

Informed consent for genetic research in adult patients in a research entity in South Africa: an ethico-legal inquiry

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DECLARATION

I, Aina Christina Lundgren, declare that this research report is my own work. It is being submitted for the degree of Master of Science in Medicine in Health Law and Bioethics at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

.....Aina Christina Lundgren

.....day of 2015

In memory of my mother

Aina Maria Lundgren

1921 - 2014

ABSTRACT

Research on human subjects in South Africa is guided by the Research Ethics Guidelines produced by the National Department of Health, as well as many other documents such as the Bill of Rights, the National Health Act and ethical guidelines published by the Health Professions Council of South Africa.

The fundamental issue when considering the ethics of human research is to ensure that vulnerable people are protected from exploitation. The ethics of research is based on principle-based ethics, which is made up of the principles of autonomy, beneficence, non-maleficence and justice. Supporting principles include respect for autonomy and the issue of informed consent, scientific integrity, privacy and confidentiality.

Many clinical trials initiated by researchers and/or pharmaceutical companies include a genetic component in addition to the main clinical study. The genetic component entails the taking and storing of patients' blood or other tissues for up to twenty years, often in a foreign country in a biobank or similar repository. Acquiring informed consent for this genetic component of these studies is often problematic, in that the exact nature of the research is not always known at the time that the samples are taken. In addition the patient may not understand the consequences of giving up these samples to various organisations for future experimentation and international data exchange and sharing.

The empirical limb of this study investigated the type of consent given by patients for genetic research in studies submitted to the Wits Health Consortium during

2013. Additional factors such as length of time and site of storage of the genetic samples, as well as data storage and sharing were explored, as well as the complexity of the language used for the informed consent.

Less than a third of the protocols with a genetic component that were studied, complied with South African regulations and guidelines governing the obtaining of informed consent for genetic research. Recommendations made in order to improve this included a standardized informed consent process, attention to the language used when obtaining informed consent, the type of informed consent obtained, and improved communication with the research participants on the ethical issue of data sharing.

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CHAPTER 1

INTRODUCTION

Preface

This research report is written in the first person, using the Vancouver system for referencing.

The study in this research report arose from my role as a member of the Protocol Review Committee (PRC) for clinical trial applications submitted for ethics approval by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, through the Wits Health Consortium Ethics secretariat. The purpose of my role on the PRC is to ensure that the facility where the research is being conducted is not exposed to additional risk, for example unplanned costs. I became intrigued when reading the informed consent forms for storage of specimens for future research, including genetic research. There appeared to be an increase in these, with many protocols having a genetic component, with variation in the amount of information presented. As a result the plan for this current study was to perform a two-fold literature review, and a descriptive pilot study of the relevant PRC applications approved by the Human Research Ethics Committee (Medical) during 2013.

1.1 General remarks

“The elucidation of the causes of complex diseases pivots on understanding the interaction between biological (genetic) and environmental factors that give rise to

disease risk. The modest effects of genetic factors in complex diseases supports the need for large-scale studies of high-quality human biological materials, paired with detailed clinical data, to adequately detect these effects. To this end, human tissue biobanks or biorepositories have been developed around the world, by public and private entities alike, to provide researchers the opportunity to study collections of human biospecimens annotated with clinical and other health-related measurements”(1).

Human tissue biobanks can be considered as “an organized collection of human biological material and associated information or data for one or more research purposes”(2). These biobanks usually incorporate cryogenic storage facilities for the samples, and may range in size, with reference to the number of samples that can be stored in the facility. The advantages of using biobank samples for genetic research instead of conventional sampling methods for research are as follows:

- Secure sources of well-stored research material;
- Unlimited numbers of studies can be performed;
- Many different disciplines can be involved;
- Research is less costly;
- International collaboration and data sharing is enabled.

However, these major advantages to researchers come at a considerable ethical “cost” to the individual donors of genetic material. In addition there are associated legal and social issues, which are being grappled with all over the world.

Research on human subjects in South Africa is guided by the Research Ethics Guidelines(3) produced by the National Department of Health. This document is informed by various other documents such as the National Health Act(4) and Declaration of Helsinki(5). Other guidelines include the Bill of Rights of the Constitution of South Africa(6), the National Health Act(4), guidelines for Good Clinical Practice(7) and also the ethical guidelines of the Health Professions Council of South Africa. International guidelines include the Nuremberg Code(8), the Universal Declaration of Human Rights (this has informed section 12 of the South African Bill of Rights), and the guidelines of the Council of International Organisation of Medical scientists (CIOMS)(9) the Good Clinical Practice (GCP) guidelines(7) and the Singapore Statement on Research Integrity(10). The latter is due to be updated in the second half of 2015.

1.2 Ethical and legal basis of the research

The fundamental issue in the context of the ethics of medical research is to ensure that vulnerable people are protected from exploitation.

Ethics of research is based on principle-based ethics(11), which comprises the following principles:

- Autonomy, which deals specifically with the issues of consent and confidentiality;
- Beneficence and non-maleficence, looking at a positive risk-benefit ratio;
- Justice, which is largely distributive justice, ensuring research subject dignity and protection of rights in the context of the greater good.

In South Africa we have ethical principles as outlined in the Department of Health Ethics in Health Research document(12) that need to be followed, and these include the fundamental principles outlined above, with additional supporting principles(11), namely:

- Relevance, indicating that the research needs to be relevant to the individual on whom the study is conducted, and also relevant to the community or the country(11).
- Scientific integrity, meaning that the research needs to be based on sound science(11).
- Investigator competence, which embraces integrity as well as competency in the research process, by the principal investigator(11).
- Informed consent, which. is a key factor in human research, indicating respect for persons and their rights(11).
- Privacy and confidentiality, which needs to be respected in terms of an individual's right to protect personal records, as well as the confidentiality of the data that is collected.
- Risks and benefits refer to the risks to the individual, balanced against the benefits to both the individual and the community.
- Justice, which addresses the benefits following on from the research, such as post-trial access to drugs.
- Ethical review by a human research ethics committee needs to be carried out prior to all human research.

While informed consent is essential in all medical research on humans, a unique situation exists in South Africa in that the Constitution entrenches informed consent in the Bill of Rights(6). No other country has anything similar. A second important consideration is the rapid growth of genetic research in medicine in South Africa and the world.

1.3 Problem statement and aim

The aim of this dissertation is to answer the question: Is the consent obtained from adult patients for genetic research informed, morally justified and in keeping with South African and International laws, regulations and guidelines?

1.4 Objectives

The research objectives are:

- to ethico-legally evaluate the current South African and international laws, regulations and professional guidelines governing consent for genetic research in adults.
- to perform a conceptual analysis examining the history and origin of the concepts of autonomy and informed consent in law.
- to retrospectively analyze the type of informed consent given by adults participating in genetic research through the Wits Health Consortium (WHC).

1.5 Study design

A retrospective descriptive research design will be used using research records of the Wits Health Consortium (WHC) containing consent for genetic research over a period of 1 year.

1.6 Research report outline

This research report will comprise the following chapters:

Chapter One: the introduction and a brief summary of the methodology used;

Chapter Two: an ethico-legal evaluation of the current South African and international laws, regulations and professional guidelines governing human and human genetic research in adults;

Chapter Three: a conceptual analysis examining the history and origin of the concepts of autonomy and informed consent in law, and their application to human genetic research;

Chapter Four: methodology and results of the empirical limb of the study comprising a retrospective review;

Chapter Five: discussion and recommendations.

CHAPTER 2

AN ETHICO-LEGAL EVALUATION OF THE CURRENT SOUTH AFRICAN AND INTERNATIONAL LAWS, REGULATIONS AND PROFESSIONAL GUIDELINES GOVERNING HUMAN AND HUMAN GENETIC RESEARCH IN ADULTS.

This chapter will initially describe the various international documents guiding research on human subjects, followed by those guiding genetic research. The second part of the chapter will discuss the South African laws, regulations and guidelines governing human research, followed by those guiding genetic research.

Terms used are:

- Human tissue research refers to the collection and storage of various types of human tissue for the purposes of genetic and other research.
- Genetic research covers gene therapy, genetic screening and testing, patenting human genes and proteins and cloning.
- Participant is the word used in South Africa, whereas research subject is the term used elsewhere.

Human tissue research and genetic screening and testing will be covered in this thesis under the heading of human genetic research.

2.1 International laws, regulations and guidelines

2.1.1 Human research

2.1.1.1 Nuremberg Code(8)

One of the first international ethics documents to be published, (and also the most important historically) was the Nuremberg Code(8), which was drawn up in 1947 as a result of the Nazi doctors' trial at the Nuremberg Trials(13, 14), held after the Second World War. The Nazi doctors were tried by American judges for crimes against humanity, in that they “unlawfully, willfully, and knowingly were principals in, accessories to, ordered, abetted, took a consenting part in, and were connected with plans and enterprises involving medical experiments, without the subjects' consent, upon German civilians and nationals of other countries, in the course of which experiments the defendants committed murders, brutalities, cruelties, tortures, atrocities, and other inhuman acts”. (13)

The experiments performed involved the use of high altitude, freezing, malaria, mustard gas, bone, muscle and nerve degeneration, bone transplantation, sea water, epidemic jaundice, and sterilization.

The Doctors' Trial began on the 9th December, 1946 and ended on the 19th July 1947(14).

Three American judges presided over the case.

Sixteen doctors were found guilty; of those 7 were hanged; 5 were sentenced to life imprisonment, while the others were sentenced to prison terms of various lengths of time.

The Nuremberg Code(8) was drawn up by two medical experts, Leo Alexander and Andrew Ivy(14) and unnamed prosecutors who participated in the trials. The Code served as a blueprint for today's ethical principles protecting individuals' rights in medical research.

The Code(8) mandates the following, with regard to human experimentation:

- The voluntary informed consent of the human subject is essential.
- The experiment should yield meaningful results for society, unprocurable by other means.
- The experiment should be designed and based on the results of animal studies.
- The experiment should avoid physical and/or mental suffering and injury.
- No experiment should be conducted where it is thought that death or disablement may occur, unless the experimental physicians are also the subjects.
- The degree of risk must be reasonable.
- The experiment should be conducted by scientifically qualified persons.
- During the course of the experiment the subject may withdraw participation.
- The scientist must be prepared to stop the experiment if it is thought that injury, disability or death may occur.

