 2010, Salvaterra *et al*. 2008**,** Elger and Caplan, 2006). Each providing arguments for and against their specific recommendations (Mello and Wofle 2010, Salvaterra *et al*. 2008, Elger and Caplan, 2006, Arnason cited by Hansson *et al*. 2006). In empirical studies, the majority of US (72-92%) and Ugandan (85%) research participants [Pentz *et al*. 2005, Wendler *et al.*2005, Chen *et al*. 2005] compared to 54% of Egyptian (Abou Zaidi *et al* . 2010) and 37% of Saudi (al Qadire *et al*. 2010) research participants, favoured broad consent. Murphy *et al.* (2009) reported that US residents expressed a range of IC preferences towards the creation of a national genome databank. Less than 50% of African Americans and Hispanics preferred broad IC and an overwhelming desire for a legal contract between researchers and themselves (ibid). Even though research participants in developing and developed countries are reluctant to give broad consent to conduct research with their stored HBMs (Abou-Zaidi *et al*. 2010, Al Qadire *et al*. 2010, Murphy *et al*. 2009) and the Havasupai Indian Tribe case (Mello and Wolf 2010)

highlighted the problem with broad consent,the majority of protocols in this study solicited broad consent. A Court decision in the USA suggested that “an omission to discuss with the research participants their right to withdraw their samples from storage, limits the individual’s right to withdraw HBMs from research” (Washington University vs. Catalona*)*. This situation has yet to be tested in South African courts. However, not fulfilling all the elements of IC, including the right to withdraw HBMs, would be violating statutory law (NHA) and section 12 of the Bill of Rights of the RSA Constitution. In addition, not to provide the opportunity to either consent or object is a failure to fulfil a basic tenet of ethics viz. Respect for Autonomy.

Local REC are best positioned to evaluate the risks and benefits that research may pose to participants within the context of the local scientific and cultural environment. However, when HBMs storage sites are located abroad, when other users of HBMs are not identified and when only 45.6% of protocols inform participants that all new future studies with their stored HBMs will be reviewed by the local REC, the local REC effectively does not have the oversight authority on the re-use of stored HBMs in most instances. Hence control of the ethical use of their HBMs is denied to local participants in research. Local participants can not even be given the assurance that their HBMs will be protected and used in accordance to the principles and doctrines as espoused in ethics.

All Clinical Trials have to be registered with the South African National Research Registry at the National DOH. There has been intense debate and criticism in the scientific literature of researcher’s and investigator’s financial relationships with industry and sponsors and their limited disclosures to research participants (Weinfurt *et al*. 2009, Steinbrook 2008 and 2009). The US Congress has mandated the on line

disclosure of all financial relations on a federal government website under the Physician Payments Sunshine Act (PPSA) (Steinbrook 2009). Many leading institutions and pharmaceutical companies in the US have revised their codes of conduct and are disclosing their financial relationships online (Steinbrook 2009). There have been discussions even within the NIH about expanding the disclosures to cover research grants (Steinbrook 2004). The failure of the researchers in the current study to make any financial disclosures to research participants could be construed as a lack of transparency by the researchers on pertinent issues with the research participants

Whilst the results from an empirical study in the USA (Wolf *et al.* 2010) addressed similar ethical issues to the current study, investigators in those studies appear to have been more forthcoming with their research participants with regard to ethical issues pertaining to the option to withdraw specimens, specified genetic studies, issues with benefit-sharing, confidentiality, other users and re contact with results. However both the Kenyan (Langat 2005) and US (Wolf *et al* 2010) empirical studies did not address issues regarding export permits and MTAs. There are differences between the three empirical studies. The current study included 151 eligible protocols submitted over 6 years to one REC in RSA in which HBMs were being used in collaborative research with developed countries. The Kenyan study included 388 research protocols submitted to two RECs over a period of 2 years of which 60% of proposals submitted included retrospective studies to use archived HBMs by medical students who also explored patients' medical and other clinical reports (Langat 2005). The US study on the other hand was a review of 139 protocols and corresponding consent forms from 20 Clinical Research Centres (general and paediatric) or Specialised Programs for Research that received the most funding from the NIH for genetic research.

On the one hand the guideline documents of most developed countries consider it an ethical imperative that its researchers who undertake their biomedical research in developing countries with limited resources whose communities are vulnerable to exploitation, to give-back and to consider the equitable distribution of benefits that is consistent with social justice, solidarity and equity. Yet in the current study less than 20% of protocols discussed benefit sharing with research participants from discoveries commercialisation, issues of ownership, a paucity of MTAs and export permits of HBMs. The position adopted by most developed countries in this study demonstrates a lack of congruence between their guidelines which espouse an ethical approach and their actions which could be construed as unethical. The empirical arm of the research report is the first empirical study conducted in South Africa that explored the ethical issues regarding the use, storage, distribution and benefit-sharing of HBMs in collaborative research with developed countries. This study demonstrates a disregard by local researchers of local in country guidelines and policies.

