

**ETHICS IN HEALTH RESEARCH:
PRINCIPLES, STRUCTURES
AND PROCESSES**

**RESEARCH ETHICS
GUIDELINES**

DEPARTMENT OF HEALTH

2004

PREAMBLE

Progress in science has resulted in the development of innovative medical treatments, many of which could be beneficial to people living in low-income countries.

In recent years, South Africa has become a sought-after venue for conducting health research that could lead to the development of some of these innovative new medical treatments. Scientists who conduct research are bound by the requirements of evidence-based medicine. Nevertheless, in the course of the work that is done, the human rights of poor and marginalized people and those who do not understand the processes of research are frequently violated. This is of great concern to the South African government, which seeks to uphold the human dignity of all of its citizens and to protect their human rights. In particular, we must provide adequate protection for people who are especially vulnerable as a result of poverty or who might currently be underserved.

Research ethics are bound by various national and international codes and guidelines, supplemented by the *Universal Declaration of Human Rights (1948)*. In terms of these documents, all research involving human subjects should be conducted in accordance with four basic ethical principles, namely: respect for human beings; beneficence, non-maleficence; and justice.

These guidelines, entitled "*Ethics in Health Research: Principles, Structures and Processes*" contain our national policy on the ethical practice of research, in accordance with our specific national needs. They establish mechanisms for the ethical review of studies conducted on human subjects, and draw attention to the need to consider the ethical implications of professional action. In this way we are endeavouring to inculcate high professional standards in regard to both human attitudes and quality of research.

These guidelines are intended for use by investigators, ethical review committees, administrators, health-care practitioners, policy-makers, and community representatives. Ethics Committees should be especially vigilant when considering research proposals involving vulnerable populations like children, pregnant and nursing women, persons with mental illnesses or handicaps, members of communities unfamiliar with medical concepts, and persons with restricted freedom, such as prisoners. Similar vigilance should be applied to proposals for invasive research that has no direct benefit for its subjects.

The writers of these guidelines wanted to incorporate into them some reference to the work of traditional health practitioners, since this is the one of the latest branches of healing to be given official recognition in South Africa. However, this proved to be impossible as a result of the paucity of available information. Hopefully, with the strengthening of intellectual property rights in South Africa, more information will become available in this significant area, and considerations

ETHICS IN HEALTH RESEARCH: PRINCIPLES, STRUCTURES AND PROCESSES

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- (4) The removal contemplated in subsection (3) may not be effected if-
- the removal of the tissue is likely to affect the outcome of the examination; or
 - the body or tissue in question has been donated or if the removal would be contrary to a direction given by the deceased before his or her death.

Regulations relating to tissue, cells, organs, blood, blood products and gametes

68. (1) The Minister may make regulations regarding-
- the post-mortem examination of bodies of deceased persons
 - the preservation, use and disposal of bodies, including unclaimed bodies;
 - the removal of donated tissue or cells from persons, tissue or cells obtained from post-mortem examinations and the procurement, processing, storage, supply and allocation of tissue or human cells by institutions and persons;
 - tissue transplants;
 - 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 importation and exportation of tissue, human cells, blood, blood products or gametes
 - the withdrawal of blood from living persons and the preservation, testing, processing, supply or disposal of withdrawn or imported blood; the administering of blood and any blood product to living persons;
 - the production, packaging, sealing, labelling and supplying of blood and blood products;
 - the bringing together outside the human body of male and female gametes, and research with regard to the product of the union of those gametes;
 - the artificial fertilisation of persons;
 - the appointment and functions of inspectors of anatomy and investigating officers;
 - the records and registers to be kept by persons and institutions;
 - the returns and reports, including extracts from registers, to be submitted to specified persons and institutions;
 - the acquisition, storage, harvesting, utilisation or manipulation of tissue, blood, blood products, organs, gametes, oocytes or human stem cells for any purpose;
 - the appointment and functions of inspectors of the national blood transfusion service and progenitor cell transplant institutions; and
 - any other matter relating to regulating the control and the use of human bodies, tissue, organs, gametes, blood and blood products in humans.
- (2) The Minister, with the concurrence of the Cabinet member responsible for finance, may make regulations concerning the payment of persons or institutions in connection with procurement, storage, supply, import or export of human bodies, tissue, blood, blood products or gametes.
- (3) The Minister may, if it is consistent with the objects of this Act and upon such conditions as the Minister may deem fit, by notice in the Gazette exempt a person or category of persons from any or all of the regulations made under this section.

regarding research related to traditional medicine can, in future, be incorporated into an updated version of these guidelines.

I wish to thank all of those who participated both formally and informally in the writing of these guidelines. Your work will greatly enhance the dignity of South African citizens.



DR MANTO TSHABALALA- MSIMANG
MINISTER OF HEALTH

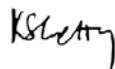
ACKNOWLEDGEMENTS

The guidelines on Ethics in Health Research: Principles, Structures and Processes have been developed to ensure that research conducted in South Africa adds value to the country and promotes protection of human participants in health research. These guidelines have therefore been developed to protect the rights of individual research participants. Internationally accepted standards and the following were considered.

- There should be an increasing focus on research relevant to the needs of vulnerable populations. Exploitation of participants, or their use as mere means to the ends of others, should be explicitly excluded by ensuring that the research is of relevance to the individuals participating in the research as well as to their communities.
- The potential benefits of research should considerably outweigh potential risks or harms to vulnerable individuals and communities.
- Research participants should be encouraged to participate in planning and conducting studies.
- Research in developing countries should be linked with capacity building in health care, and with economic and educational empowerment that has beneficial effects on the delivery of health care and on progress generally in the host country.
- The results of research should have the potential to produce long-term benefit for communities who participate in research.
- The National Health Research Ethics Council in due course will modify and adapt these guidelines as required.

The Department is grateful to the Directorate: Health Systems Research, Research Coordination and Epidemiology for the development of these guidelines. The Chairperson of the Interim National Health Research Ethics Committee Prof. Solomon Benatar and his team are also acknowledged for the expert and technical input into and finalisation of these guidelines.

These guidelines serve as a technical reference to all research institutions and organisations involved in research on human participants, and it is hoped that they will be used in the context of protecting all humans participating in such research.



**ACTING DIRECTOR-GENERAL
DEPARTMENT OF HEALTH**

- (2) This Act does not apply to the preparation of the body of a deceased person for the purposes of embalming it, whether or not such preparation involves the-
- (a) making of incisions in the body for the withdrawal of blood and the replacement thereof by a preservative; or
 - (b) restoration of any disfigurement or mutilation of the body before its burial.

Revocation of donation

65. A donor may, prior to the transplantation of the relevant organ into the donee, revoke a donation in the same way in which it was made or, in the case of a donation by way of a will or other document, also by the intentional destruction of that will or document.

Post-mortem examination of bodies

66. (1) Subject to subsection (2), a post mortem examination of the body of a deceased person may be conducted if-
- (a) the person, while alive, gave consent thereto;
 - (b) the spouse, partner, major child, parent, guardian, major brother or major sister of the deceased, in the specific order mentioned, gave consent thereto;
 - (c) or such an examination is necessary for determining the cause of death
- (2) A post mortem examination may not take place unless-
- (a) the medical practitioner in charge of clinical services in the hospital or authorised institution or of the mortuary in question, or any other medical practitioner, has authorised the post mortem examination in writing and in the prescribed manner; or
 - (b) in the case where there is no medical practitioner in charge of clinical services, a medical practitioner authorised by the person in charge of such hospital or authorised institution, has authorised the post mortem examination in writing and in the prescribed manner.

Removal of tissue at post-mortem examinations and obtaining of tissue by institution and persons

67. (1) (a) The Minister may, on the written application of an institution or person requiring tissue for a purpose contemplated in section 64(1), authorise that institution or person, in writing, to obtain such tissue from a medical practitioner contemplated in subsection (3) or a person or an institution contemplated in section 63.
- (b) The Minister may impose any condition on the institution or person to which or to whom he or she has granted an authorisation in terms of paragraph (a)
 - (c) This Act does not prevent persons or institutions from acquiring tissue in terms of the National Heritage Resources Act, 1999 (Act No.25 of 1999), for the purposes of that Act.
- (2) The medical practitioner in charge of clinical services in the hospital or authorised institution or of the mortuary in question, or any other medical practitioner authorised by such practitioner, or, in the case where there is no medical practitioner in charge of clinical services, a medical practitioner authorised by the person in charge of such hospital or authorised institution, may, in writing and in the prescribed manner, authorise-
- (a) a prescribed institution or person contemplated in section 63; or
 - (b) an authorised institution making application thereof in writing, to remove any specified tissue from the body concerned before burial thereof.
- (3) Despite anything to the contrary in any other law, a medical practitioner who conducts a post mortem examination in terms of-
- (a) section 3 of the Inquests Act, 1959 (Act No.58 of 1959); or
 - (b) section 71 (1)(a) or (b), must remove or cause to be removed from a body such tissue as may be specified in an authorisation under subsection (1) and must hand it over to the institution or person in possession of the authorisation.

- (2) Human organs obtained in terms of subsection (1) must be allocated in accordance with the prescribed procedures.
- (3) An organ may not be transplanted into a person who is not a South African citizen or a permanent resident of the Republic without the Minister's authorisation in writing.
- (4) The Minister must prescribe-
- criteria for the approval of organ transplant facilities; and
 - procedural measures to be applied for such approval.
- (5)(a) A person who contravenes a provision of this section or fails to comply therewith or who charges a fee for a human organ is guilty of an offence.
- Any person convicted of an offence in terms of paragraph (a) is liable on conviction to a fine or to imprisonment for a period not exceeding five years or to both a fine and such imprisonment.

Donation of human bodies and tissue of deceased persons

- 62.** (1) (a) A person who is competent to make a will may-
- in the will
 - in a document signed by him or her and at least two competent witnesses; or
 - in an oral statement made in the presence of at least two competent witnesses, donate his or her body or any specified tissue thereof to be used after his or her death, or give consent to the post mortem examination of his or her body, for any purpose provided for in this Act.
- (b) A person who makes a donation as contemplated in paragraph (a) must nominate an institution or a person contemplated in section 63 as donee.
- (c) If no donee is nominated in terms of paragraph (b), the donation is null and void.
- (d) Paragraph (b) does not apply in respect of an organ donated for the purposes contemplated in section 61 (1) and the donee of such organ must be determined in terms of section 61 (2).
- (2) In the absence of a donation under subsection (1) (a) or of a contrary direction given by a person whilst alive, the spouse, partner, major child, parent, guardian, major brother or major sister of that person, in the specific order mentioned, may after that person's death, donate the body or any specific tissue of that person to an institution or a person contemplated in section 63.
- (3) (a) The Director-General may, after the death of a person and if none of the persons contemplated in subsection (2) can be located, donate any specific tissue of that person to an institution or a person contemplated in subsection (2).