2.1.1.2 Universal Declaration of Human Rights(15)

The Nuremberg Code was followed in 1948 by the Universal Declaration of Human Rights, issued by the General Assembly of the United Nations(15). This

document comprises a general preamble, followed by thirty articles, which cover a variety of fundamental basic human rights. Article 5 states the following: “No one shall be subjected to torture or to cruel, inhuman or degrading treatment or punishment.”(15)

Despite the existence of the Nuremberg Code and the Universal Declaration of Human Rights, some researchers continued to exploit vulnerable participants and perform unethical research(16).

2.1.1.3 Declaration of Helsinki(17)

In June 1964 the World Medical Association(WMA) developed the Declaration of Helsinki(17) as a statement of ethical principles for medical research on human subjects. This is considered a cornerstone document which has influenced subsequent legislation and guidelines.

This publication was much needed, as despite the Nuremberg Code and Universal Declaration of Human Rights, patients continued to be exploited for research purposes, as was discussed by Henry Beecher in June 1966(16). He highlighted numerous studies, where patients did not understand the risks involved. In fact some did not even realise that they were participating in an experiment. There were many ethical violations in research conducted by respected researchers and funding bodies.

The original Declaration(17) has been amended by the World Medical Association in 1975, 1983, 1989, 1996, 2000, 2004, 2008 and 2013.

The latest version includes the following phrase “including research on identifiable human material and data”.(18)

The Declaration of Helsinki is divided into the following sections(18):

- “Preamble
- General Principles
- Risks, Burdens and Benefits
- Vulnerable Groups and Individuals
- Scientific Requirements and Research Protocols
- Research Ethics Committees
- Privacy and Confidentiality
- Informed Consent
- Use of Placebo
- Post-Trial Provisions
- Research Registration and publication and Dissemination of Results
- Unproven Interventions in Clinical Practice”

All of these sections are relevant to different aspects of research involving human participants. The section on informed consent is very detailed and specific, and serves to protect all categories of patients for various types of research. The importance of the individual is emphasized over and above family and community members. The type of information that must be given to research participants is also

specified, as well as the participants' right to withdraw at any stage, without any ensuing consequences.

2.1.1.4 The Belmont Report(19)

In 1974 the United States Congress signed the National Research Act into law, thereby establishing a National Commission for the Protection of Human Subjects in order to develop ethical principles for all research involving human subjects. This was triggered by the blatant lack of ethics used during the “shameful” Public Health Service Syphilis Study in Tuskegee, Alabama(20). The document that resulted was the Belmont Report(19).

This document highlights the key ethical principles that should guide all clinical research, namely:

- Respect for persons, involving two important ethical principles, namely that individuals should be treated as autonomous agents, and secondly that those with diminished ability to be responsibly autonomous are protected.
- Beneficence, ensuring the well-being of research participants. In other words, “do no harm”, and maximize the possible benefits.
- Justice, particularly when deciding who bears the burden of research and who receives the benefits.

The Belmont Report applies these principles to the following:

- Informed consent, with specific reference to information and disclosure, comprehension of this information, and voluntariness.

- Assessment of risks and benefits, specifically the nature and scope of these, as well as whether they are balanced or in a favourable ratio. This applies particularly to vulnerable research subjects.
- The selection of subjects for the research, ensuring justice in selecting the group/community of research subjects, as well as the individuals.

All of these principles from the Belmont Report(19) should be considered when deciding on the ethics of particular clinical research.

2.1.1.5 International Ethical Guidelines for Biomedical Research Involving Human Subjects {Prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO)}(9)

This is the current definitive document on research internationally. The first edition was produced in 1982, followed by revisions in 1993 and 2002. The importance of these guidelines is that they draw the attention of all those involved in research in human subjects to all of the pertinent ethical issues. The 2002 edition makes the following comments on the relevance of culture:

“An issue, mainly for those countries and perhaps less pertinent now than in the past, has been the extent to which ethical principles are considered universal or as culturally relative—the Universalist versus the pluralist view. The challenge to international research ethics is to apply universal ethical principles to biomedical research in a multicultural world with a multiplicity of health-care systems and

considerable variation in standards of health care. The Guidelines take the position that research involving human subjects must not violate any universally applicable ethical standards, but acknowledge that, in superficial aspects, the application of the ethical principles, e.g., in relation to individual autonomy and informed consent, needs to take account of cultural values, while respecting absolutely the ethical standards".(9)

The document is divided into 21 comprehensive guidelines, which include the following:

- Ethical review committees.
- Ethical review of externally sponsored research.
- Individual informed consent and obtaining it, as well as the obligations of sponsors.
- Inducement to participate.
- Benefits and risks of participation, and limitations on risk.
- Choice of control in clinical trials, and equitable distribution.
- Research involving vulnerable persons and children.
- Women and pregnant women as research subjects.
- Safeguarding confidentiality.
- Rights of injured subjects to treatment and compensation.
- Ethical obligations of external sponsors to provide health care services.

These are followed by various appendices, which include research trials requirements, the Declaration of Helsinki and an explanation of the phases of clinical trials of vaccines and drugs.

2.1.2 Human genetic research

There are far fewer laws, guidelines and regulations specifically for genetic research.

The following documents make mention of human genetic research.

2.1.2.1 Declaration of Helsinki(18)

The latest version (2013) of the Declaration of Helsinki includes the following phrase in the first sentence of the preamble: “as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data”.(18) This indicates that the entire document applies to (but is not limited to) human genetic research as well as research on human subjects.

2.1.2.2 International Ethical Guidelines for Biomedical Research Involving Human Subjects {Prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO)}(9)

The Introduction section of these guidelines makes the following comment: “Certain areas of biomedical research are not represented by specific guidelines. One such is human genetics. It is, however, considered in Guideline 18 Commentary under Issues of confidentiality in genetics research”(9).

Guideline 18 states the following under issues of confidentiality in genetics research: “An investigator who proposes to perform genetic tests of known clinical or predictive value on biological samples that can be linked to an identifiable individual must obtain the informed consent of the individual or, when indicated, the permission of a legally authorized representative.

Conversely, before performing a genetic test that is of known predictive value or gives reliable information about a known heritable condition, and individual consent or permission has not been obtained, investigators must see that biological samples are fully anonymized and unlinked; this ensures that no information about specific individuals can be derived from such research or passed back to them.

When biological samples are not fully anonymized and when it is anticipated that there may be valid clinical or research reasons for linking the results of genetic tests to research subjects, the investigator in seeking informed consent should assure prospective subjects that their identity will be protected by secure coding of their samples (encryption) and by restricted access to the database, and explain to them this process.

When it is clear that for medical or possibly research reasons the results of genetic tests will be reported to the subject or to the subject’s physician, the subject should

be informed that such disclosure will occur and that the samples to be tested will be clearly labelled.

Investigators should not disclose results of diagnostic genetic tests to relatives of subjects without the subjects' consent. In places where immediate family relatives would usually expect to be informed of such results, the research protocol, as approved or cleared by the ethical review committee, should indicate the precautions in place to prevent such disclosure of results without the subjects' consent; such plans should be clearly explained during the process of obtaining informed consent.”(9)

These are very specific guidelines and very important in the context of genetic research.

2.1.2.3 The Organization for Economic Co-operation and Development (OECD) Guidelines on Human Biobanks and Genetic Research Databases(21)

The Organization for Economic Co-operation and Development (OECD) is a forum of 30 democracies who work together to address various issues. South Africa was not a member of the committee when they drew up this guidelines document in 2009.

The guidelines are divided into two sections.

The first deals with general principles, best practice, establishment of human biobanks and genetic research databases (HBGRD) as well as governance and oversight/monitoring. This is followed by a detailed discussion of all of the principles

involved in the terms of participation in genetic research, such as informed consent, as well as the type of informed consent. This is followed by details of the content of HBGRDs and the principles and practices involved in the protection of human biological material and data. Access, custodianship, intellectual property and disposal of materials and data are also dealt with. An important clause pertaining to ownership of the genetic material states: “The operators of the HBGRD should have a clearly articulated policy and explicitly indicate to participants whether they and/or the HBGRD retain any rights over the human biological materials and/or data and the nature of such rights.”(21)

The second section of the guidelines is titled “Annotations”, and basically explains statements from the first section, as well as giving examples to clarify various issues.

The annotation on terms of participation is very detailed, explaining the various types of consent that may be obtained for genetic research. These will be described in detail in Chapter 3 of this research report.

2.2 South African laws, regulations and guidelines

2.2.1 Human research

Research on human participants in South Africa is guided by the Research Ethics Guidelines(12) produced by the National Department of Health. This document is informed by various other documents such as the National Health Act(4) and Declaration of Helsinki(17). Two laws include the Bill of Rights of the Constitution of South Africa(6) and the National Health Act(4). Additional guidelines that have been

produced are the Medical Research Council's Guidelines on Ethics for Medical Research in 2002(22), which pre-dated those of the Department of Health, and also the ethical guidelines of the Health Professions Council of South Africa(23).

2.2.1.1 The Bill of Rights of the Constitution of South Africa(6) and the National Health Act(4)

Chapter 2 of the Constitution of South Africa is also known as the Bill of Rights(6), and is the supreme law of South Africa. The pertinent sections are paragraph 10, which states that "everyone has inherent dignity and the right to have their dignity respected and protected"(6), and paragraph 12.2. This covers the right to bodily and psychological integrity, which includes the right "to security in and control over their body", as well as "not to be subjected to medical or scientific experiments without their informed consent"(6).

Chapter 9 of the National Health Act of 2003(4) deals with the law pertaining to human research. Paragraph 71 states the following "Experimentation on a living person may only be conducted in the prescribed manner, and with the written consent of the person after he or she has been informed of the objects of the research or experimentation and any possible positive or negative consequences on his or her health"(4).

2.2.1.2 The Department of Health (DOH) Ethics in Health Research: Principles, Structures and Processes; Research Ethics Guidelines 2004(3)

The first section of this document deals in detail with the importance of ethics in research. This document has many similarities to the Belmont report(19), but with additional ethical principles.

The 3 important principles from the Belmont report(19) are:

- Respect for persons, which highlights the issue of informed consent, as well as privacy and confidentiality.
- Beneficence, which includes protecting the individual, and incorporates minimizing risk and maximizing benefit.
- Justice, particularly distributive justice, in that the benefits and risks of research should be equally distributed amongst the various classes of society.