CHAPTER 6

CONCLUSION AND RECOMMENDATION

The fragmentation of the regulatory systems is a serious obstacle to ethical conduct of biomedical research and there is an urgent need not only to harmonise laws and regulations regarding the use of HBMs in developing countries and BRICS regions, but globally as well. Confusing and conflicting standards of ownership and control of HBMs confound the efforts of researchers and RECs to ensure that research is conduced ethically. Unified national and international harmonised guidelines that will simplify practical implementation to regulate HBMs are needed to embrace the interests of communities in developing countries as legitimate stakeholders to advance medical knowledge and improve health care without compromising and or hindering collaborative research. As funding and research collaborations between South Africa and developed countries increase so too will the cross border flow of HBMs and data increase. Sound principles to conduct ethical research exist. Satisfying these principles on the one hand requires that researchers respect the autonomy and the right of self-determination of those who participate and provide their HBMs for the research.

South Africa's national bioethics policies, laws and guidelines draw reference to and embrace international codes, declarations and guidelines. With regard to HBMs these documents draw the attention of researchers from developed countries entering into collaborative research with developing countries to take cognisance of and abide by national guidelines of the collaborating country; treat HBMs with respect and dignity taking into consideration the cultural and religious implications associated with HBMs;

that researchers consider the equitable distribution of benefits, if any, available to participants when the study/research ends; build local capacity; must be culturally sensitive and enter into collaborative partnerships with the respective communities and its indigenous populations. Whilst collaborations in biomedical research between developed and developing countries may be considered as being philanthropic, it too often creates the impression of the wealthier and powerful partner experimenting and imposing its set of rules on the population of its disadvantaged and at times subservient partner. What makes it even more complex is that HBMs obtained from communities with diverse cultural practices from developing countries and exported to developed countries in collaborative research are subjected to standards that conflict with local culture (McIntosh *et al*. 2008, Upshur *et al*. 2007).

The ability of South African researchers to attract vast sums of funding from international donors for research and to build state of the art research facilities is adequate evidence that researchers and institutions in South Africa can function as centres of research excellence on the African continent and internationally. Yet the evidence from the empirical study suggests that a natural resource of the country, HBMs, may be leaving the country unaccounted for. The benefits and accolades accruing primarily to foreign and a select few local researchers and their institutions. These local institutions and their researchers acting as African proxies for the sponsor of HBMs to their more wealthy and illustrious collaborators and funders from developed countries. In addition the empirical study gives some credibility to the anecdotal evidence from South African ‘informants” that HBMs are leaving the country at a regular pace, unaccounted at a national level, without export permits and MTAs in place. It endorses Hardy *et al’s* (2008) conclusion, that this “potentially affects the

ability of South Africans, more generally Africans, *who are the majority research participants* (authors own inclusion in italics); to capitalise on the results of the associated research and negotiate benefit-sharing that accrues from such research using their HBMs".

Research participants provide their HBMs altruistically, assuming that researchers will use the HBMs in their best interest and for the common good (Dressler 2007). However, when the results of research with HBMs become patentable and lucrative and HBMs become commercial assets, it is possible that the altruistic element in providing HBMs for research could become strained, thus affecting research, progress and the generation of knowledge . Given the troubled history of exploiting of vulnerable populations in developing countries for their HBMs and in order not to discourage collaborative research and to instill the moral imperative of social and distributive justice in biomedical research, not only must the WHO secretariat heed the call of developing countries in safeguarding their interests in collaborative research using HBMs, but there also has to be a paradigm shift from viewing HBMs not as a proprietary good but as a national resource for the common good.

Andanda (2008) and NCI's OBBR (2007) independently made several recommendations regard custodianship/ownership of HBMs in research. These recommendations addressed the issue of harmonisation of national and international frameworks, IPR and benefit sharing addressed through MTAs between collaborating countries/researchers and recasting the doctrine of IC and, importantly, that the recommendations, regulations, guidelines and framework are implemented by competent RECs in their respective collaborating countries. However in my opinion,

the requirement of MTAs regarding the use of HBMs in collaborative research should be incorporated not only into South African national guidelines but into legal frameworks as well. The results of this empirical research makes compelling argument to endorse the recommendations by Andanda (2008) and NCI's OBBR (2007).

Whilst both the Department of Health's South African National Health Research Database and the Clinical Trial Registry requires registration of all clinical research trials, it should include and encourage, if not already, on-line disclosure of financial relationships between physicians, researchers, industry and sponsors to promote and encourage transparency. In the case of research using HBMs routine disclosures of relevant financial ties and the possibility of intent to commercilise research products, might help to alleviate concerns of research participants, bolster transparency and the credibility of researchers. Such disclosures may not eliminate conflicts of interest but will make information accessible to the public and allow for open debate and questions.