Human bodies, tissue, blood, blood products or gametes may be donated to prescribed institution or person

- 63.** A human body, tissue, blood, blood products or gametes may be donated by any person contemplated in section 55(a) or 62 to any prescribed institution or person for any purpose contemplated in section 56 or 64 (1)

Purposes of donation of body, tissue, blood or blood products of deceased persons

- 64.** (1) A donation in terms of section 62 may only be made for-
- the purposes of the training of students in health sciences;
 - the purposes of research;
 - the purposes of the advancement of health sciences;
 - therapeutic purposes, including the use of tissue in any living person; or
 - the production of a therapeutic, diagnostic or prophylactic substance.

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- (ii) in the case where there is no medical practitioner in charge of the clinical services at that hospital or authorised institution, a medical practitioner authorised thereto by the person in charge of the hospital or authorised institution.
- (2) The medical practitioner contemplated in subsection (1) (b) may not participate in a transplant for which he or she has granted authorisation in terms of that subsection

Removal, use or transplantation of tissue, and administering of blood and blood products by medical practitioner or dentist

59. (1) For the purpose of this Chapter, only a registered medical practitioner or dentist may remove any tissue from a living person, use tissue so removed for any of the purposes contemplated in section 56 or transplant tissue so removed into another living person.
- (2) Subject to Medicine and Related Substances Control Act, 1965 (Act No. 101 of 1965), only a registered medical practitioner or dentist, or a person acting under the supervision or on the instructions of a medical practitioner or dentist, may for the purposes of this Chapter administer blood or a blood product to, or prescribe blood or a blood product for, a living person.

Payment in connection with the importation, acquisition or supply of tissue, blood, blood products or gametes

60. (1) No person, except-
- (a) a hospital or an institution contemplated in section 58(1)(a), a person or an institution contemplated in section 63 and an authorised institution or, in the case of tissue or gametes imported or exported in the manner provided for in the regulations, the importer or exporter concerned, may receive payment in respect of the acquisition, supply, importation or export of any tissue or gamete for or to another person for any of the purposes contemplated in section 56 or 64.
- (b) A person or an institution contemplated in section 63 or an authorised institution, may receive any payment in respect of the importation, export or acquisition for the supply to another person of blood or blood products.
- (2) The amount of payment contemplated in subsection (1) may not exceed an amount which is reasonably required to cover the costs involved in the importation, export, acquisition or supply of the tissue, gamete, blood or blood product in question.
- (3) This section does not prevent a health care provider registered with a statutory health professional council from receiving remuneration for any professional service rendered by him or her.
- (4) It is an offence for a person-
- (a) who has donated tissue, gamete, blood or blood product to receive any form of financial or other reward for such donation, except for the reimbursement of reasonable costs incurred by him or her to provide such donation; and
- (b) to sell or trade in tissue, gametes, blood or blood products, except as provided for in this Chapter.
- (5) Any person convicted of an offence in terms of subsection (4) is liable on conviction to a fine or to imprisonment for a period not exceeding five years or to both a fine and such imprisonment

Allocation and use of human organs

61. (1) Human organs obtained from deceased persons for the purpose of transplantation or treatment or medical or dental training or research, may only be used in the prescribed manner.

Use of tissue, blood, blood products or gametes removed or withdrawn from living persons

56. (1) A person may use tissue or gametes removed or blood or a blood product withdrawn from a living person only for such medical or dental purposes as may be prescribed.
- (2) (a) Subject to paragraph , the following tissue, blood, blood products or gametes may not be removed or withdrawn from a living person for any purpose contemplated in subsection (1):
- (i) tissue, blood, a blood product or a gamete from a person who is mentally ill within the meaning of the Mental Health Care Act, 2002 (Act No. 17 of 2002);
 - (ii) tissue which is not replaceable by natural processes from a person younger than 18 years;
 - (iii) a gamete from a person younger than 18 years; or
 - (iv) placenta, embryonic or foetal tissue, stem cells and umbilical cord, excluding umbilical cord progenitor cells,
- (b) The Minister may authorise the removal or withdrawal of tissue, blood, a blood product or gametes contemplated in paragraph (a) and may impose any condition, which may be necessary in respect of such removal or withdrawal.

Prohibition of reproductive cloning of human beings

57. (1) A person may not-
- (a) manipulate any genetic material, including genetic material of human gametes, zygotes or embryos; or
 - (b) engage in any activity, including nuclear transfer or embryo splitting, for the purpose of the reproductive cloning of a human being.
- (2) The Minister may, under such conditions as may be prescribed, permit therapeutic cloning utilising adult or umbilical cord stem cells.
- (3) No person may import or export human zygotes or embryos without the prior written approval of the Minister.
- (4) The Minister may permit research on stem cells and zygotes, which are not more than 14 days old on a written application and if-
- (a) the applicant undertakes to document the research for record purposes; and
 - (b) prior consent is obtained from the donor of such stem cells or zygotes.
- (5) Any person who contravenes a provision of this section or who fails to comply therewith is guilty of an offence and is liable on conviction to a fine or to imprisonment for a period not exceeding five years or to both a fine and such imprisonment.
- (6) For the purpose of this section-
- (a) "reproductive cloning of a human being" means the manipulation of genetic material in order to achieve the reproduction of a human being and includes nuclear transfer or embryo splitting for such purpose; and
 - (b) "therapeutic cloning" means the manipulation of genetic material from either adult, zygotic or embryonic cells in order to alter, for therapeutic purposes, the function of cells or tissues.

Removal and transplantation of human tissue in hospital or authorised institution

58. (1) A person may not remove tissue from living person for transplantation in another living person or carry out transplantation of such tissue except-
- (a) in a hospital or an authorised institution; and
 - (b) on the written authority of-
 - (i) the medical practitioner in charge of clinical services in that hospital or authorized institution, or any other medical practitioner authorised by him or her; or

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APPENDIX E: NATIONAL HEALTH ACT, 2003 (ACT NO. 61 OF 2003) (CHAPTER 8: SECTION 53-68)

CONTROL OF USE OF BLOOD, BLOOD PRODUCTS, TISSUE AND GAMETES IN HUMANS

Establishment of national blood transfusion service

53. (1) The Minister must establish a blood transfusion service for the Republic by granting a licence to a non-profit organisation, which is able to provide a blood transfusion service throughout the territory of the Republic.
- (2) The holder of the licence granted in terms of subsection (1)-
- (a) must comply with prescribed norms and standards and must provide the prescribed blood transfusion and related services.
 - (b) may establish regional units, for the delivery of blood transfusion services, which must function under the control of the licence holder: and
 - (c) has the sole right to provide a blood transfusion service in the Republic.
- (3) Any person other than the holder of the licence granted in terms of subsection (1) who provides a blood transfusion service in the Republic, is guilty of an offence and liable on conviction to a fine or to imprisonment for a period not exceeding five years or to both a fine and such imprisonment.

Designation of authorised institution

54. (1) The Minister may, by notice in the Gazette, designate any institution other than an institution contemplated in section 63 as an authorised institution.
- (2) An authorised institution may-
- (a) acquire, use or supply the body of a deceased person for any of the purposes referred to in section 64:
 - (b) acquire or use any tissue lawfully imported or removed from the body of living or deceased person for any of the purposes referred to in section 56 or 64, as the case may be:
 - (c) supply any tissue preserved by it to an institution or person contemplated in section 63 for any of the purposes referred to in section 58 or 64: and
 - (d) acquire, use and supply blood products for any of the purposes referred to in section 56 or 64.
- (3) The Minister may, in the notice contemplated in subsection (1), impose conditions in respect of the exercise of a power referred to in subsection (2).

Removal of tissue, blood, blood products or gametes from living persons

55. A person may not remove tissue, blood, a blood product or gametes from the body of another living person for the purpose referred to in section 56 unless it is done-
- (a) with the written consent of the person from whom the tissue, blood, blood products or gametes are removed granted in the prescribed manner: and
 - (b) in accordance with prescribed conditions.

- results in death;
- is life-threatening;
- requires in-patient hospitalisation or prolongation of existing hospitalisation;
- results in persistent or significant disability or incapacity;
- results in a congenital anomaly or birth defect.

Sponsor

An individual, company, institution or organisation that assumes financial responsibility for all or part of a particular research study or clinical trial.

Therapeutic

Descriptive of interventions directed to the wellbeing of the individual or community involved.

Vulnerable Participants

Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other vulnerable participants include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent.

Well-being (of the trial participants)

The physical and mental integrity of the participants participating in a clinical trial.

1. THE IMPORTANCE OF ETHICS

1.1 Introduction

South Africa is undergoing transformation into a non-racial, non-sexist, democratic state in which human dignity, equality and the advancement of human rights are respected, promoted and protected under the South African Constitution Act, 1996 (Act No.108 of 1996). In particular, section 12(2) of the Bill of Rights provides that Everyone has the bodily and psychological integrity, which includes the right (b) to security in and control over their body; and (c) not to be subjected to medical or scientific experiments without their informed consent.'

South Africa provides a unique and highly attractive research environment, with its mix of developed-country skills, expertise and infrastructure and its developing-country burden of disease. This environment has attracted many researchers. The clinical trial industry in South Africa reportedly increased by 40% between 1997 and 1998 (Christley, 1998) and yielded an estimated total budget of R826 million during 2000 (Joffe, 2000).

Increasing research activity, competition in research and the attractive research environment may sometimes result in dishonest and fraudulent practice. The need for a broad statement on ethics and health research in South Africa is therefore urgent.

1.2 Key Texts

Much work has been done internationally to develop guidelines for the conduct of health research in human participants. Key texts, which should be essential reading and reference sources for South African-based researchers, are listed in Appendix A with some additional references of interest.