Additional principles specified in the DOH Ethics in Health Research: Principles, Structures and Processes; Research Ethics Guidelines 2004(3) include:

- Relevance: all human research should be relevant to both the individual and the greater community involved.
- Scientific Integrity is an essential component of all research on human subjects.
- Investigator competence and principal investigator responsibilities include sensitivity and integrity, as well as competence in performing the research. In addition safety monitoring is imperative.

- Conflict of interest applies particularly to sources of funding, which must be disclosed.
- Standard of care is described in the DOH Research Ethics Guidelines(3) as “the provision of equal standards of medical care to all during research is a requirement for demonstrating equal respect for the dignity of research participants”(3).
- Ethical review is a requirement for all human research in South Africa.

The second section discusses Ethics Committees and ethical review in detail. A discussion on participants requiring additional attention, such as children, is dealt with in great detail.

The section dealing with human tissue use and genetic research will be dealt with in paragraph 2.2.2.

2.2.1.3 Medical Research Council’s (MRC) Guidelines on Ethics for Medical Research(22)

This is a very comprehensive document covering the general principles of ethics in medical research.

The first few sections explain the MRC’s ethics policy, clarify research on humans, explain the concept of research ethics, as well as the medical justification for research.

Section 5 covers the legal and moral justification for research, discussing all of the issues pertaining to consent in great detail. This will be dealt with in chapter 3 of this research report.

These sections are followed by the conduct of research, research principles and ethical issues in qualitative research. The following two sections look at the assessment of the ethics of research and include ethics committees and how they function, and also monitoring the conduct of research. The final section covers international collaborative research and ethics guidelines for epidemiology.

2.2.1.4 Health Professions Council of South Africa (HPCSA) General Ethical Guidelines for Researchers 2008(23)

This document emphasizes the ethical duties that health researchers have, mainly in the context of human research.

The introductory section deals with various definitions, and as with all of the other guidelines, basic ethical principles in health research.

The duties that are dealt with in the document include the following:

1. Duties to research participants:
 - Acting in the best interests of research participants;
 - Respect for research participants;
 - Informed consent;
 - Research participant confidentiality;
 - Impartiality and Justice;
 - Health research and medical care;

- Potential conflicts of interest.
- 2. Duties to research colleagues and other professionals.
- 3. Duties to health researchers themselves, which include:
 - Knowledge and skills;
 - Equipment, hygiene and record keeping.
- 4. Duties to society, which include:
 - Respect for life;
 - Reporting scientific misconduct;
 - Access to scarce resources;
 - Legal regulations.
- 5. Duties to the health care profession, which is basically adhering to the guidelines for review processes.
- 6. Duties to animals.
- 7. Duties to the environment.

2.2.2 Human genetic research

2.2.2.1 The Department of Health (DOH) Ethics in Health Research: Principles, Structures and Processes; Research Ethics Guidelines 2004(3)

Section 8 and 9 of this DOH document(3) deal with the use of human tissue samples and human genetic research. In addition, section 68 of the National Health Act(4) makes provision for the Minister of Health to introduce regulations relating to tissue, cells, organs, blood, blood products and gametes. Of relevance to this research report are the following sentences:

“The Minister may make regulations regarding:

- The production, packaging, sealing, labelling, storage and supplying of therapeutic, diagnostic and prophylactic substances from tissue;
- The supply of tissue, organs, oocytes, human stem cells and other human cells, blood, blood products or gametes; the withdrawal of blood from living persons and the preservation, testing, processing, supply or disposal of withdrawn blood;
- The acquisition, storage, harvesting, utilization or manipulation of tissue, blood, blood products, organs, gametes, oocytes or human stem cells for any purpose.”(4)

The DOH guideline(3) also emphasizes that when human tissue is going to be used in research, the researchers and the human research ethics committee need to be satisfied that the research conforms to both the DOH guidelines(3) and the MRC guidelines(24). The latter will be discussed under paragraph 2.2.2.2. It is also recommended that local research ethics committees draw up guidelines to ensure that all research on human tissue conforms to the National Health Act(4).

The fundamental ethical principle that should be taken into consideration when performing research on human tissue is respect for persons. The DOH document states that the following needs to be done, in order to comply with this principle:

- “Provision to the donor of full information about the purposes of the sampling and/or an outline of the research proposal;
- The donor’s consent to the use of the sample in the experiment being planned;
- The donor’s consent to storage and future use of the sample for other research;
- Giving donors the assurance that all secondary use of donated tissue samples will require approval of an accredited research ethics committee;
- Reassuring donors that no tests of known clinical value for diagnosing or predicting disease on samples can be linked to them without their consent;
- Provision for appropriate and secure storage of tissue samples;
- Provision for and maintenance of appropriate and secure systems to ensure confidentiality and privacy in the recording, storage and release of data;
- Accountability in the care and usage of samples;
- A statement of the duration of sample storage.”(3)

Institutional responsibility is highlighted, and includes the following: “It is the responsibility of the institution or organization at which research involving human tissue samples is conducted, to ensure that all uses of human tissue samples are in accordance with the consent given by the donors.”(3) Proper detailed records must

also be kept. Samples that are not needed anymore should be disposed of “safely and sensitively.”(3)

Human tissue repositories are discussed, and described as having 3 components:

1. “Collection of samples;
2. Storage and data management in an appropriate repository;
3. Investigation of recipients.”(3)

All of these functions need to be strictly overseen by a research ethics committee.

Human genetic research generates ethical issues unique to this type of research; namely the fact that although genes are personal, they are not unique to one individual, and are shared with family members. This has many ramifications for the individual concerned, the blood relatives, and the non-blood relatives such as partners and spouses. There are potential social and cultural consequences of genetic research and the results that may be produced, as well as life-changing decisions if certain genetically-linked disease states are unearthed.

The ethical issues pertaining to human genetic research are as follows:

- Privacy and confidentiality of the stored genetic information or research results. The research protocols need to specify whether genetic information or genetic material, and any information derived from them will be stored in a potentially identifiable format, or whether they will be de-identified at all times. As with the CIOMS guidelines, the research results may not be released to the family without the individual’s informed consent.

- Informed consent and waiver of consent under certain circumstances. These will be dealt with in chapter 3 of this thesis. Genetic counselling must be offered to individuals who consent to the use of their genetic material and information for future research, as this may have unanticipated consequences.

2.2.2.2 Medical Research Council (MRC) Guidelines on Ethics for Medical Research: Reproductive Biology and Genetic Research(24)

This is a very comprehensive booklet which deals with the ethical issues pertaining to genetic screening and testing, gene therapy and cloning.

Gene therapy, genetic testing and cloning are not in the scope of this research report, but the ethical issues pertaining to genetic screening fall under human tissue and genetic research.

Genetic screening may be divided into three phases from the process point of view.

This is useful when examining the ethical aspects. They are:

1. Preparation of the participant or patient, which centres around informed consent.
2. Analysis of the genetic material, during which phase one needs to consider adequacy of procedure and confidentiality.
3. Interpretation of the analysis coupled with ensuing support programmes. This may involve the management of the findings and the impact they may have on the participant and the family.

Screening programmes for various cancers and chronic diseases that may have a genetic basis are currently the most commonly performed genetic screening in adults in South Africa.

As has been discussed, genetic counselling is an important aspect of genetic screening. There are numerous ethical principles involved as follows:

- Respect for participants and their families, as well as their decisions, “according to the principles underlying informed consent”(24);
- “Preservation of family integrity”(24);
- Full, honest and unbiased disclosure. This may prove difficult at times, if a totally unexpected result is found;
- Protection of privacy of the participant and family;
- Informing individuals that it is their ethical duty to disclose possible genetic risks to blood relatives and moral duty to the public if relevant to their safety. (This should perhaps be included in the initial informed consent in the preparation for screening?);
- To observe “the duty to re-contact if appropriate and desired”(24).

At times it may be felt that clinicians are placed in a difficult situation knowing the results of a genetic screening test. There is no law in South Africa that dictates that a clinician may disclose results to other parties such as family members, unless consented to by the participant. Privacy and confidentiality must be maintained at all times. There may be exceptional circumstances when non-disclosure may have

serious consequences. It is advised that even in these situations a serious attempt must be made to obtain the participant's consent to disclose findings to other family members.

As can be seen, in contrast to many countries, South Africa has very detailed laws, guidelines and policy statements on the issues pertaining to human genetic research, particularly the ethical principles involved. An area of concern is the complex issue of data sharing. There is a lack of a section dealing with this in the South African guidelines, unlike in the OECD guidelines(21).

CHAPTER 3

A CONCEPTUAL ANALYSIS OF AUTONOMY AND INFORMED CONSENT

Autonomy and respect for autonomy are key ethical principles involved when analyzing and understanding informed consent. These will be outlined and discussed, particularly in the South African context of human genetic research.

At the outset, it is important to note that irrespective of patients' legal and ethical right to autonomy, doctors have an ethical and legal *duty of care* to their patients. Strauss(25), the doyen of medical law in South Africa, gives the following example to clarify this: "when performing an operation or treating a patient, the procedure should be so executed with such professional skill as to avoid injuring the patient. Failure to do so amounts to a delict (civil wrong), entitling the patient to claim damages. Liability of a doctor to a patient is, therefore, not dependent on the existence of a contract between the parties or on the patient having given consent to undergo treatment"(25).

3.1 Autonomy

The following was stated by Isaiah Berlin in 1969: "I wish my life and decisions to depend on myself, not external forces of whatever kind. I wish to be the instrument of my own, not of other men's acts or will. I wish to be a subject, not an object: to be moved by reasons, by conscious purposes, which are my own, not causes which

affect me, as it were from outside. I wish to be somebody, not nobody: a doer – deciding, not being decided for, self-directed and not acted upon by external nature or by other men as if I were a thing, or an animal, or a slave....I wish, above all, to be conscious of myself as a thinking, willing, active being, bearing responsibility for my choices and able to explain them by references to my own ideas and purposes”(26).

This epitomizes the exact meaning of autonomy, which is derived from two Greek words, *autos*, meaning self, and *nomos*, to rule. In other words, autonomy means to rule oneself, and to therefore make one’s own decisions. “Autonomous actions are the outcome of deliberations and choices by rational persons in the moral sense”(27). When applied to healthcare, this means that once a patient is supplied with all of the relevant information, he or she is entitled to make the final decision on the treatment that has been recommended, even though the healthcare practitioner may not agree with the patient’s final decision.