The South African government's commitment to research and development of its health biotechnology programmes require the establishment and support of a national biobank (Hardy *et al*. 2008a) under the control of government and not private individuals or the private sector (SADOH 2005). Commercial enterprises like Pharmaceutical companies, private or commercial laboratories providing diagnostic services that also function as private biobanks are subject to *inter alia* mergers, take-overs, liquidation, and sequestrations. Under these circumstances HBMs stored in such institutions may be lost, displaced, change ownership and be lost to REC oversight. In the absence of robust legislation and guidelines on biobanking (SADOH 2004a), the first set of draft regulations of section 68 of the NHA (Act no. 61 of 2003), Chapter 8 relating to Tissue banks was published recently for public comment (NHA 2011c).

Prior to embarking on an ambitious programme viz. to establish a national biobank in South Africa, researchers, policy makers, ethicists and other stake holders must undertake cost-benefit analysis, feasibility and sustainability studies to establish if a national biobank is a public health priority. Other recommendations proposed to address the concerns with regard to he use, storage and redistribution of HBMs include the resurrection of the South African Human Tissue Act (Act 65 of 1983) along the lines of the UK Human Tissue Act (2004) and the establishment of an oversight body for HMBs similar to that of the Human Tissue Authority in the UK (McQuoid-Mason 2011).The establishment of a tissue trust model for Biobanks for developing countries has been proposed as a safeguard against the exploitation of HBMs by developed countries (Emerson *et al*. 2011). The authors inspired by the Charitable Trust model for biobanks (Winickoff and Winickoff 2003) argue that whilst the concept has not been tested in developing countries by empirical research, such a model would prevent exploitation, engage communities, minimize conflicts of ownership, provide long term benefits to the source communities, build local capacity and restore trust in collaborative research with developed countries (Emerson *et al*. 2011).

Admittedly there are omissions in the RSA regulatory and ethical frameworks regard ing HBMs that need to be addressed . Presently the provisions of the Human Tissue Act 65 of 1983, the NHA 61 of 2003 and national ethics guidelines (SADOH 2004a) are inadequate to deal with new challenges associated with the use of HBMs. Current draft regulations of section 68 of the NHA Act no. 61 of 2003 [NHA 2011b] if promulgated, will define the export of HBMs without an export permit a criminal offence. In addition, the regulations (section 68 of the NHA 2004 (Act no. 61 of 2003)[2011b] will

allow “a maximum of 5000 milliliters (mls) of HBMs for export in a single shipment from a “single authorized organisation, institute or person.” Since all of the export permits are valid for one year from the time of application, I would recommend the above be amended to read “a maximum of 5000 milliliters (mls) of HBMs for export in a single shipment from a “single authorized organisation, institute or person *in one calendar year* (authors inclusion in italics).” Alternativley, the regulations must clearly state that an export permit is required for every new shipment of HMBs exported, because it is not known for certain if the same export permits are used on more than one occasion to export more than the maximum permitted. Given the long delays in harmonizing and publishing new regulations and changes, specifically within the South African context, outdated regulations and regulatory frameworks create opportunities for the proliferation of undesirable and unethical practices.

The current study has illustrated that there are ethical issues that require immediate attention viz. the cultural appropriateness of broad consent; the lack of REC oversight of HBMs that are stored abroad and accessible to others outside the jurisdiction of local RECs in some instances for unlimited time periods and beyond the life span of the research), the justification and rationale for exporting HBMs to developed countries in exchange for capacity building and sharing gains and the lack of full disclosures. South African policymakers and RECs need to be more vigilant and proactive in implementing the laws and accompanying guidelines with regard to the use, reuse and export of HBMs in collaborative research with developed countries. The lack of information and full disclosures places research participants at unknown risks, compromises their integrity, dignity, and their cultural values and violates their right to self determination and autonomous decision making. It also confounds the efforts of the

REC to ensure that research is conducted ethically. It is recommended that the NHREC amend its guidelines to include the need for MTAs in collaborative research.

More importantly, additional empirical studies should be undertaken to solicit the opinions, perspectives and perceptions of South Africans to explore the ethical and cultural issues regarding the use, reuse, storage, biobanking and export of HBMs in collaborative research with developed countries. Importantly, and as a matter of urgency, research participants need to be educated and be made aware of their rights and their obligations with regard their HBMs. Additional empirical studies to assess the generalisability of the results of the current empirical research to other RECs in RSA should be embarked upon. The findings of this research report will be compiled into a discussion document for presentation to RECs in the country, policymakers at the level of the Departments of Health , Science and Technology and civil society organisations.

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