1.3 Scope of the Guidelines

The term 'research' covers a broad range of activities and can be defined as, 'the systematic search or inquiry for knowledge' (Katzenellenbogen, Gear & Tollman 1997). A more detailed understanding of health research and of a research project may be obtained from the description provided by the US National Commission for the Protection of Human Subjects:

'A research project generally is described in a protocol that sets forth explicit objectives and formal procedures designed to reach those objectives. The protocol may include therapeutic and other activities intended to benefit the subjects, as well as procedures to evaluate such activities. Research objectives range from understanding normal and abnormal physiological or psychological functions or social phenomena, to evaluating diagnostic, therapeutic or preventive interventions and variations in services or practices. The activities or procedures involved in research may be invasive or non-invasive and include surgical interventions; removal of body tissues or fluids; administration of chemical substances or forms of energy; modifications of diet; daily routine or service delivery; alteration of environment; observation; administration of questions or tests; randomisation; review of records etc.'

For the purposes of this document, the above statement should be used to guide the reader's understanding of health research.

1.4 Ethics and Research

To be ethical, all health research on animals and on human participants must be scientifically sound. Ethics are as important as scientific considerations when reviewing a research project. A South African-based ethics committee must review the ethical and scientific rigor of all research projects to

be conducted in South Africa. More information on the process of ethical approval in South Africa may be found in Section 2 of this document.

1.5 Ethics and Legislation

In due course, South African ethics committees will receive guidance from the National Health Research Ethics Council. The role of the Council will be to promote and monitor compliance of South African ethics committees within relevant legislation and regulations, ethical guidelines and standards. The National Health Research Ethics Council is to be established in terms of the National Health Act, 2003 (Act No. 61 of 2003).

1.6 Applicability of these Guidelines

The principles outlined in this document should guide all research involving animals and human participants in any discipline relating to health. South African ethics committees are encouraged to adopt these principles to guide their efforts in assessing all health research projects.

All health research in South Africa, including research undertaken by military and other national bodies, should be subject to these Guidelines. Those who conduct 'secret' research involving human participants should be held to the same levels of accountability.

Compliance with these standards and with other national and international scripts reassures the public that the rights, safety and well being of study participants are protected.

1.7 Research and Animals

The researcher should assure an Animal Ethics Committee that the study will be conducted in compliance with policies and standards required for performing research on animals. Under the provision of the South African Medical Research Council Act, No 58 of 1991, the Medical Research Council (MRC) is compiling guidelines: Use of Animals in Research (Book 3). Guidelines concerning animals in biomedical research are also available in the 'National Code for Animal Use in Research, Education, Diagnosis and Testing of Drugs and Related Substances in South Africa' published by the Director General of Agriculture.

Personal Information

Personal Information is defined as information or an opinion (including information or an opinion forming part of a database), whether true or not, and whether recorded in a materials form or not, about an individual whose identity is apparent, or can reasonably be ascertained, from the information or opinion (Privacy Act No.119 of 1988 as amended).

Placebo

A product or substance known to be without effect; usually used as a control to be compared against a potentially effective substance or method that is being subjected to clinical trial.

Principal Investigator

A principal investigator is a South African-based researcher who has sole or joint responsibility for the design, conduct, analysis and reporting of the trial. The principal investigator is also responsible for the delegation of responsibilities during research.

Privacy

Privacy implies a zone of exclusivity where individuals and collectivities are free from scrutiny of others. It may also include control over the extent, timing and circumstances of sharing oneself with others, whether physically, intellectually or in terms of behaviour.

Protocol

A document that provides the background, rationale and objectives of the research and describes its design, methodology, organisation and the conditions under which it is to be performed and managed.

Qualitative Research

Qualitative research attempts to understand phenomena in entirety. It comprises research to understand social and cultural problems, and focuses on interactive processes to collect subjective information that is not structured numerically, but intuitively. Qualitative research attempts to understand human experience. It analyses thematic and narrative information. The investigator interacts with people in a sustainable manner.

Randomisation

The process of assigning trial participants to treatment or control groups, using chance to determine the assignment

Research

This involves systematic investigations to establish facts, principles and knowledge.

Research Participant

Living individual (or group of living individuals) about whom a researcher conducting research obtains data through intervention or interaction with the person or identifiable private information.

Respect for Persons

This has two fundamental aspects:

- Respect for the autonomy of those individuals who are capable of making informed choices, and respect for their capacity for self determination;
- Protection of persons with impaired or diminished autonomy, that is, those individuals who are incompetent or whose voluntariness is compromised.

Risk

The magnitude of a harm and the probability of its occurrence.

See also Minimal risk

Serious Adverse Effect (event or reaction)

Any untoward medical occurrence that at any dose:

placing a person at social disadvantage.

Health

WHO defines health as 'a state of physical, mental and social well-being and not merely the absence of disease or infirmity'.

Human Tissue

Includes the substance, structure and texture of which the human body or any part or organ of it is composed, that is removed or separated from living human being; and includes blood, blood components and waste products.

Identified Samples or Data

Data that enables the identification of a specific individual is referred to as 'identified data'. Examples of identifiers may include the individual's name, date of birth or address. In particularly small sets of data even information such as a post code may be an identifier.

See also: De-identified Samples or Data and Potentially Identifiable Samples or Data.

Informed Consent

A process by which participants voluntarily confirm their willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to their decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form. Informed consent is a process seeking to encapsulate a researcher's moral duty to provide sufficient information to allow potential participants to make an informed, free and rational choice whether or not to participate in a research project.

Justice

This concept concerning fairness or equity is often divided into three parts. Procedural justice is concerned with the fair methods of making decisions and settling disputes; distributive justice seeks to ensure fair distribution of benefits and burdens, while corrective justice is concerned with correcting the wrongs and harms through compensation or retribution.

Minimal Risk

This anticipates that the probability and magnitude of harm or discomfort to be experienced in the research will not be greater than those ordinarily encountered in daily life.

Monitoring

The review by a research ethics committee of ongoing research. Monitoring may take several forms, including review of annual reports, formal review of the informed consent process, establishment of a safety monitoring committee, a periodic review by a third party of the documents generated by the study, a review of reports of adverse events, and a random audit of the particular processes.

Multi-centre Research

The conduct of a research project by researchers in several autonomous institutions or organisations. This includes multi-centre clinical trials.

Multi-centre Trial

A clinical trial conducted according to a single protocol but at more than one site, and therefore, carried out by more than one investigator.

Non-therapeutic

Interventions not directed to the benefit of the individual but rather towards improving scientific knowledge or technical application.

2. GUIDING PRINCIPLES

The purpose of statement on ethical principles for health research in South Africa is to identify good, desirable and acceptable conduct, to protect the welfare and rights of research participants, and to reflect the basic ethical values of beneficence, justice and respect for persons. Both national and international accords and texts, outlined at Point 1.2 of this document, guide these principles and values.

Health researchers must conform to the following ethical principles and values, which must underscore all health research activities in South Africa.

2.1 Respect and Dignity

Respect for the dignity, safety and well-being of participants should be the primary concern in health research involving human participants. Culture, language, beliefs, perceptions, and customs must all be considered.

2.2 Relevance

Researchers in South Africa have ethical responsibility to ensure that their research is relevant both to the broad health and development needs of the country and to the individual needs of those who suffer from the diseases and concerns under study (Department of Health, 1999a). The findings of the research must be translatable into mechanisms for improving the health status of South Africans.

2.3 Scientific Integrity

In addition to fulfilling a need and being of value, the research proposed must demonstrate sound methodology and a high probability of providing answers to the research questions posed. The research protocol must show knowledge of relevant literature, derived from a systematic review of that literature and, where appropriate, from laboratory and animal studies (National Health and Medical Research Council, 1998). Moreover, research methods and results must be open to peer review and scrutiny.

2.4 Investigator Competence

A suitably qualified investigator should conduct the study. The investigator's competence is assessed mainly by technical competence, which includes research competence, and is itself assessed in terms of education, knowledge, certification and experience. Compassion and empathy are among the characteristics required of a technically competent researcher. A proper clinical and research environment, encompassing good research mentoring, provides this. In all cases the local principal investigator must be a South African-based researcher; that is, one who is ordinarily permanently resident in South Africa.

2.5 Principal Investigator Responsibilities

The Principal Investigator (PI) must submit an application to the MCC and/or an appropriate and accredited local ethics committee. All clinical trials must be reviewed by the MCC and by a local ethics committee. Both of these reviewing institutions must approve the project before the study may commence. Principal Investigators bear full responsibility for the scientific and ethical aspects of their study, and are the means of communication with the ethics committee while obtaining approval. Once a study is in progress all reports of adverse events and management issues dealt with by the sponsoring company should be transmitted to the ethics committees, ideally through the Principal Investigator, who should be fully informed of these issues. To expedite the process, data could be

copied both to the Principal Investigator and to the ethics committee. However, it should be made clear that the Principal Investigator is responsible for the study. In addition, a system to ensure tracking of all research will be set up through the National Health Research Ethics Council and local ethics committees. This will involve each study being allocated a national study number and a position in the national database. It is envisaged that ethics committees will be allocated cohorts of notification numbers. When the data capturer has allocated a number to a particular project, this will be communicated to the National Health Research Ethics Council for inclusion in their database. A research project may not commence before receiving a national study number from the local ethics committee, which bears the responsibility of ensuring that the National Health Research Ethics Council receives a full list of numbers allocated.

The information in the national database should be available publicly, with the reservation that it be limited to information that would not jeopardise commercial interests. It is visualised that it would include:

- Title of research projects;
- Duration of the projects;
- PI name and affiliation.

A regular update of an anonymised research profile from database may be placed on the Department of Health's website with information such as:

- The number and proportion of studies by type (for example, trials or non-trials) proportions by study site
- Total sponsorship by type of study and study site

2.6 Informed Consent

Informed consent must be obtained from research participants before the research can begin. Both written and verbal informed consent must be obtained, unless there are good reasons to the contrary, such a situation of coma, emergency, or mental incapacity as indicated in 5.9 and 5.14 below. Prior approval of the ethics committee must be obtained in all situations in which it is justifiable to initiate research without the informed consent of the participant. Verbal consent, where the participant is illiterate, should be obtained in the presence of a literate witness who should verify in writing, duly signed, that informed verbal consent was obtained. Informed consent means that a participant has been informed about the risks and benefits of the research, understands such risks and benefits and is able to give consent to participation, without coercion, undue influence or inappropriate incentives.