The Roman law maxim “*volenti non fit iniuria*”(28), means if someone consents, then no harm can be done to that person. These are the original legal grounds of consent. However, ethically, doctors always relied on their own judgment about their patients’ need for information and medical care, as long as the ethical principles of beneficence and non-maleficence guided this. Hence the paternalistic approach by many health care practitioners to patients’ medical needs. In the mid twentieth century together with various civil rights movements and moves for social reform,

people and patients started demanding rights to information and the freedom to make informed choices and decisions.

The ethical principle of patient autonomy in South African medical law was judicially recognized in 1923 in the case of *Stoffberg v Elliot*(25). The judge instructed as follows: “In the eyes of the law every person has certain absolute rights which the law protects. They are not dependent on statute or contract, but they are rights to be respected, and one of the rights is absolute security to the person. Any bodily interference or restraint of man’s person which is not justified in law, or excused in law or consented to is a wrong, and for that wrong the person whose body has been interfered with has a right to claim such damages as he can prove he has suffered owing to that interference. A man, by entering a hospital, does not submit himself to such surgical treatment as the doctors in attendance upon him may think necessary; he may submit himself for medical treatment, but I am not going into that; I am not going to attempt to define the exact limits of the medical treatment, because they do not seem to me to be material in this case, but he does not consent to such surgical treatment as a doctor may consider necessary. By going into hospital, he does not waive or give up his right of absolute security of the person; he cannot be treated in hospital as a mere specimen, or as an inanimate object which can be used for the purposes of vivisection; he remains a human being; and he retains his rights of control and disposal of his own body; he still has the right to say what operation he will submit to, and, unless his consent to an operation is expressly obtained, any operation performed upon him without his

consent is an unlawful interference with his right of security and control over his own body, and is a wrong entitling him to damages if he suffers any”(28).

Thus as far back in the early 1920's in South African law, patients have had a legal right to autonomy.

This was followed by the case of *Castell v de Greef*(29) in 1994. This is considered to be the landmark case with a definitive ruling on how much needs to be disclosed to the patient in terms of informed consent, thus re-emphasizing the importance of patient autonomy. In this case it was judged that for consent to be informed, a patient needs to fully appreciate the nature and extent of the harm or risk to which he or she is consenting. This is referred to as material risk, which means a risk that a reasonable person would consider significant. If applied to anaesthesia, an example would be the complication of paraplegia following spinal anaesthesia. Although rare, this would be considered a material risk. Likewise if applied to human research, a severe drug reaction, although rare when taking certain drugs, would be considered a material risk and would warrant disclosure to the participant.

The interpretation of material risk has been considered too vague, in the legal world. The HPCSA ethical guidelines booklet on informed consent(30) uses similar terminology, quoted from *Castell v de Greef*, without specifically explaining material risk. In *Castell v de Greef*(29) the “reasonable doctor test” was also discussed. However, this leaves the determination of the doctor's obligation or duty in the hands of the medical profession. Judge Ackermann concluded that the focus needed to change from a doctor-centred approach to a patient-centred approach.

He stated: “it is clearly for the patient to decide whether he or she wishes to undergo the operation, in the exercise of the patient’s fundamental right to self-determination”(31). Thus the principle of patient autonomy was upheld.

However, this right to self-determination cannot be fully exercised if the patient is not given the correct and sufficiently detailed information.

Thomas aptly wrote in his article on the lessons learnt from this case: “The subsequent adoption of the Constitution and entrenchment of the rights to dignity and bodily integrity highlight that South African society is currently founded on the underlying values of individual autonomy and self-determination. Indeed, section 12(2)c of the Constitution expressly requires informed consent for certain medical procedures(6). The National Patients’ Rights Charter, issued in 2001 by the Department of Health, and the National Health Act 61 of 2003(4) both seek to give effect to these values”(31).

However, once again the degree of disclosure in informed consent was not fully explained.

3.2 Respect for Autonomy

Beauchamp and Childress(32) proposed the following rules, when considering respect for autonomy:

- “Tell the truth.
- Respect the privacy of others.
- Protect confidential information.

- Obtain consent for interventions with patients.
- When asked, help others make important decisions”.

Moodley makes the point that “these rules and the principle of respect for autonomy are not absolute, but rather prima facie. A prima facie rule refers to one that must be fulfilled unless it conflicts on a particular occasion with an equal or stronger rule”(33).

On the basis of these rules we therefore are obliged to indicate our respect for autonomy in the following ways:

- Obtain informed consent;
- Confidentiality;
- Truth telling;
- Communicate effectively.

The HPCSA has produced a document entitled “General ethical guidelines for the health care professions(34)”. Section 2 lists the core ethical values required of health care practitioners. They include the following:

- Respect for persons;
- Best interests or well-being: non-maleficence;
- Best interests or well-being: Beneficence;
- Human rights (recognition of);

- Autonomy: “Health care practitioners should honour the right of patients to self-determination or to make their own informed choices, and to live their lives by their own beliefs, values and preferences”.
- Integrity, truthfulness, compassion and tolerance;
- Confidentiality;
- Justice;
- Professional competence and self-improvement;
- Community.

Section 4 deals with duties of health care practitioners, describing a duty as an obligation. Duties are described as being ethical, legal (duties imposed by common and statute law) or both, and form part of their personal, social, professional and/or political lives.

3.2.1 Informed consent as applied to medical treatment

Carstens and Pearmain in their book *Foundational Principles of South African Medical Law* stated the following in the chapter on grounds of justification for medical interventions and other defenses in medical law(28): “Informed consent is undoubtedly the foundation or core of the patient / doctor relationship, emanating from the law of obligations and underscored by ethical considerations”.

The application of the doctrine of informed consent is often controversial, because of the understanding and perceptions associated with the doctrine, and the fact that many health care practitioners are not very comfortable with it. In addition, decisions

in courts on the issue appear inconsistent. However, once the doctrine of informed consent was incorporated into our South African law, it necessitated a paradigm shift from medical paternalism to patient autonomy. This is exactly what Judge Ackermann stated in *Castell v de Greef*(29).

One of the fundamental issues that was highlighted in this case was the degree of disclosure required in order for consent to be informed to allow for full patient autonomy.

If one considers the law of contract, (which is what the informed consent agreement is considered in law), the following holds:

- “The patient’s consent will be obtained with regard to treatment that is administered to him or her prior to the administration of such treatment;
- The provider undertakes to render the health services in accordance with the patient’s consent and *on the basis of the information supplied to the patient in order to obtain that consent*”(28).

In *Oldwage v Louwrens*(28) in 2004, Judge Yekiso found that the plaintiff had not been given sufficiently detailed information in order for the consent for surgery to have been informed, and that this constituted a violation of the plaintiff’s right to bodily and psychological integrity, and was therefore assault. This decision was overturned on appeal, and has been debated and contested in many subsequent cases.

Informed consent has been described as a process, consisting of the following elements(32):

- “Threshold elements: Competence to understand and decide, and voluntariness in deciding.
- Information elements: Disclosure of a plan, recommendation of that plan and understanding the information and plan.
- Consent elements: Decision against or in favour of the plan, and subsequently authorising it”.

In 1991, prior to the advent of our South African Constitution and National Health Act, Strauss simplified the process, and proposed “four golden rules(25)” for obtaining informed consent:

- “Obtain consent from the person legally competent to give consent;
- Obtain informed consent;
- Obtain clear and unequivocal consent;
- Obtain comprehensive consent.”

The current HPCSA guidelines include all of these.

The HPCSA has published guideline booklet 9, titled: “Seeking patients’ informed consent: the ethical considerations(30)”. This is a comprehensive document, which highlights the essential components when seeking informed consent from patients. These are based on ethics and South African law.

The following components of informed consent are discussed:

- Provide the patient with sufficient information, as is laid down in the National Health Act(4). The following needs to be disclosed to patients:
 - “Their patient’s health status except in circumstances where there is substantial evidence that the disclosure of the patient’s health status would be contrary to the best interests of the patient;
 - The range of diagnostic procedures and treatment options generally available to the patient;
 - The benefits, risks costs and consequences generally associated with each option; and
 - The patient’s right to refuse health services and to explain the implications, risks and obligations of such refusal.
 - Patients have a right to information about any condition or disease from which they are suffering. This information should be presented in a language that the patient understands and in a manner that takes literacy into account”.
- The issue of withholding information is discussed in detail, referring to significant risks as material risks. Of relevance is the following paragraph:

“Health care practitioners should not withhold information necessary for decision making unless they judge that disclosure of some relevant information would cause the patient serious harm. In this context, serious harm does not mean that the patient would become upset or decide to refuse treatment.”
- The consent must be comprehensive, exploring all possible eventualities.

- It is recommended that the health care practitioner obtains the consent, but if this task is delegated, it must be delegated to someone who acts in accordance with the HPCSA booklet 9.
- Health care practitioners must ensure voluntary decision-making, and not superimpose paternalistic consent-giving, incorporating whatever the practitioner thinks that the patient should decide.

These excerpts from the National Health Act(4) and the HPCSA guidelines(30) are more specific than *Castell v de Greef*(29) in the extent of disclosure that is required, in order for consent to be informed.

In addition, the guidelines emphasise that the process of informed consent can only occur between a health care practitioner and an adult patient (older than 18 years) who has the mental capacity to give consent.

3.3 Autonomy and respect for autonomy as applied to human research

Research on human subjects in South Africa is guided by the Research Ethics Guidelines(12) produced by the National Department of Health. This document is informed by various other documents such as the National Health Act(4) and Declaration of Helsinki(18). Other guidelines include the Bill of Rights of the Constitution of South Africa(6), the National Health Act(4), guidelines for good clinical practice(7) and also the ethical guidelines of the Health Professions Council of South Africa(23).

The fundamental issue when looking at the ethics of human research is to ensure that vulnerable people are protected from exploitation.

Ethics of research is based on principle-based ethics(11), which comprises the following principles:

- Autonomy, which deals specifically with the issues of consent and confidentiality;
- Beneficence and non-maleficence, looking at a positive risk-benefit ratio;
- Justice, which is largely distributive justice, ensuring research subject dignity and protection of rights in the context of the greater good.