In South Africa, researchers must be particularly aware of the vulnerability of prospective participants in terms of access to health services and education levels. Research details must be provided in a clear, simple and culturally appropriate manner. If a participant lacks capacity to exercise an informed choice to participate, an appropriate person to make the choice for them must be identified by the investigator. A participant is free at any time to withdraw consent to further involvement in the research, without having to face any unfair negative consequence or disadvantage. The following essential elements must be understood before a participant is capable of giving informed consent.

- That consent is being given to participate in research;
- The purpose of the research;
- The expected duration of the participant's involvement;
- A description of the procedures to which the participant will be subjected, including any experimental procedures that are innovative and have not been used in medical practice;

Prospective participants should be helped to arrive at an informed decision by, for instance, use of appropriate language, selection of a non-threatening environment for interaction and the availability of peer counseling. Participants may find information about the following points useful.

- The investigators' qualifications;

Confidentiality

Prevention of disclosure, other than to authorized individuals, of a sponsor's proprietary information or of a participant's identity.

Consent

The voluntary agreement of a person or group, based on adequate knowledge and understanding of relevant material, to participate in research. Informed consent is one possible result of informed choice, the other possibility is refusal.

Deception

Deception includes the withholding of essential information from research participants, deliberately misleading them about procedures and purposes, including studies in which participants are deliberately given misleading information about the purpose of a research study.

De-identified (not re-identifiable, anonymous) Samples or Data

The process of de-identification may be irreversible where the identifiers have been removed permanently or the data has been identified. These data are referred to as 'identified'. It should be recognised that the term 'de-identified' is used frequently, in documents other than this statement of the Ethics and Health Research: Principles, Structures and Processes, to refer to sets of data from which only names have been removed. Such data may remain 'potentially identifiable'. *See also Identified Samples or Data and Potentially Identifiable Samples or Data.*

Ethics

A branch of moral philosophy concerned with the rational evaluation of right and wrong, justice and injustice, virtue and vice, good and bad, and related concepts and principles.

Ethical and unethical

Right or morally acceptable on one hand, wrong or morally unacceptable on the other. Conforming to the rationally acknowledged norms and standards of behaviour, or failure to conform to such norms and standards.

Ethics Committee

An independent body whose responsibility is to ensure the protection of the rights, safety and wellbeing of human participants involved in medical research (a trial). An ethics committee provides public assurance of that protection, by, reviewing and approving the trial protocol, the suitability of the investigator's facilities, and the methods and material to be used in obtaining and documenting the informed consent of the participants. Ethics committees should be independent of political, institutional, professional and market influences. The legal status of ethics committees in South Africa is established under the National Health Act, 2003 (Act No. 61 of 2003).

Families

A family is a primary social group most often consisting of parents and their offspring. However, a family may also be a group of people occupying the same dwelling place and consisting of persons who are not biologically related.

Foetus

In humans, a conceptus of seven to eight weeks' development until birth (term).

Genetic Material

Any source of DNA or RNA that can be tested to obtain genetic information. It includes cells, whether as single cells or as part of tissues, and extracted DNA and RNA.

Harm

That which adversely affects the interest or welfare of an individual or a group;

Harm extends to physical harm, discomfort, anxiety, pain, psychological disturbance and includes

APPENDIX D: GLOSSARY

The definitions provided within this Glossary apply as they are used in the ethics and health research principles, structures and processes. These are based on the definitions in the Canadian Code of Ethical Conduct for Research Involving Humans (1996) and the ICH Guidelines for Good Clinical Practice.

Adverse Drug Reaction (ADR)

In pre-approval clinical experience with a new medicinal product or its new usages, particularly where the therapeutic dose has not been established, all noxious and unintended responses to a medicinal product should be considered as 'adverse drug reactions'. The phrase ADR indicates at least the probability of a causal relationship between a medicinal product and an adverse event. With regard to marketed medicinal products, the term applies to a drug-response that is noxious and unintended and which occurs at doses normally used in humans. (See the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.)

Adverse Event (AE)

An adverse event may be any untoward medical occurrence in a patient or research participant who has received a pharmaceutical product that does not necessarily have a causal relationship with the treatment being researched. An adverse event (AE) may therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease associated with the use of a medicinal product under investigation, whether or not related to the medicinal (investigational) product (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

Anonymous Samples or Data

See De-identified samples or data

Approval (in relation to Research Ethics Committees)

The research ethics committee's affirmation that the clinical trial has been reviewed and may be conducted at the nominated institution according to the constraints set out by the ethics committee, the institution, Good Clinical Practice (GCP), and legal requirements.

Benefit

That which positively affects the interest or welfare of an individual or group, or the public generally.

Child

Subject to law in the relevant jurisdiction, a child is a minor who lacks the legal ability to make a decision whether or not to participate in research.

Clinical Trial

This is a preplanned, usually controlled, clinical study to determine the safety, efficacy or optimum dosage schedule (if appropriate) of one or more diagnostic, therapeutic, or prophylactic drugs, devices or interventions in humans selected according to predetermined criteria of eligibility.

Collectivities

Distinct human groups with common identity, their own social structures, common customs and designated leaders or other persons who represent collective interests in dealing with researchers. Collectivities may include cultural or ethnic groups, and indigenous communities.

Competence

The ability of a person or a group to understand and make choices in accord with their own fundamental values. The term 'legal competence' indicates that a person's age and mental state satisfy certain basic legal requirements.

- Explanation of participants' responsibilities;
- Description of foreseeable risks or discomforts;
- Description of benefits to the participants or to others, both during and after the research;
- Disclosure of alternative procedures or courses of treatment;
- Description of the extent to which confidentiality will be maintained;
- Statement that sponsors of the study may be able to inspect research records;
- Statement that the research has been approved by an accredited research ethics committee;
- Contact details of research ethics committee representatives;
- Explanation as to whether compensation will be given for research-related injuries;
- Explanation as to the consequences of injury, including medical treatments;
- Explanation of whom to contact in the event of research-related injury.

Investigators must assure potential participants that participation is voluntary, and that refusal to participate, or a decision to discontinue participation, will not involve any form of penalty. The approximate number of participants should be disclosed. Details of treatment must be supplied and, where appropriate, the possibility of random assignment to various treatments or procedures must be made clear. The nature of experimental and control groups must be explained, as well as circumstances that might lead to the termination of participation.

Unforeseeable risks obviously cannot be foreseen, but participants must be told the nature and extent of risks – including financial risks – attendant on participation. Participants must be made aware of their right to be informed of relevant new findings, and of the consequences of their withdrawal from research. They should know, too, whether the investigator might terminate participation.

The above points may be regarded as essential elements of informed consent, and all should be incorporated in an Informed Consent Form or document.

Informed consent is a vital requirement in ethical conduct, and is valid only when it is obtained without deceit or misrepresentation. The informed consent requirements are not intended to pre-empt the laws of the country, which may require that additional information be provided to the participants. The moral duties of the medical practitioner or other investigator are in no way limited by these requirements.

2.7 Privacy and Confidentiality

In its simplest form privacy is concerned with access to personal records, while confidentiality refers to the use of personal information once it has been disclosed (Berglund, 1990). A participant's right to both privacy and confidentiality must be protected. The researcher must ensure that 'where personal information about research participants or a community is collected, stored, used or destroyed, this is done in ways that respect the privacy or confidentiality of the participants or the community and any agreements made with the participants or community' (National Health & Medical Research Council, 1998:5).

2.8 Inclusion and Exclusion Criteria

The selection, recruitment, exclusion and inclusion of research participants must be just and fair, based on sound scientific and ethical principles. No person may be inappropriately or unjustly excluded on the basis of race, age, sex, sexual orientation, disability, education, religious beliefs, pregnancy, marital status, ethnic or social origin, conscience, belief or language.

2.9 Risk and Benefits

A risk/benefit analysis of the study should precede the research itself. Risk/benefit analysis should take full notice of benefits and harms beyond the duration of the research, particularly in the case of chronic life-threatening conditions. Alternative ways of providing benefits to the participants might be available. The principal investigator has the ethical duty to exclude participants who might be placed at undue risk.

2.10 Publication of Results

Investigators have an obligation to disseminate research results, whether positive or negative, in a timely and competent manner. This is particularly important in clinical trials, where investigators are duty bound to ensure that findings are made public for all outcomes assessed. It is, however, important that the release of research findings be done in an ethical manner, to ensure that false expectations are not raised in a vulnerable population. Research results should not be prematurely released or published, or unreasonably delayed. It is advisable that the main results should be disseminated, using appropriate communication formats, to the participants and other interested members of the communities in which the study was conducted.

Results of a study, whether sponsored by government or industry, should be the intellectual property of the investigators, not the sponsor, and all results that have scientific merit should be published. Requests to withhold findings, to change or tone down the content of a report are not acceptable in good ethical practice. However, sponsors or stakeholders should be afforded the opportunity to comment on research findings prior to publication, without any entitlement to veto, change the conclusions, or unreasonably delay publication of results.

In collaborative research with pharmaceutical or other companies, the conditions of publication should be spelt out clearly in the protocol. Research ethics committees should be satisfied that there is no interference with the right to publish results.

2.11 Conflict of Interest

A researcher must disclose the sources and extent of funding to the research participants, the ethics committee and, where appropriate, to the regulatory authority. Commercial affiliations or financial interests at the time of proposing and reporting the research must also be disclosed.

2.12 Safety Monitoring

Safety monitoring of research activities is imperative, particularly in a clinical trial. This involves the prompt reporting of serious adverse events, including post-study events. It is the researcher's responsibility to ensure that adequate provisions are made to deal with any adverse event. The processes for this should be outlined in the research protocol.

2.13 Multi-Centre Studies

The number of multi-centre clinical trials and studies being undertaken in South Africa has increased dramatically in recent years. Prior to commencement of a study, approval should be obtained from the local research ethics committee. Designs should be appropriate to the local setting and particular modifications should be made to the local study when required, in the case of inclusion and exclusion criteria, for instance. It is unacceptable for developed-country participants to be offered better standards of care than are offered to South African participants in a similar study. In particular, when South Africa is chosen for a trial or study that has not been undertaken in the country of origin, an explanation should be sought as to why this is the case. In terms of study design, special attention should be paid to the sampling strategy. Other issues in international studies include financing of the

APPENDIX C: ICH GUIDELINE FOR GCP AND DECLARATION OF HELSINKI

ICH GUIDELINE FOR GOOD CLINICAL PRACTICE

1. Clinical trials should be conducted in accordance with the ethical principles that have their origin in Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).
2. Before a trial is initiated, foreseeable risk and inconveniences should be weighed against the benefit for the individual trial subject and society. A trial should be initiated and continued if the anticipated benefits justify the risk.
3. The rights, safety and well being of the trial participants are the most important considerations and should prevail over interest of science and society.
4. The available non-clinical and clinical information on an investigational product should be adequate to support the proposed clinical trials.
5. Clinical trials should be scientifically sound, and described in a clear, detailed protocol.
6. A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/ favourable opinion.
7. The medical care given to, and medical decisions made on behalf of, participants should always be the responsibility of the qualified physician or, when appropriate, of a qualified dentist.
8. Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).
9. Freely given informed consent should be obtained from every participant prior to clinical trial participant.
10. All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.
11. The confidentiality of records that could identify participants should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
12. Investigational product should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.
13. Systems with procedures that assure the quality of every aspect of the trial should be implemented.

APPENDIX B: KEY TEXTS

The following are international key texts that have directed the development of these guidelines:

- Nuremberg Code, 1949
- Belmont Report, 1973
- Declaration of Helsinki, October 2000

Some other useful references include:

- ICH Guideline for Good Clinical Practice, ICH Harmonised Tripartite Guideline, May 1997
- International Guidelines for Ethical Review of Epidemiological Studies, Council for International Organisations of Medical Sciences (CIOMS), 1991 Geneva.
- Institutional Review Board (IRB) Guidebook. Office for the Protection from Research Risks – National Institute of Health, USA, 1993
- International Ethical Guidelines for Biomedical Research Involving Human Subjects. Council for International Organisations of Medical Sciences in collaboration with World Health Organisation (WHO). Geneva 2002.
- World Health Organisation 2000. Operational Guidelines for Ethics Committees that Review Biomedical Research. Geneva.TDR/PRD/ETHICS/2000.1

Guidelines for Good Clinical Practice (GCP) for Trials on Pharmaceutical Products. In: The use of essential drugs. Model list of Essential Drugs (Eight List). Sixth report of the WHO Expert Committee. Geneva, World Health Organisation, 1995:97 (WHO Technical Report Series, No 850).

study, the appropriateness of incentive packages to research participants and remuneration packages for investigators.

Multinational Collaborative Research

The challenge to international research ethics is the development of universal rules for research at a time when health care is being delivered within very different health care systems (even within a single country) and in a multicultural world in which people live under radically different economic conditions. Variable trajectories of emancipation of individuals from community have also given rise to a wide spectrum of self-image, what it means to be ill and how health care systems should be structured. With recognition of the role of social conditions in shaping the world, and how privileged people view the world and themselves, comes the realisation that research cannot be considered in isolation. Medical research, health care, conditions of life around the world and how humans flourish may seem disparate, but all are interdependent. The global perspective adds complexity to the task of crafting universal guidelines for research ethics. It is necessary to ensure that:

- Benefits accrue to participants in the host country. Research with benefits limited to the sponsoring country is exploitative and unacceptable;
- The potential benefits of research considerably outweigh potential risks or harms to vulnerable individuals and communities;
- Research is non-exploitative and in the best interests of the research participants and their community;
- Groups already vulnerable are provided with improved access to research - in all countries;
- Research participants are encouraged to participate in planning and conducting studies;
- Research in developing countries is linked to capacity-building in health care, and to economic and educational empowerment to promote the delivery of health care and progress generally in the host country;
- Consideration is given to the risks and potential benefits to research participants, in proportion to the magnitude of benefit to sponsors;
- Honest efforts are made to translate research findings into components of accessible care in the community being researched;
- Conflicts of interest are avoided;
- Research protocols are modified to suit the situation in local communities;
- Publication of articles should be inclusive of investigators as authors from both host and sponsoring countries where appropriate contributions have been made.

2.14 Standard of care

In the past 'standard of care' has not been clearly defined. It has generally been assumed to refer to 'drug treatments'. This is inadequate and the definition should be clarified and extended beyond consideration of drugs to consideration of other aspects of care that are either under the control of investigators or that could be influenced by them.¹

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. An adequate definition of 'standard of care' should include:

- Equal respect for the human dignity of all participants irrespective of their location;
- Obtaining informed consent in the research participants' home language, coupled with an understanding of their world-view or value system;

¹ Benatar S R, Singer P A. A new look at international research ethics. *Brit Med J* 2000; 321: 824-26.

- Provision of equal general care facilities, through access to the same modern technology and other external factors that may have contributed to the 'best proven' use of the drugs elsewhere, such as medications and care for other diseases, and access to advice and support to sustain compliance;
- The same follow-up facilities for research participants after completion of the study and the same access to ongoing care.

It is suggested that in determining the standard of care that should apply to research in developing countries it is not justifiable to be selective and choose only one aspect of a standard of care – such as drug treatment – without giving adequate reasons for such choice. In the absence of justification, the choice of only one of the elements of the standard of care may seem arbitrary. It may not be possible to meet all requirements in any developing country, but there are bound to be aspects of treatment or intervention that can be met immediately – those that are under the direct control of the investigator. It is suggested, then, that researchers from highly resourced countries bear some responsibility to promote better health care and research conditions by garnering additional support from partners in their own countries.²

2.15 Placebo-controlled studies

Research must be designed so that the foreseen benefits and risks to the research participants are equivalent in all aspects. The choice of intervention (placebo or some treatment) to administer to participants in the control arm of a study may require the balancing of many factors, but the welfare of participants must be paramount. The choice of control should be justified as part of the research protocol. Ethics review committees should verify that the control is appropriate, does not impose risks that are unreasonable in relation to the anticipated benefits, and that placebo controls are not employed without compelling justification. The research design should have the potential to yield scientifically valid results relevant to the population in which the research takes place.

Justifications for using a placebo in the control arm are that:

- No treatment or intervention is accepted as being effective for the condition;³
- Treatments or interventions are accepted as being effective for the condition, but the use of a placebo will not result in more than minimal adverse effects that are entirely reversible;
- Treatments or interventions are accepted as effective for the condition, but no scientifically justifiable control option, other than a placebo, meets the objective of the research, and the anticipated benefits of the research substantially outweigh the risks to participants.⁴

Exceptions to the general rule may thus be permissible in research where the foreseen benefits or risks may be greater in one or more arms, but sound scientific and ethical justification is provided in the research protocol. This imbalance should be clearly communicated to the ethics committee as well as in the informed consent procedure.

² Just as prison doctors, who have no direct influence over the conditions in which they treat prisoners, are expected to work towards better health care services for prisoners, so researchers from developed countries have an ethical obligation to improve the often deplorable conditions in countries in which they undertake research. Attention to such considerations will ensure that the overall conditions under which research is undertaken will continuously improve for the benefit of research participants and their community.

³ The UNAIDS Guidance Document (Ethical Considerations in HIV Preventive Vaccine Research, May 2000 (Guidance point 11, commentary) advises as follows:

"A vaccine with proven efficacy in preventing infection or disease from HIV does not currently exist. Therefore, the use of a placebo control arm is ethically acceptable in appropriately designed protocols. ... In an effort to address the concern of lack of benefit to those randomly placed in a placebo group arm, ... it is recommended that the provision to these persons of another vaccine, such as for hepatitis B or tetanus, be considered."

Other preventive interventions should also be offered so that participants may protect themselves.

⁴ This calls for judgement and legitimacy within specific contexts. Guidelines are less like instruction manuals and more like Constitutions that require interpretation.

10. SPECIAL CONSIDERATION TO SPECIFIC SUBGROUPS OF THE SOCIETY

In addition to vulnerable communities, there are populations that require special consideration. These include women, prisoners, and children.

10.1 Women should be appropriately considered as research participants unless there are compelling reasons to support their exclusion.

10.2 In research involving prisoners, researchers should ensure the voluntary nature of the informed consent provided. Ethics committees reviewing research proposals involving prisoners should consider the inclusion of prisoners or prison representatives on such reviews.

7.2 Releasing and publishing research results

In recent years investigators have released preliminary research data prematurely to the Press, with serious and negative consequences. Premature release may result in the broadcast of sensational, inaccurate, misleading and irresponsible information on HIV and AIDS. Unfounded and insupportable claims may mislead the public and create unrealistic expectations. To prevent the creation of unrealistic or misleading expectations the following must be carefully considered:

- Researchers should not communicate the results of clinical trials or of any research to the public without first subjecting the study to peer review and to the normal rigorous scientific scrutiny needed for therapeutic and vaccine trials.
- Phase I and II trials should be published in scientifically refereed journals or be presented to scientific forums where results can be openly viewed and scrutinised.
- Important findings that need to be urgently released, should be released via the 'fast track' system employed by most reputable scientific journals. Most medical journals have now developed this system to fast-track review and publish important research findings.

7.3 Implementing research findings

Research with direct public-health implications, such as vaccine trials, requires wide consultation. This should include discussions with the South African Department of Health and the Medical Research Council, so that implementation of study results may be addressed at an early stage.

7.4 Research ethics committees and field support

Proposals for clinical and epidemiological research should be submitted for approval to relevant local research ethics committees and or to the South African Medicines and Medical Devices Regulatory Authority. Principal researchers or investigators must provide adequate supervision to ensure that ethical considerations are properly observed by their delegated staff.

8. HIV VACCINE RESEARCH

There are various international and national vaccine research initiatives in South Africa. This research is highly specialised and raises many ethical issues. This document will not address the range of issues that are being addressed by the appropriate vaccine research groups, including the Guidelines on Ethics for Medical Research: HIV Vaccine Trials (MRC Book 5). Some of the important ethical considerations include:

- The implications of widespread HIV testing on high-risk populations;
- The impact of local HIV prevention initiatives on research outcomes;
- The possible influence of receiving a vaccine candidate on reducing incentives for participants to take necessary precautions to prevent HIV transmission;
- The implications of 'false positive' HIV tests in patients who agree to vaccine trials;
- The appropriateness of the vaccine clade to the local population.

Vaccine research should be done in consultation with national and international initiatives.

9. INVOLVEMENT OF PEOPLE LIVING WITH HIV/AIDS (PLWHA/PWAs)

The many tensions, dilemmas and ethical considerations surrounding HIV/AIDS-related research necessitate a wide consultative process. PWAs are essential participants in this process and should form part of the consultation from the very early stages of the research process.