In South Africa we have ethical principles as outlined in the Department of Health's Ethics in Health Research document(12) that need to be followed, and these include the fundamental principles outlined above, with additional supporting principles(11), namely:

- Relevance, indicating that the research needs to be relevant to the individual on whom the study is conducted, and also to the community or the country(11).
- Scientific integrity, meaning that there needs to be sound science as the basis of the research(11).
- Investigator competence, which embraces integrity as well as competency in the research process, by the principal investigator(11).
- Informed consent, which. is a key factor in human research, indicating respect for persons and their rights(11)

- Privacy and confidentiality, which needs to be respected in terms of an individual's right to protect personal records, as well as the confidentiality of the data that is collected(11).
- Risks and benefits refer to the risks to the individual, balanced against the benefits to both the individual and the community(11).
- Justice, which addresses the benefits following on from the research, such as post-trial access to drugs(11).
- Ethical review by a human research ethics committee needs to be carried out prior to all human research(11).

3.3.1 Informed Consent for human research

“Informed consent in the context of medical research and human experimentation is now firmly entrenched in section 12(2)c of the Constitution of South Africa(6), which states that everyone has the right to bodily and psychological integrity, which includes the right not to be subjected to medical research or scientific experiments without his or her informed consent”(28). In addition, chapter 9 of the National Health Act(4) deals with the issues pertaining to informed consent for research on human subjects.

With reference to the DOH principles(3), the process of informed consent and confidentiality indicating respect for the autonomy of the research subject is often treated superficially, but is in fact one of the cornerstones of research. In addition,

the issue of disclosure is fully described, in comparison with the disclosure for consent for medical treatment alluded to in the National Health Act(4).

The process of informed consent involves the following(11):

- Full and prior disclosure of all aspects of the research (how it differs from clinical practice, nature, duration and purpose) to the research participant, including possible risks and benefits. Other aspects of the study that need to be discussed are reimbursement or compensation (if any), and whether or not the participant will have access to the treatment or intervention afterwards. In addition, the participant needs to understand that he/she may withdraw from the study at any time.
- Total confidentiality and the means by which this will be maintained, and whether there is any potential breach of confidentiality. For example, all personal identifiers such as name, identity number, address, date of birth and others must be protected.
- The process of obtaining informed consent must entail full understanding of the proposed research, including all questions being fully answered by the researcher in a manner and language understood by the participant. As is stated in the CIOMS(35) guidelines, “the investigator must bear in mind that the prospective subject’s ability to understand the information necessary to give informed consent depends on that individual’s maturity, intelligence, education and belief system. It also depends on the investigator’s ability and willingness to communicate with patience and sensitivity”. Britz and le Roux-

Kemp highlight this issue in their article in the South African Medical Journal(36) by stating: “A once-off meeting with the researcher may be insufficient for the prospective participant to comprehend the research, since informed consent requires sufficient time for understanding. Language barriers are common in a culturally diverse country like South Africa. Ethically and legally the language used to discuss informed consent must be one that participants choose and feel comfortable with”.

- Informed consent needs to be totally free and voluntary. As is stated in the South African Department of Health Research Ethics guidelines(12), “consent may not be induced by fear, force, threats, duress, coercion, compulsion, deceit, fraud, undue influence, perverse incentives or financial gains”.
- Research participants must have the capacity to give informed consent. In South Africa, the Bill of Rights of the Constitution(6) states that capacity from the age point of view is 18 years. Capacity also entails being of sound mind. Special guidelines are also in place for research that is being performed as part of emergency treatment(12) in an individual who would have capacity under normal circumstances.

Another issue that also warrants discussion when considering informed consent of research participants is that some of the challenges to the research process in the context of multi-centre studies must be declared. These are parameters such as the cultural environment of the participant, the socioeconomic context of the participant,

participant vulnerability and therapeutic misconception. The latter is common, where the research participant believes that the purpose of the clinical trial is to benefit the patient rather than the acquisition of data for scientific knowledge.

Finally, when dealing with informed consent, there is the issue of deception of participants, of concealment or of covert observation. The South African Department of Health guidelines(12) state that “ as a general principle, deception of identifiable participants, concealment of the purposes of research or covert observation are not considered ethical because they are contrary to the principle of respect for persons and the obtaining of informed consent”. There are circumstances, however, such as in studies of human behaviour, where concealment is necessary. Under these circumstances, special criteria need to be fulfilled(12).

3.3.2 Research vulnerabilities

The issue of research vulnerability falls into the domain of respect for autonomy, when one examines human research. This discussion is particularly pertinent in the South African context(11). All participants in research studies need to be protected against exploitation and other forms of harms, and those who fall into the vulnerable groups need additional protection as per the CIOMS guidelines(35).

There are six categories of vulnerability, which are as follows(11):

1. Cognitive, which describes an individual's ability (or lack thereof) to freely give consent to participate in a study. Some of these considerations have already been alluded to. There are 4 types of cognitive vulnerability, which include:
 - People not of sound mind (dementia, other mental illness, mental retardation);
 - Children, which is defined as being less than 18 years of age;
 - Adults undergoing emergency treatment which is part of a research study;
 - Participants with language barriers, who may not fully understand the research.
2. Juridic vulnerability, which describes the investigator authority or power over the research participant, limiting the participant's ability to give proper informed consent. Potential participants referred to in this group include government officials, prisoners, military personnel, students, institutionalized people and similar, all of whom may feel pressurized into participating.
3. Deferential vulnerability, which is a type of vulnerability where participants feel obligated to participate because of cultural or social norms or pressures. An example of this is a cultural environment where a woman feels obligated to participate in order to please her husband. Community leaders are often able to assist in these circumstances.
4. Medical vulnerability, where the research participant may be desperate for treatment for a certain condition, such as cancer or HIV/Aids, and may have

a “therapeutic misconception” about the value of the actual research itself. A subgroup of medical vulnerability is research on fetuses. In South Africa this may only be performed(12) if the research is of minimal risk to foetus and mother. In addition, both parents must be legally competent and have already given informed consent.

5. Allocational vulnerability, which often arises in disadvantaged population groups, where individuals may feel pressurized to participate because of social or financial distress. The incentives offered to participate in the research may appear as help to alleviate this. There is a grave concern about unfair exploitation in this population group.
6. Infrastructural vulnerability, which occurs when there are inadequate resources in a community to carry out the research. Examples of this are the requirement for a telephone, for electricity, or for access to a health care centre which may be some distance away.

In addition to individual vulnerabilities and potential harms, socially vulnerable groups or communities may be adversely harmed as a result of the research itself, or possibly the dissemination of the results of the research. These “group” harms can include physical, economic, social (stigmatization), legal and psychological damages. Prior to conducting research studies that have the potential to cause harm to a group or community, it is advised to consult with the community beforehand, in order to appreciate the potential for group harms, as well as benefits.

3.4 Autonomy and respect for autonomy as applied to human genetic research

The general ethical considerations which apply to research in human participants apply equally to human genetic research. However, there are additional ethical considerations, (of which the first four apply to autonomy), which include the following(11):

- Concerns about discrimination/stigmatization of individuals and communities;
- Patenting and the consequent commercial interest may retard or confine “discoveries” from the research point of view;
- Reducing human beings to their DNA sequence may have serious and disparate consequences. The research may yield important information for family members which may have legal, moral, social and biological consequences. The results may even be useless, with the research causing unnecessary stress and anxiety. Unrelated family members such as spouses may have an additional interest because the results may ultimately involve offspring;
- The possible lack of respect of values, traditions and the integrity of families and individuals, with a total lack of involvement of the community;
- The ethical principle of justice plays a key role in the following ways:
 - ✓ “Compensatory justice, meaning that the individual, group or community should receive fair compensation for contribution/s;

- ✓ Procedural justice, whereby the decisions that are made about benefit sharing are impartial and exclusive;
 - ✓ Distributive justice, meaning that there needs to be equitable allocation and access to resources”.
- Benefit sharing in a variety of ways which include therapeutic, monetary, capacity building and new information generation(11).

3.4.1 Informed consent for human genetic research

When one considers human genetic research, one needs to apply these same aforementioned ethical principles. Once again the process of informed consent (from the individual, the family or community) is a vital ethical component, which raises many concerns and unanswered questions at this time.

From the point of view of informed consent, the whole issue of individual autonomy and confidentiality needs to be re-visited, as tissue and genetic research often extends beyond the genes of one individual research participant. Where others, such as family or a cultural group are involved each research participant needs full disclosure, confidentiality, understanding and appreciation, voluntariness and capacity, as has been discussed previously.

Genetic research requires a whole different mindset.

The differences arise with the manner in which the biological samples are taken and stored, and the people who have access to them. The main differences are as follows(37):

- “Those obtaining the samples may be intermediaries who are not involved in the actual research;
- The samples stored can be used for a multitude of different research studies. This includes future studies which cannot necessarily be specified at the time of taking the sample;
- Whether or not samples are identifiable is a key factor:
 - If research results are disclosed with identifiable samples it is an invasion of the donor’s privacy, unless the donor has given permission for this. This could lead to stigmatization and genetic discrimination;
 - If unidentifiable samples are used, the research may be such that the donor would not approve of it for cultural, religious or moral reasons”. A simple example is stigma that might be attached to a community; for example Huntington’s chorea.

The issue of informed consent in this environment is very problematic in terms of conventional informed consent for conventional human research. As has been alluded to previously, protecting patient autonomy is crucial, but at the same time genetic research is supposed to be for the greater societal good. With genetic research one has to ask the question: “Is it really possible to obtain proper informed consent?” or is it just permission, with disregard for patient autonomy, accompanied by trust that the genetic research is for the greater good?

The expert conference that was held in Cape Town in December 2012 to discuss changes that are needed in the Declaration of Helsinki(5) discussed the issue of consent for genetic research, amongst other issues. Tasse et al in the European Journal of Human Genetics(38) discussed various solutions to the problem of informed consent, particularly with retrospective access to data.

Kirchhoffer and Dierickx in an article on consent for tissue and genetic research(39) emphasized the importance of human dignity (as is enshrined in our South African Constitution(6)) when considering guidelines for informed consent and genetic research. The National Health Act(4) reiterates that health legislation must take into account section 10 of the Bill of Rights of the Constitution(6), which emphasizes the need to respect and protect people's dignity. Chapter 9 of the National Health Act of South Africa therefore insists that informed written consent be given prior to research on human subjects.