A placebo-control group need not be untreated. In so-called 'add-on studies' the treatment to be tested and the placebo are each added to a standard treatment. Such studies are considered permissible where a standard treatment is known to decrease mortality or irreversible morbidity but a trial with standard treatment as the active control cannot be carried out or would be difficult to interpret (ICH Guideline: Choice of Control Group and Related Issues in Clinical Trials, 2000). In evaluating improved treatments for life-threatening diseases such as cancer, HIV/AIDS or heart failure, add-on trials are a particularly useful means of finding improvements in treatment or interventions that are not fully effective or that may cause intolerable side-effects. Such studies also have a place in treatment for epilepsy, rheumatism and osteoporosis, for example.

2.16 Ethical Review

All health research conducted in South Africa must be reviewed by a research ethics committee and should not commence until the ethics committee has granted approval. This provides an objective appraisal of the effect of the proposed research as it affects the potential participants and the general day-to-day functioning of the health system. Section 3 of this document outlines in more detail the process of ethical review in South Africa.

2.17 Distributive Justice

Research proposals should provide sufficient information to determine whether there is a reasonable likelihood that the population on whom research is to be carried out will benefit from the research and its results. Selection of participants from groups who are unlikely to be beneficiaries of subsequent applications of the research should also be justified. Research proposals should indicate whether long-term therapy would be provided to participants after the completion or termination of the study.

3. ETHICAL REVIEW IN SOUTH AFRICA

Section 3 outlines the systems that exist in South Africa for the review of research projects involving human participants. It should be read in conjunction with the principles outlined in Section 2.

As mentioned in Section 2, a research ethics committee must review all research involving human participants in South Africa. When appropriate, research should be reviewed also by the South African drugs regulatory authority – the Medicines Control Council (MCC). Research may not commence unless the investigator has been granted documentation stating that the required approvals have been given.

This Section provides details of current research ethics committees in South Africa, the National Health Research Ethics Council and the Medicines Control Council, and outlines the process for gaining approval to conduct a clinical trial in South Africa.

3.1 Ethics Committees in South Africa

In South Africa, most higher education and research institutions, and even some of the large service-rendering health institutions have ethics committees, which are mainly responsible for the ethical review of research protocols. Currently the present number of research ethics committees is 34.

The National Health Act, 2003 (Act No.61 of 2003), proposes that the functions of Ethics Committees will include:

- Reviewing research proposals and protocols to ensure that research will be conducted in the spirit of endeavouring to promote health, and to prevent or cure disability and disease;
- Ensuring that humans involved in research are treated with dignity and that their well-being is not compromised, and that animals involved in research are treated compassionately;
- Ensuring that informed consent is obtained in the case of human participants;
- Granting approval in instances where research proposals and protocols meet ethical standards.

3.2 National Health Research Ethics Council

Apart from ethics committees and the MCC, no other body is empowered to promote and monitor good ethical practice in South African health research. On the basis of a discussion document developed by The National Department of Health proposing for the establishment of a National Health Research Ethics Council (NHREC), this is legislated by the National Health Act, 2003 (Act No.61 of 2003). The proposed structure, which appears below, is explained as follows: Parliament, through the National Health Act, 2003 (Act No.61 of 2003) establishes NHREC. The Act guarantees basic funding and empowers the Minister of Health to appoint NHREC members. NHREC consists of 15 members and elects its own chairperson. It meets four times per year, submits an annual report and advises the Minister about policy.

NHREC may establish ad-hoc committees to monitor or investigate the following:

- Policy standards and Standard Operating Procedures (SOP)
- Training and capacity-building;
- Appeals;
- Sub-committees.

NHREC is supported by a secretariat in the National Department of Health (DOH), which maintains a database of health research activities in South Africa. The DOH secretariat also appoints suitably qualified inspectors to monitor NHREC functions.

4.4 Linked anonymous HIV testing

In linked anonymous testing the HIV result is linked to a patient's other clinical data, but the patient remains anonymous. An independent person randomly assigns code numbers to patients' sera prior to HIV testing. The patients' identities are then removed from the database and the order of patients is changed. The HIV result is added to the database and 'linked' to the other data obtained before being returned to the investigators. This form of testing is best suited to research where HIV infection is a major confounder and not where HIV infection is the endpoint. Patients should provide informed consent to linked anonymous testing and be offered confidential HIV testing (see Confidential HIV testing).

In unlinked anonymous and linked anonymous HIV testing, researchers should not be able to identify, either directly or indirectly, the HIV test results of individuals.

5. POPULATION-BASED STUDIES TO PREVENT HIV TRANSMISSION

These are studies designed to assess the effect of an existing or proposed intervention on the transmission of HIV in a particular population; the effect of long-term use of contraceptives on the risk of acquiring HIV infection, post-sexual-abuse anti-retroviral prophylaxis, or placebo-controlled mother-to-child transmission.

Observational research studies may not provide immediate personal benefits and usually require large numbers of participants. Such studies require active community participation in both design and monitoring if the intervention is to be applied to a population. Consent of community representatives is not a substitute for individual consent.

Where an intervention has been shown to effectively reduce HIV transmission, it should not be withheld from research participants. All participants must be given information and the means to prevent HIV transmission by practising safer sex and effective treatment for sexually transmitted diseases. Any treatment offered should conform at least to the local standard of care.

6. INFORMED CONSENT AND INCENTIVES

Informed consent may be difficult to obtain, especially in disadvantaged and vulnerable communities where literacy and education are inadequate, and where there are language barriers. However, every effort must be made to achieve informed consent despite the challenge of linguistic and cultural barriers.

Incentives for patients to submit to research need careful consideration. Incentives should not be so excessive as to unfairly influence patients to submit themselves to the trial. Incentives relating to financial benefit, transport, and food should be fair and reasonable without 'making the patient an offer they cannot refuse' and thereby influence the patient to overlook other important considerations.

7. RESEARCHER ISSUES

7.1 Incentives

Pharmaceutical companies conducting research on their products frequently offer incentives to researchers. Researchers should be wary of incentives that may affect their objectivity and neutrality, while seeking to promote excessive allegiance to a particular pharmaceutical company. Researchers and members of ethical committees are required to disclose their financial involvements and other conflicts of interest relating to proposed research projects.

HIV testing is a complex issue with important implications and consequences to the individual. Informing persons that they are HIV-positive severely affects their quality of life and should be considered to be a major intervention.

4.1 Advantages and disadvantages of knowing one's HIV status

Selected advantages may include:-

- The opportunity to avail oneself of health care and counselling for HIV, which has many benefits;
- Access to antiretroviral treatment;
- Preventing the transmission of the HIV to sexual partners;
- Informing one's sexual partners;
- Not offering blood for transfusion;
- Preventing mother-to-child HIV transmission.

Selected disadvantages of knowing one's HIV status may include:

- Mental stress, depression and despair;
- Stigmatisation;
- Discrimination;
- Rejection by family, friends and sexual partners.

The advantages and disadvantages of HIV testing should be carefully considered and included in informed consent forms.

4.2 Confidential HIV testing

In confidential HIV testing, the following criteria should be met:-

- Adequate pre-test counselling;
- Informed consent in the case of children must be obtained from the parent or lawful guardian, as well as from the child if sufficiently mature. Consent to HIV testing should form part of the consent document for research that requires HIV testing.
- Adequate post-testing counselling;
- Referral to an accessible centre for ongoing psychosocial support and basic medical care. The centre should provide care that conforms at least to the national standard of care for HIV prevention and treatment, including the provision of condoms.

4.3 Unlinked anonymous HIV testing

This form of HIV testing is done for surveillance purposes, such as the National Antenatal Survey and the HIV and AIDS Behavioral Surveillance. It is considered ethically acceptable to conduct unlinked anonymous testing without individual consent if the following criteria are met:

- Blood is routinely collected for a reason other than HIV testing;
- After routine testing, personal identifiers are removed;
- Leftover blood or blood products are used for HIV testing;
- No other non-routine interventions, including the completion of questionnaires, are carried out.

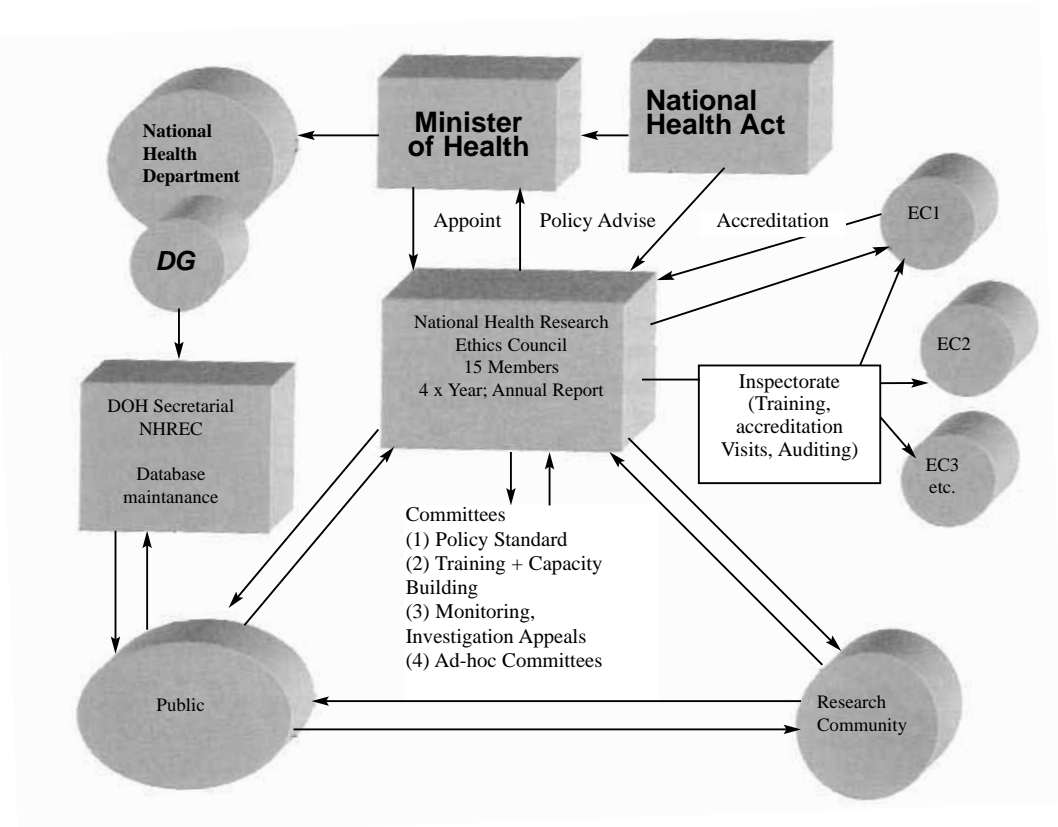
Ideally, confidential HIV testing should be available to individuals in the target population where unlinked HIV testing is conducted. Referring individuals to voluntary counseling and testing centres should be considered.

This inspectorate has functions relating to training, assessment of accreditation, and ad-hoc visits. It reports to NHREC, which may also interact directly with Ethics Committees.

NHREC maintains active, bilateral relations with the research community, and consults them on ethical issues. NHREC also exercises a public relations function.

It is envisaged that this National Health Research Ethics Council will be a central body to advise the Department of Health on the management of health research ethics in South Africa.

NHREC will not replace existing committees but would serve as a body to regulate matters of research ethics. All ethics committees approving health research in South Africa will be subjected to the registration/accreditation process and criteria determined by the NHREC. Continued education and regular auditing of ethics committees will be promoted by the NHREC to assist committees in attaining acceptable standards of operation.



3.3. Registration, Auditing and Accreditation of Research Ethics Committees in South Africa

3.3.1. Background to accreditation of Research Ethics Committees

Health research has the potential to make a substantial impact on health practice and on the wellbeing of individuals. While clinical trials and drug research are central to the health research agenda, such studies have the potential to expose participants to significant risk, and therefore ethical review for the conduct of such studies is essential to protect research participants. While the risks posed by non-pharmaceutical research are likely to be less severe, such studies vary in complexity and potential impact on participants, therefore ethical review is also required. Research ethics committees (RECs) which undertake the ethical review of trials require differing levels of skill and knowledge to deal with these different types of studies. Consequently, the process of registration, auditing and accreditation of Research Ethics Committees (RECs) needs to differentiate between ethics committees responsible for the approval and monitoring of different types of research.

The National Health Research Ethics Council (NHREC) has among its mandates the registration, auditing and accreditation of Research Ethics Committees (RECs) in South Africa. The need to formally evaluate the capacity of ethics committees is gaining importance globally. The South African model of accreditation has moved away from a prescriptive approach that only aims to control and enforce standards, to one that also promotes guidance, training, and support. Central to the proposed accreditation and audit process is the principle of empowering RECs. However, for those committees who persistently fail to comply with the standards set for accreditation, the National Health Act makes provision for the NHREC to legally enforce such standards. This document confines itself to the process for registration, audit and accreditation of RECs and has not considered enforcement. To enable RECs to develop the capacity that is required to satisfy the proposed accreditation procedure, an incremental approach of RECs is proposed. However, all health research ethics committees relating to human research are required to register with the NHREC.

3.3.2. Definition of Level 1 and Level 2 Research Ethics Committees

Level 1 comprises RECs that have the capacity to assess straightforward research designs that involve minimal risk to human participants. These include health research proposals *that do not* involve drug research, biomedical research involving human tissues, high-budget research (more than R250,000 per annum), and high-technology research (invasive, radiological, radio-active, and other research requiring substantial equipment). In addition, collaborative international health research, multi-centre studies, and long-term studies exceeding one year in duration, are not considered to be within the competence of Level 1 RECs. In brief, Level 1 Committees are meant to review 'minimal risk' research only, and are viewed as a stepping-stone to Level 2 accreditation. Level 1 RECs should err on the side of caution in judging what research they will review.

While Level 1 RECs are encouraged to develop their skills of a Level 2 within a five-year period, there may be some RECs that prefer to remain as a Level 1 approval committee. The NHREC may withdraw accreditation at any time should Level 1 RECs review research that is considered to be outside their level of competence, or does not meet the required standard for review.

Level 2 comprises RECs that may review all types of health research proposals.

Patient autonomy must be respected. endeavours to promote autonomy should be pursued through seeking opinions of representatives of vulnerable communities, including persons living with HIV and AIDS.

3.2 Placebo-controlled trials

Ethical guidelines that apply to controlled therapeutic trials are generally adequate to protect the rights of HIV-infected persons. A special case involves the use of placebo after an intervention has already been shown to be effective. The general principle is that the use of placebo in these circumstances is unethical. However with increasing disparities in health care between wealthy and poor countries, therapy that has been shown to be effective is often unaffordable in resource-poor settings. This is particularly true of therapeutic advances in HIV infection, which a far bigger health care problem in poor countries in sub-Saharan Africa than in industrialised countries. It may on occasion be justifiable to use placebo in communities that do not have access to interventions that are the standard care in resource-rich settings. However, placebos may only be used when the anticipated benefits will outweigh the risks to participants, and participants will not be harmed, and full justification must be provided for use of placebo.

3.3 Adverse drug effects

Drug trials have the potential to cause short- and long-term ill effects. The patient information section of the informed consent document should specify the action to be taken if the study drug or drugs are withdrawn because of side effects. In such a situation, appropriate therapy to manage the adverse drug effects should be made available within the study framework at no cost to the patient, by referral to the local health service, or through the patient's medical insurance, unless exceptions have been agreed upon by all parties.

3.4 Patient management after withdrawal from a study

Where patients withdraw from a study for any reason, or where a study is completed, the patients should be advised about the ongoing management of their condition. Except in cases where therapeutic efficacy is demonstrated (see below), ongoing therapy should be administered according to the local standard of care. Costs of this care should be borne by the local health service, the patient's medical insurance or the patient.

3.5 Access to study medications following the completion of clinical trials

Many patients who participate in HIV and AIDS treatment trials have no other access to drug therapy. Where a patient shows a therapeutic response to a study drug, that patient should be offered ongoing treatment. In designing studies, consideration should be given to the costs of long-term provision of study drugs and of clinical monitoring, including the costs of medical staff. The duration of drug therapy in a study should also be clearly stated in the patient information section of the informed consent document.

4. HIV TESTING

HIV testing is frequently required in clinical and epidemiological research, including:

- Epidemiological studies, such as sentinel surveillance on pregnant women;
- Observational studies, such as the effect of long-acting progestins on the risk of HIV transmission in women;
- Drug trials, to establish efficacy and safety;
- Vaccine trials.

country and to ensure sensitivity to the needs of vulnerable communities. Vulnerable communities are defined by UNAIDS as having some or all of the following characteristics:

- Limited economic development;
- Inadequate protection of human rights and discrimination on the basis of HIV antibody status;
- Inadequate cultural experience or understanding of scientific research;
- Limited availability of health care and treatment options;
- Limited ability of individuals in the community to provide informed consent.

As a result of past exploitation and oppression, South Africans are vulnerable to ethical abuses. Care and sensitivity should be applied to prevent exploitation of South Africa's disadvantaged communities.

Research initiated in developed countries, including Phase I and Phase II clinical trials, should not be conducted in South Africa merely because this country can offer better research opportunities. Research conducted in South Africa should be relevant to the health needs of the country.

Research and clinical trials, however, should be conducted within various settings and applied to communities in different social and economic circumstances. Research projects undertaken in South Africa should be carefully evaluated and examined as to their current and future relevance. The science of HIV and AIDS is developing rapidly and proposed interventions, which may seem to be costly and inappropriate at present, may indeed become realistic options in the future.

2.2 Research standards

Vulnerable communities are often characterised by sub-optimal living conditions and poor access to health and social services. This should not lessen the need for high-standard research and use of universally accepted ethical standards. It is imperative that good research and ethical standards be applied in vulnerable and non-vulnerable communities.

3. HIV-RELATED DRUG TRIALS

HIV-related clinical trials not only refer to anti-retroviral drugs but also to trials with medications such as immune modulators, and drugs for the treatment and prevention of HIV-related opportunistic infections.

3.1 Access to HIV related medication

Drug trials are conducted to determine various outcomes such as efficacy, safety, impact on health status of the individual, short and long term side effects, survival benefits, quality of life, adherence to drug regimens, compliance with therapy and comparisons with other therapeutic options.

While anti-retroviral therapy is effective, it is expensive and efforts have been made to make it available in the South African public sector. Participation in drug trials is often the easiest way of gaining access to anti-retroviral therapy. Drug trials should not be conducted solely because they facilitate access to drugs for some patients, although this may often provide benefits to the individual.

The rationale for drug trials should be independently assessed and evaluated on its merits. Researchers must ensure that patients in drug trials provide informed consent and understand the implications of the trial. This includes the advantages and disadvantages of all drug regimens, and the potential limitations in taking medications only for the period of the drug trial.

The ethics committees must consider these advantages and disadvantages to the trial participants and the general community to determine whether such trials are appropriate and relevant in the South African context.

3.3.3. The registration, accreditation and auditing process

3.3.3.1 Registration

All RECs are required to lodge a registration form with the NHREC within the first year of the establishment of the Council. Based on this registration application, the REC will be recorded in a register that will be publicly listed by NHREC. Following this, the NHREC will perform an audit of the application, and depending on the structure and functioning of the REC will accredit the committee as either a Level 1 or Level 2 REC.

Once the NHREC has evaluated the registration documents, further information may be requested, and/or remedial action may be required, for accreditation to proceed. A three months grace period is set for Level 2 RECs and a one-year grace period for Level 1 RECs to provide the relevant information. Failure to comply with the requests of the NHREC may result in rejection of the registration, or refusal to accredit the REC, depending on the problems identified by the NHREC.

3.3.3.2 Criteria for accreditation

The NHREC will develop criteria to be used for accreditation of RECs which will be based on the South African Guidelines for Medical Research and on other internationally recognised guidelines. The NHREC will evaluate the initial registration submissions of the RECs with the aim of ensuring that RECs comply with all the essential prerequisites that allows them to perform their functions as either a Level 1 or Level 2 committee.

Once the first comprehensive Accreditation Questionnaire has been completed, a much-simplified questionnaire focusing on 'change of status' will be completed annually, while every three years a further comprehensive assessment will be done to validate the interim 'change of status' reports.

3.3.3.3 Audit

The criteria for the accreditation of RECs may be altered as part of an annual review process performed by the NHREC, and such changes will reflect new ethical concerns or standards that have arisen as part of the national or international ethics dialogue. Any additional requirements will be published by the NHREC.