Human tissue biobanks

For purposes of clarity, human tissue biobanks can be considered as “an organized collection of human biological material and associated information or data for one or more research purposes”(2). These biobanks usually incorporate cryogenic storage facilities for the samples, and may range in size, with reference to the number of samples that are able to be stored. The advantages of using biobank samples for genetic research instead of conventional sampling methods for research are as follows:

- Secure sources of well-stored research material;
- Unlimited numbers of studies can be performed;
- Many different disciplines can be involved;
- Research is less costly;
- International collaboration is enabled.

However, as with many things in life, these major advantages to researchers come at a considerable ethical “cost” to the individual donors of genetic material. In addition, there are associated legal and social issues, which are being grappled with all over the world.

Kirchhoffer and Dierickx(39) further emphasize that there are features of biobanking that might lead people to refuse to be involved in biobank research on the basis of human dignity in the following circumstances:

- Biobanking cannot guarantee what type of research the samples will be used for in the future. There is no guarantee that the research results will not be used for malicious or profit orientated purposes, resulting in possible genetic discrimination;
- Biobanks store human tissue and genetic material, and for religious reasons (being created in the image of God), people may feel that biobank research is an affront to dignity; (This is a personal opinion)
- Biobank research may receive opposition because it could be the basis for a trade on body parts or body tissues, the latter being closely governed by our National Health Act(4);

- Of particular interest is the use of biobanks for the storage of stem cells, which “contribute to innate healing and harbour a promising role for regenerative medicine. Stem cell banking through long-term storage of different stem cell platforms represents a fundamental source to preserve original features of stem cells for patient-specific clinical applications”(40). Apart from opening up fantastic opportunities for medicine, healing and research, this also lends itself to possible abuse and exploitation, with stem cells being punted at huge cost as a possible elixir to immortality.

This research report will discuss human genetic research, specifically pertaining to human tissues and genetic screening and testing, including samples stored in biobanks or other similar human tissue repositories.

How then, in the context of South Africa, with our Bill of Rights and our National Health Act, are we going to manage to obtain informed consent with full disclosure in human genetic research?

Various authors have suggested the following possible solutions to the consent issue(38, 39):

- Broad or blanket consent, which would allow the use of a sample for genetic research in general, including future unspecified projects. New consent would then be necessary if the next research project differs from the wide ambit of the original. From the perspective of human dignity, the case for broad consent “explicitly acknowledges the existential importance of being

able to decide on morally meaningful matters for oneself. In addition the belief that one can contribute to the good of others plays a role”(39);

- Multilayered or tiered consent, with secondary use as another alternative. In this case a comprehensive consent form is used, allowing the genetic sample owner to choose from a number of options in advance, as well as specific research domains. The latter is covered by a “secondary use statement”. This form of consent has been described as costly and complex;
- Presumed consent, where opting out is a totally different approach to informed consent, and is currently in use in some developed countries. Samples are banked for research because it is believed that the donors of the samples would be satisfied with this. There is an accompanying “opt out” clause, and ethically this form of consent is justified by “participating for the good of the dignity of everyone in the population”(39);
- Re-contact/re-consent, which is very costly and labour intensive. It may also be seen as an invasion of privacy, having to be recontacted for every new study. Nevertheless, it probably fulfils the criteria of fully informed consent with disclosure.
- Waived consent has been introduced by some Research Ethics Committees where re-contact consent has been impossible. Strict criteria need to be applied in these circumstances in order to prevent abuse.
- Recently the concept of Dynamic consent was introduced by a research group at Oxford University(41). It entails “an interactive personalized interface that allows participants to engage as much or as little as they

choose and to alter their consent choices in real time. It allows the same samples/information to be (re)used with the knowledge and consent of the individual, enabling him/her to give and revoke consent to the use of their samples and information in response to their changing circumstances”.(41) This form of consent is not paper based, but uses a technology-based platform, and is probably the only type of consent that takes into account full disclosure, as well as the option to revoke the consent in real time.

The literature is seemingly unanimous in allowing tissue sample donors to withdraw their consent and their samples at any time. This raises another ethical issue in that this is not always possible, as samples are exchanged and data are sent all over the world. In addition, samples may undergo transformation into specific cell lines, which can also be duplicated and exchanged. This challenges the supremacy of consent, autonomy and human dignity.

Other ethical and legal issues that require consideration for consent in genetic research are as follows:

- Confidentiality is the predominant ethical concern with regard to identifiability. When giving consent, tissue sample donors need to understand the concept of identifiability and the different levels of anonymisation of samples.
- Anonymity of the individual does not always guarantee anonymity of the group or community. There are different levels of anonymity, which seem to

be a non-exhaustive list of terms(42), such as anonymised, de-identified and coded, which the donor needs to understand, as part of the consent process.

- Benefit sharing is a reality associated with genetic research. It includes the sharing of information, licensing, capacity building and the sharing of financial benefits. Benefit sharing agreements need to be drawn up before a study begins, particularly where huge multinationals may be involved with the potential for exploiting vulnerable groups or populations. In addition, the benefit sharing must be bidirectional, with both parties benefiting, in the following potential areas:
 - Information sharing, particularly informing the research participants of important scientific discoveries;
 - Sharing information from the study, only if there is clinical benefit, preferably with the donor's own doctor involved (with the donor's prior consent);
 - Financial benefits need to be shared, and this must be decided on in a binding legal agreement beforehand.

An important issue that has not been explored when considering ethical and legal issues in genetic research is that of closure of the facility where human genetic tissue is stored(11). May one sell the tissue samples? May one destroy them? Does one need to contact the donors of the samples? If the donors have died, may the family make the decisions concerning the samples? These are all important issues impinging on autonomy and informed consent.

3.4.2 South African guidelines on informed consent for genetic research

As discussed in chapter 2, the DOH Ethics in Health Research(3) document highlights the following when considering informed consent for genetic research:

- “Provision to the donor of full information about the purposes of the sampling and/or an outline of the research proposal;
- The donor’s consent to the use of the sample in the experiment being planned;
- The donor’s consent to storage and future use of the sample for other research;
- Giving donors the assurance that all secondary use of donated tissue samples will require approval of an accredited research ethics committee;
- Reassuring donors that no tests of known clinical value for diagnosing or predicting disease on samples can be linked to them without their consent;
- Provision for appropriate and secure storage of tissue samples;
- Provision for and maintenance of appropriate and secure systems to ensure confidentiality and privacy in the recording, storage and release of data;
- Accountability in the care and usage of samples;
- A statement of the duration of sample storage.”(3)

Institutional responsibility is highlighted, and includes the following: “It is the responsibility of the institution or organization at which research involving human

tissue samples is conducted, to ensure that all uses of human tissue samples are in accordance with the consent given by the donors.”(3) Proper records must also be kept. Samples that are not needed anymore should be disposed of “safely and sensitively.”(3) This does not mention what needs to be done if the donor has died. The DOH guideline document(3) specifies that a research ethics committee should oversee this functioning of human tissue repositories, especially the process of informed consent.

The issue of informed consent for genetic research is dealt with in great detail in the DOH document. The following relevant issues are specified:

- Participants may refuse consent without prejudice, and do not need to feel obliged to participate to serve the interests of his/her family;
- If genetic samples are de-identified, participants will not be able to receive results. If not de-identified, the participant has a choice on whether to receive results that relate to the individual;
- If the research may have implications for other family members, consent from participants for this disclosure will be obtained beforehand;
- If relatives are required to participate in the research, the original participant will be consulted first, bearing in mind potential family dynamics and relationships;
- Disposal of genetic material at completion of the research needs to be discussed in detail with participants;
- “Genetic material and information may have uses unrelated to research approved by a research ethics committee. Participants should be advised

that their material and information will not be released for other uses without their consent, unless required by law. If consent is given, the duration of storage should be specified. If consent for future use is refused, the genetic material and information should be disposed of at the end of the research, once the sample storage and record-keeping requirements of good research practice have been met”(3).

This is very specific consent, and falls into the domain of multi-layered consent, as opposed to the more commonly used blanket consent.

The CIOMS international guidelines have an added comment on informed consent, as follows: “renew the informed consent of each subject in long-term studies at pre-determined intervals, even if there are no changes in the design or objectives of the research”(9). This would ensure that participants are still aware of the importance of autonomy and informed consent, and would allow a formal setting should they wish to withdraw consent.

Waived consent has been mentioned in the general discussion on informed consent in this context. The DOH document states that a research ethics committee may waive the participants consent, with or without conditions, subject to the following:

- “The nature of existing consent relating to the collection and storage of the sample;

- The justification presented for seeking waiver of consent, including the extent to which it is impossible or difficult or intrusive to obtain consent;
- The proposed arrangements to protect privacy, including the extent to which it is possible to de-identify the sample;
- The extent to which the proposed research poses a risk to the privacy or wellbeing of the donor;
- Whether the research proposal is an extension of, or closely related to, a previously approved research project;
- The possibility of commercial exploitation of derivatives of the sample and relevant statutory provisions”(3).

The MRC document on ethics for medical research(22) and the MRC guidelines for genetic research(24) both discuss informed consent in great detail.

Consent is described as being absolutely essential, and “in the absence of compelling reasons to the contrary, written information and consent forms should be the norm for health research interventions”(22).

The pre-requisites of consent are as follows:

- The capacity of a person to consent is described as being someone who is legally and factually capable of consenting.
- Informed consent must include the participants understanding of what they are consenting to, and he/she must have full participant autonomy, without investigator paternalism (the researcher knows best). Participants must

understand the right to refuse or withdraw, and must give clear, unequivocal, free and voluntary comprehensive and revocable consent.

- Investigators have a duty to fully disclose the following:
 - The exact nature of the research in great detail;
 - The nature, scope and possible consequences;
 - The anticipated benefits and possible disadvantages;
 - The foreseeable prognosis, additional risks, dangers and complications;
 - The possible personal benefits, which may include financial.
- Genetic research also requires consent for genetic counseling, which has its own specific detailed guidelines.

The MRC guideline for genetic research states the following:

“Informed consent is an accepted norm in the clinician-patient relationship, implying the patient’s knowledge of the major characteristics of their medical disorder, an understanding of the test or procedure they are to undergo, the limitations of the test or procedure, and the possible consequence of their participation in the test or procedure followed by their agreement, or not, to undergo the test or procedure.

This term includes a right on the part of the participants or patients to be informed of risks not actually related to the medical impact of the test or procedure, including possible socio-economic consequences of an unfavourable test result, such as loss of health or life insurance, refusal of employment, discrimination by schools,

adoption agencies, etc. should where applicable, be included under the description of risks”(24).

This illustrates the extent of the detail of the risks and possible consequences that participants need to consider, prior to consenting to genetic research.

And finally, The HPCSA General Ethical Guidelines for Health Researchers(23) discusses the health researchers’ duties to research participants. Included in these duties are:

- Acting in the best interests of research participants;
- Respect for research participants
- Research participant confidentiality;
- Impartiality and justice;
- Informed consent.

Informed consent is broken down into many components which have been covered by the DOH guidelines(3) and both MRC guideline documents(22, 24). Issues that are highlighted are the following:

- Research participants need sufficient information in a suitable language;
- The well-being of the participants rests with the researcher;
- Consent must not be coerced or obtained under duress;
- Information must not be purposefully withheld;
- Informed consent should be regarded as an ongoing process, giving the participants opportunities to withdraw;

- Consent must be adequately documented.

In conclusion, we have come a long way since *Stoffberg v Elliot*(25) and *Castell v de Greef*(29) from the point of view of informed consent. Our South African Constitution, the National Health Act and all of the national research guidelines and regulations go a long way in protecting vulnerable research participants, particularly in the arena of genetic research.

CHAPTER 4

INVESTIGATION OF CONSENT DOCUMENTS IN CLINICAL TRIALS WITH A GENETIC COMPONENT EVALUATED DURING ONE YEAR.

4.1 Objective

To carry out a pilot study retrospectively analyzing the type of consent given by adults participating in genetic research.

The reason for a pilot study is that this research has not been done previously, and it was necessary to obtain a “feel” for the type of information available in order to guide future research.

4.2 Methodology

4.2.1 Study design

This study was a retrospective descriptive study of sponsored clinical trial applications submitted to the Human Research Ethics Committee (Medical) of the University of the Witwatersrand [HREC(Medical)] through the Wits Health Consortium (WHC). The WHC is a not for profit organisation and a private company, wholly owned by the University of the Witwatersrand. The Ethics Secretariat at the WHC manages sponsored clinical trial applications for the HREC (Medical). (See at www.witshealth.co.za/ethics/)

4.2.2 Ethical considerations

4.2.2.1 Ethics approval

This study was approved by the Human Research Ethics Committee of the University of the Witwatersrand before data were collected. **(Appendix A)**

4.2.2.2 Postgraduate committee approval

This study was approved by the Postgraduate Committee of the Faculty of Health Sciences of the University of the Witwatersrand. **(Appendix B)**

4.2.2.3 Declaration of Helsinki

The research was conducted in keeping with the principles as described in the Declaration of Helsinki (2013)(18).

4.2.3 Study site

The study site was the Wits Health Consortium (WHC). The records were those in which patients had been asked to participate in genetic research, in particular, the documentation on informed consent. The data are stored in a database purpose-designed by the WHC for the management of clinical trials.

4.2.4 Study population

The study population comprised all patients who participated in genetic research through the Wits Health Consortium during the specific dates in section 4.2.5.

4.2.5 Study period

The records that were studied were from clinical trials that were initiated between the 1st January 2013 and the 31st December 2013.

4.2.6 Sample population

No patient records were studied. The research protocols for studies that had been submitted to the Wits Health Consortium were used.

4.2.7 Exclusion criteria

Studies that were not approved by the Wits Research Ethics Committee were excluded, as well as studies involving paediatric patients. All other studies were included.

4.2.8 Data Collection

After discussion with a supervisor and a statistical advisor (Emeritus Professor LP Fatti) the following data were collected: **(Appendix C)**

- Protocol number
- Genetic sample, site of storage and the length of time of storage
- Specific mention of data sharing
- Type of consent
- Complexity of language used for consent

- Benefit sharing

4.2.9 Data analysis

The data were entered into an Excel spread sheet and analysed using descriptive statistics.

4.2.10 Funding

The study was self-funded.

4.3 Results

4.3.1 General comments

Ninety-two protocols were studied. 30 had an adult storage component, of which 19 were to be subjected to some form of genetic study.

The balance (sixty-two) were either studies that were rejected or withdrawn, involved children, or had no storage component for genetic research.

What was striking about the protocols with a storage component (with or without genetic experimentation), was the very large variation in the types of consent, the documentation, complexity of language used, and the components of the genetic research. These components varied from actual DNA research, to sample storage, with often limited information on the site of repository and length of storage time, as well as the actual genetic research. It occasionally included the issue of data sharing, but this too was inconsistent.

4.3.2 Results: Descriptive statistics on the protocols for 2013

These will be discussed under the following headings:

1. A breakdown of all of the protocols studied.
2. Details on the protocols with a storage component.
3. The types of informed consent.

The following table illustrates all of the protocols from 2013 that were used for this study. The sample storage column indicates the number of the stored samples that were used for genetic testing in brackets.

Table 4.1 Overall breakdown of the protocols

Month	Total	Number with sample storage (genetics)	Number without storage, genetics	Paediatric	Study withdrawn
January	5	3 (2)	1	1	0
February	9	7 (3)	1	0	1
March	10	3 (3)	5	1	1
April	8	1 (0)	6	1	0
May	9	1 (1)	6	2	0
June	9	3 (1)	3	1	2
July	2	1 (1)	0	1	0
August	13	3 (2)	6	3	1
September	4	0 (0)	2	2	0
October	9	4 (2)	2	2	1
November	14	4 (4)	7	3	0
Totals	92	30 (19)	39	17	6

4.3.2.1 The breakdown of all of the protocols

As can be extrapolated from table 4.1, sixty-two (67%) of the protocols submitted to the Wits Health Consortium in 2013 did not include a storage component, and therefore were not involved in genetic research. The breakdown is as follows:

- Thirty-nine (42%) protocols involved research in adults where no samples were to be stored, and no genetic research was to be performed.
- Seventeen (18%) involved research in children and were therefore excluded.
- Six (7%) of the protocols submitted were either declined or withdrawn.

4.3.2.2 Details on the protocols with a storage component.

The 30 protocols (listed in table 4.2) with a storage component were studied in detail. They were given a study number, and an attempt was made to elucidate the following:

- The type of sample for storage, an indication of whether genetic testing would be done, the site of storage, and the length of time of storage;
- Whether there was specific mention of data sharing;
- The complexity of the English language used for the consent documentation;
- The type of consent that was required for the genetic research component.

The different types of consent have been described in chapter 3 of this research report.

Table 4.2 Protocols with a storage component, indicating whether genetic testing would be done (REC = Research Ethics Committee; b.m. = bone marrow)

Study number	Storage sample	Genetic study	Site of storage	Length of time	Data sharing	Type of consent	Simple English
001	Blood	No	USA	15 years	Not stated	Tiered	Yes
002	Blood	Yes	USA	5 years after study done	Yes	Presumed with REC later	No
003	Blood	Yes	UK plus 3 rd party	15 years	Not stated	Blanket, REC later	No
004	Blood	No	Germany	15 years	Not stated	Blanket	Yes
005	Blood and tissue	Yes	Not stated	Not stated	Not stated	Blanket, REC later	No
006	Blood, urine, stool	Yes	Switzerland DNA testing USA	Not stated	Not known	Blanket plus REC;	No
007	Blood, urine, stool	No	Switzerland	Not stated	Not stated	Blanket	No
008	Blood	No	USA	Sample destroyed after analysis	No	Specific	Yes
009	Tumour Blood	No	Germany	15 years	Not stated	Tiered	Yes
010	Blood	Yes	Not stated	Not stated	Not stated	Blanket; REC later	No

Study number	Genetic sample	Genetic study	Site of storage	Length of time	Data sharing	Type of consent	Simple English
011	Blood	Yes	Belgium	20 years	Not stated	Blanket; REC later	Yes
012	Blood	Yes	Belgium	20 years	Not stated	Blanket; REC later	Yes
013	Blood	Yes	Not stated	15-20 years	Not stated	Specific; REC later	No
014	Blood, urine, b.m.	No	Not stated	Not stated	Not known	Specific; REC later	Yes
015	Blood, cells	Yes	The World	15 years	Not stated	Blanket	No
016	Blood	Yes	SA and USA	3-15 years	Yes	Blanket; REC later	No
017	Blood, cells	No	Not stated	Not stated	Not stated	Specific	No
018	Cells	No	Not stated	Not stated	Not stated	Specific	No
019	Blood	Yes	Not stated	Not stated	Yes	Blanket; REC later	Yes
020	Blood	Yes	USA	Not stated	Not stated	Specific	No
021	Blood, cells	Yes	Brussels	15 years	Not stated	Specific	Yes
022	Blood, cells	No	Not stated	10 years	Not stated	Specific; REC later	No

Study number	Genetic sample	Genetic study	Site of storage	Length of time	Data sharing	Type of consent	Simple English
023	Blood, urine	Yes	USA	Not stated	Not stated	Blanket; vague REC later	No
024	Blood	No	Belgium, Switzerland	Not stated	Not stated	Specific; REC	No
025	Blood	No	USA	One year	Not stated	Specific; REC	No
026	Blood	Yes	USA	20 years	Data kept; sharing not stated	Blanket; vague REC later	No
027	Blood	Yes	RSA, then not specified	15 years	Not stated	Specific; vague	No
028	Blood, tissue	Yes	Switzerland USA	15 years	Not stated	Blanket; vague	No
029	Blood	Yes	The World	15-20 years	Not stated	Blanket	No
030	Blood	Yes	USA	Not stated	Yes	Blanket	No

4.3.2.3 The type of sample for storage, whether genetic testing would be done, the site of storage and the length of time of storage

In 29 of the 30 samples (96%), blood was one of the components that was to be stored. Other samples included cells, tissue, bone marrow, urine, stool and tumour. Nineteen of the 30 samples (63%) were to be subjected to genetic testing, which in most protocols was not very specific and not described in detail.

The storage site was not always specified, and usually involved Europe and/or the United States of America (USA). Some of the protocols that did not specify the site stated the following: “storage at a laboratory designated by the sponsor”. The breakdown is as follows:

- Nine of the 30 in the USA;
- Eight of the 30 in a country in Europe;
- Four of the 30 would be stored in more than one country;
- In 9 of the 30 protocols, the site of storage was not indicated.

The length of storage time ranged from one year to 20 years, and was not specified in 12 of the protocols (40%). In one protocol the samples would be destroyed immediately after testing.

4.3.2.4 Specific mention of data sharing

Data sharing was specified in only four (13%) of the protocols. Having said that, data storage was mentioned in one, but whether this was to be shared remained unspecified.

4.3.2.5 The complexity of English language used for obtaining consent

Simple English (at the level of comprehension of school grade 10) was used in nine of the 30 (30%) protocols. This is of concern when one takes into account that South African lay persons are supposedly giving informed consent for sample storage, with or without genetic testing, and may not have understood the intricacies of the consent that was required of them. This is particularly so if the discussion was not in a language of their choice. It would appear that the various pharmaceutical companies who sponsor the research, are given a specific format for the way in which their consent forms are worded, depending on the country of origin of the head office of the company. This results in inconsistency when taking into account all of the principles specified in our various laws and regulations, as well as the way in which the informed consent document is worded.

4.3.3 Type of consent

As was previously discussed in chapter 3, the commonly used types of consent for sample storage with or without genetic research are as follows:

- Broad or blanket consent, which would allow the use of a sample for genetic research in general, including future unspecified projects. New consent would then be necessary if the next research project differs from the wide ambit of the original. From the perspective of human dignity, the case for broad consent “explicitly acknowledges the existential importance of being able to decide on morally meaningful matters for oneself. In addition, the belief that one can contribute to the good of others plays a role”(39).

- Multilayered or tiered consent, with secondary use as another alternative. In this case a comprehensive consent form is used, allowing the genetic sample owner to choose from a number of options in advance, as well as specific research domains. The latter is covered by a “secondary use statement”. This form of consent has been described as costly and complex.
- Waived consent, which has been introduced by some Research Ethics Committees (REC) where re-contact consent has been impossible. Strict criteria need to be applied in these circumstances in order to prevent abuse.

Eleven out of the 30 protocols (37%) that involved sample storage had specific consent for the tests that were to be carried out. The balance had blanket consent, except for two, which had tiered consent. Many of the consent documents stated that they would approach the Wits Human Research Ethics Committee (REC) should they wish to perform further studies. Many of these statements were very vague, and did not fulfil the category of waived consent. The impression created by some of the statements in these protocols is that they were documented because of the standing orders from the Wits Health Consortium and the Wits Human Research Ethics Committee (REC), and not because it was in the patients’ best interests. The other area of concern is that the consent taken should be dynamic, with the ability to withdraw it at any stage. This was often mentioned in the forms, but the mechanism by which consent could be withdrawn was often not stated, and not always very clear.

4.3.4 Other consent issues

4.3.4.1 Confidentiality, anonymity and identifiability were all dealt with to some extent in all of the protocols, and were in keeping with current recommendations of protection of identifiers and coding.

4.3.4.2 Benefit sharing in the form of financial benefits was discussed and clarified by some of the protocols. However, many were ambiguous. Benefit sharing from the data point of view was not mentioned by most of the protocols, and is a violation of the respect for patients' autonomy. Only four out of 30 protocols (13%) specified that data would be shared, and the sharing was usually all over the world. One protocol mentioned that data would be kept, but did not comment on whether it would be shared.

4.4 Conclusion

This study investigated the protocols that were submitted to the Wits Health Consortium during 2013. A small number (30%) fulfilled the criteria of sample storage, with or without genetic testing.

The Problem Statement laid out in chapter one of this research report asks the following:

“Is the consent obtained from adult patients for genetic research informed, morally justified and in keeping with South African and International laws, regulations and guidelines?”

If one examines the recommendations on informed consent in many of the International guidelines, the DOH guidelines(3) and both MRC guideline documents(22, 24), many of the protocols examined in this study fell short with respect to the following:

- Research participants requiring sufficient information in a language which they are able to fully comprehend.
- Full disclosure of precisely how the sample/s would be handled, where they would be sent, and who would have access to them. The attitude of many of the research companies appeared to be that once they have the samples, the patient has absolutely no say, ever again.
- Informed consent being a dynamic ongoing process, enabling the patient to withdraw consent at any stage.
- Whether data would be stored and for how long, and whether it would be shared.

As McGuire et al stated in their article on DNA data sharing: research participants' perspectives(43): "Current genomic research policy calls for public data release with specific consent for data sharing. Because most clinical investigators are not responsible for and do not anticipate data broadcast, few include information about data sharing in their informed consent process".

CHAPTER 5

DISCUSSION and RECOMMENDATIONS

5.1 General comments

The pilot study conducted for this research report has demonstrated that there is substantial room for improvement when drawing up protocols which have a genetic research component necessitating detailed informed consent from participants.

One of the important factors when examining the protocols is that there is no standardization. Many of the companies involved are multinationals, who have their own format when drawing up protocols. Whilst this may be acceptable for the informed consent for the contract research being performed, it is not recommended for the informed consent being obtained for the storage of samples and the genetic component.

5.2 Specific comments

As discussed in chapter 2, the DOH Ethics in Health Research(3) document highlights the following when considering informed consent for genetic research:

- “Provision to the donor of full information about the purposes of the sampling and/or an outline of the research proposal;
- The donor’s consent to the use of the sample in the experiment being planned;

- The donor's consent to storage and future use of the sample for other research;
- Giving donors the assurance that all secondary use of donated tissue samples will require approval of an accredited research ethics committee;
- Reassuring donors that no tests of known clinical value for diagnosing or predicting disease on samples can be linked to them without their consent;
- Provision for appropriate and secure storage of tissue samples;
- Provision for and maintenance of appropriate and secure systems to ensure confidentiality and privacy in the recording, storage and release of data;
- Accountability in the care and usage of samples;
- A statement of the duration of sample storage.”(3)

My findings will be interpreted in this context.

5.2.1 Specific recommendations

The results of this study have illustrated that many of these duties are only partially fulfilled in many of the protocols studied. In order to address these inconsistencies the following recommendations are made:

1. The informed consent process and paperwork need to be standardised for all protocols in which samples will be stored and genetic research performed.

This standardization will ensure that the following requirements are not omitted, as occurred in some of the protocols that were studied:

- The site of storage;
 - The length of time of storage;
 - Details of the sample/s being stored;
 - Specific details of the genetic research to be performed.
2. Detailed attention needs to be paid to the language used and the complexity of the terminology used when obtaining informed consent for sample storage and genetic testing. The South African MRC documents specify that research participants should receive the information in a language which they are able to fully comprehend. I recommend that the genetic consent portion of the WHC protocols needs to be translated when necessary and where appropriate, and where suitable funds are available. This would enable the ethical requirement of full disclosure to be achieved, and would be acting in the best interests of the research participants. In addition, it would allow detailed information on the commercial aspect of patenting and cell lines to be shared with the research participants. If translated versions are not available for practical or financial reasons, then a translator should be present.
3. The type of informed consent used in the various protocols is of concern. It is recommended that this too is standardised, to either specific consent, as occurred in some of the protocols, or dynamic consent, as has been described in chapter 3 of this research report. These two types of consent

lend themselves to continued involvement by the research participant in the study, as well as facilitating withdrawal of consent, which is the participant's ethical right. Where this type of consent is not possible, then multilayered or tiered consent is recommended as the next best form of ethical consent. In an interesting article in the European Journal of Human Genetics(44), Steinsbekk et al have recommended broad or blanket consent, with dynamic consent modifications, which, in time, may be worth considering.

4. Data sharing is one of the important issues in genetic consent which may undermine the ethical principles of autonomy, human dignity and the supremacy of consent. Whilst this was not an initial objective in this study, it was decided that it is such an important ethical issue, that this study would document whether this was specifically dealt with in the consent documentation. As has been described in chapter 4, very few protocols and consent documents described data storage, and data sharing. Hence it was assumed that informed consent was not obtained for data sharing from the research participants in most of the WHC protocols that were studied. It is therefore recommended that consent for data sharing is incorporated into the consent documentation as a matter of urgency.

McGuire et al performed a study looking at different types of consent for data sharing(45). They documented the willingness of participants to release data either publicly or in a restricted fashion, before and after being debriefed about the details of the study. After the debrief sessions, many participants

withdrew consent for public release, preferring the option of restricted release of their anonymized data.

This appears to indicate that we currently underestimate the importance of data sharing to our research participants. Further research in the field is necessary to determine which path should be followed.

5.3 Conclusion

It is strongly recommended that changes are implemented to the way in which informed consent is obtained from research participants involved in genetic research through the Wits Health Consortium. This is in order to fulfil the mandated ethical requirements.

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APPENDICES

Appendix A Ethics permission



R14/49 Prof Aina Christina Lundgren

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M140869

NAME: Prof Aina Christina Lundgren
(Principal Investigator)

DEPARTMENT: Bioethics
Wits Health Consortium


PROJECT TITLE: Informed Consent for Genetic Research in Adult Patients in a Research Entity in South Africa: An Ethico-Legal Inquiry

DATE CONSIDERED: 29/08/2014

DECISION: Approved unconditionally

CONDITIONS:

SUPERVISOR: Prof Peter Cleaton-Jones and Dr Anthony Egan

APPROVED BY: 
Professor A Woodiwiss, Co-Chairperson, HREC (Medical)

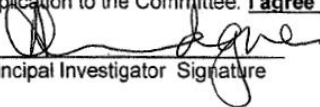
DATE OF APPROVAL: 18/09/2014

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report.**


Principal Investigator Signature

30-09-2014
Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix B Postgraduate Committee permission



Faculty of Health Sciences
Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172076

Reference: Ms Thokozile Nhlapo
E-mail: thokozile.nhlapo@wits.ac.za

26 August 2014
Person No: 7959714
PAG'

Prof AC Lundgren
PO Box 14504
Zuurfontein
1912
South Africa

Dear Prof Lundgren

Master of Science in Medicine: Approval of Title

We have pleasure in advising that your proposal entitled *Informed consent for genetic research in adult patients in a research entity in South Africa: an ethico-legal inquiry* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

A handwritten signature in cursive script, appearing to read 'S Benn'.

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