The NHREC will appoint from within its members a subcommittee to oversee the implementation of audit and accreditation. The actual data-collection will be undertaken by Department of Health staff under guidance of the subcommittee on accreditation.

3.3.4. Capacity Building for Research Ethics Committees

Part of the aim of the accreditation and audit process is to build capacity in ethics review of health research in South Africa. The accreditation criteria will be divided into 'standard' (which will entitle an REC to be listed as a Level 1 REC) and 'optimal' (which will entitle an REC to be listed as a Level 2 REC). At both levels, audit and enforcement will be introduced, using the same mechanisms and criteria.

To enable non-accredited RECs to become accredited RECs, and for Level 1 RECs to advance to Level 2, NHREC will identify resources, including Standard Operating Procedures, training materials and courses, web-based information, query and appeal procedures. Criteria related to training and maintenance of expertise, as part of the accreditation criteria will be developed by the NHREC.

Where required, NHREC will draft, summarise and clarify the legal framework within which RECs will function, in addition to the provisions of the Health Act.

Given the international nature of health research, it may be important to include international ethics expertise in reviewing NHREC activities, accreditation and audit criteria and procedures. With this objective, the NHREC may invite external experts to input into its activities.

3.4 Approval of health research including clinical trials in South Africa

Protocols for all health research (including research conducted by the private-sector) involving human participants must be submitted to an accredited ethics committee for approval.⁵ The following two steps must be taken before a clinical trial involving medicines may be conducted in South Africa:

- Ethics Committee approval must be obtained;
- Medicines Control Council approval must be obtained for both non-registered medicinal substances and new applications of registered substances.

3.5 The Medicines Control Council

The Medicines Control Council (MCC) must review all clinical trials of both registered and non-registered medicinal substances. The MCC has a statutory obligation to ensure that the drugs available in the country fulfil the necessary requirements for safety, quality and efficacy and that the decision to register a drug is in the interest of public health. In the case of an ongoing trial where there are serious breaches of Good Clinical Practice (GCP), the MCC may terminate a trial. Reference to the regulatory authority in this document refers to the MCC.

⁵ For further information refer to the Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants, in South Africa, 2000, Department of Health, Pretoria

APPENDIX A: ETHICAL CONSIDERATIONS FOR HIV/AIDS CLINICAL AND EPIDEMIOLOGICAL RESEARCH

PREFACE

This section emanated from a series of consultations held by the Task Group on Ethical Guidelines for HIV Research. The aim of this document is to provide broad ethical guidelines to address the current challenges posed by HIV and AIDS research, but it is understood that new problems will continue to present themselves. Therefore this section will be continually reviewed and revised as necessary. The particular ethical challenges posed by HIV vaccine research is set out in the guidelines on Ethics for Medical Research: HIV Vaccine Trials (MRC Book 5) which has been approved by the Interim National Health Research Ethics Committee.

1. BACKGROUND

In recent years there has been an increase in HIV-related clinical and epidemiological research. This has included advances in anti-retroviral therapy, which has influenced the clinical course of HIV infection, reduced mother-to-child HIV transmission and HIV transmission following occupational exposure to HIV. HIV vaccine research is now an international priority. HIV-related clinical research includes strategies to prevent HIV infection (through use of vaginal microbicides) and to investigate medications that may increase the risk of HIV infection, such as long-acting progestins. This research often necessitates determining the HIV status of individuals involved in clinical trials.

Clinical and epidemiological research involves complex ethical challenges. These include considerations of access to clinical trials, informed consent, use of medications after the completion of drug trials, drug toxicities, long-term side-effects, the appropriateness of proposed research to South Africa, and the release and publication of the research results.

South Africa is a middle-income country within which there are severe economic disparities; the majority of the population being of a low socio-economic status. South Africa, however, is in many ways an ideal country for clinical and epidemiological HIV-related research. It has a rapidly expanding HIV and AIDS epidemic that is favourable for research studies. The country's well-developed infrastructure offers clinical and scientific expertise, academic institutions of good standing, competent laboratory and clinical facilities and an industrial infrastructure, with high standards in communications and other relevant medical technologies. Information gained from clinical and epidemiological research could have critical implications for South Africa and in the international sphere including in research ethics.

This document attempts to address several ethical issues relating to HIV and AIDS clinical and epidemiological research in South Africa.

With many ethical issues, answers are not always clearly right or wrong. There are, however, several universally accepted ethical principles. These principles should be applied within the context of South Africa, and this document is intended to facilitate a more uniform approach to common ethical issues concerning HIV and AIDS related research.

2. SELECTED ISSUES RELATING TO HIV AND AIDS CLINICAL AND EPIDEMIOLOGICAL RESEARCH

2.1 Research should be appropriate to South Africa

International research ethical guidelines, including those of the Council for International Organisations of Medical Sciences, emphasise the need for proposed research to undergo ethical and scientific review in both the initiating and host countries. This is to avoid exploitation of participants in the host

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4. ETHICS COMMITTEES

An established research ethics committee must review and approve all research proposals involving human participants. This section details requirements for institutions in establishing an ethics committee, researchers in submitting research proposals and ethics committees in considering, reviewing and monitoring research proposals and projects.

- The primary role of a research ethics committee is to protect the rights and welfare of research participants. The primary responsibility of each member is to decide, independently, whether in his or her opinion the conduct of proposed research will so protect participants.
- Institutions or organisations that undertake research involving human participants should ensure there are adequate resources to establish and maintain an ethics committee in accordance with the prescripts outlined in this document.
- Terms of reference must be set out by the institution or organisation when establishing an ethics committee. Terms of reference must include the scope of its responsibilities, relationship to non-affiliated researchers, accountability, mechanisms for reporting and remuneration, if any, for members.
- The institution or organisation must accept legal responsibility for the decisions and advice received from the research ethics committee and indemnify the ethics committee's members.
- Researchers without affiliation to an institution or organisation with a research ethics committee must ensure that their projects are approved by an established ethics committee.

4.1 Composition

The research ethics committee should consist of members who, collectively, have the qualifications and experience to review and evaluate the science, health aspects and ethics of the proposed research. Research ethics committees should be independent, multi-disciplinary, multi-sectoral and pluralistic.

A research ethics committee must:

- Be representative of the communities it serves and, increasingly, reflect the demographic profile of the population of South Africa;
- Include members of both genders, although not more than 70% should be either male or female;
- Have at least nine members, with 60% constituting a quorum;
- Have a chairperson;
- Include at least two lay persons who have no affiliation to the institution, are not currently involved in medical, scientific or legal work and are preferably from the community in which the research is to take place;
- Include at least one member with knowledge of, and current experience in, areas of research that are likely to be regularly considered by the ethics committee;
- Include at least one member with knowledge of, and current experience in, the professional care, counselling or treatment of people. Such a member might be, for example, a medical practitioner, psychologist, social worker or nurse);
- Include at least one member who has professional training in both qualitative and quantitative research methodologies;
- Include at least one member who is legally trained.
- The institution or organisation must ensure that the membership is equipped to address all relevant considerations arising from the categories of research likely to be submitted to it.

The research ethics committee must ensure that it is adequately informed on all aspects of a research protocol, including its scientific and statistical validity, that are relevant to deciding whether the protocol is both acceptable on ethical grounds and conforms to the principles of this document.

4.2 Appointment of Members

The institution or organisation must determine procedures for recruitment and of appointment to the research ethics committee.

Members must be given formal notice of appointment and assurance that the institution or organisation will provide legal protection in respect of liabilities that may arise in the course of bona fide conduct of their duties as committee members.

4.3 Procedures

Research ethics committees should establish and record working procedures concerning:

- Frequency of meetings;
- Preparation of agenda and minutes;
- Distribution of papers prior to meetings;
- Presentation of research protocols;
- Presentation of all documents and other materials used to inform potential research participants;
- Quorum and methods of decision-making;
- Requirements for submission of research projects for ethical approval;
- Registration of applications;
- Timely review and notification of decisions;
- Written notification of decisions to researchers;
- The recording in writing of decisions made by the Committee and reasons for decisions;
- Confidentiality of the content of the protocols and of a committee's proceedings
- Reporting of adverse events;
- Reporting of amendments to protocols;
- Access to documents;
- Regular monitoring;
- Complaints procedures;
- Procedures for easy and adequate access to members of ethics committees;
- Fees charged, if any;
- End-of-trials review.

The ethics committee may approve, require amendment to, or reject a research proposal on ethical grounds. The ethics committee must record decisions in writing and should include reasons for rejection. A research ethics committee's feedback should be structured so as to be instructive to the researchers concerned. Researchers should be made aware that their statement of ethical considerations should not be a rote checklist but a real engagement with ethical issues.

In considering a research protocol, a research ethics committee may seek assistance from experts, but the committee must be satisfied that such experts have no conflicts of interest in relation to the research project under consideration.

A research ethics committee must ensure that no member of the committee adjudicates on research in which that member has any conflict of interest in relation to the research project under consideration.

A researcher must disclose to the research ethics committee the amount and sources, or potential sources, of funding for the research and must declare any affiliation or financial interest when proposing and when reporting the research.

A research proposal must include a statement of the ethical considerations involved in the proposed research. An ethics committee must be satisfied that the research protocol gives adequate consideration to participants' welfare, rights, beliefs, perceptions, customs and cultural heritage.

10. RESEARCH INVOLVING DECEPTION OF PARTICIPANTS, CONCEALMENT OR COVERT OBSERVATION

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. In studies of human behaviour there may be exceptional circumstances when studies cannot be conducted without deception, concealment or covert observation of participants. Before approving a research proposal that involves any degree of deception, concealment or covert observation, a research ethics committee must be satisfied that:

- The provision of detailed information to prospective participants about the purpose, methods and procedures of the research would compromise the scientific validity of that research;
- The precise extent of deception, concealment or covert observation is defined;
- There are no suitable alternative methods, not involving deception, concealment or covert observation, by which the desired information can be obtained;
- Participants are not exposed to an increased risk of harm as a result of the deception, concealment or covert observation;
- Adequate and prompt disclosure will be made and de-briefing provided to each participant as soon as practicable after the participant's participation is completed;
- Participants will have the opportunity to withdraw data that was obtained from them during the research without their knowledge or consent; and
- activities will not corrupt the relationship between researchers and research in general, with the community at large.

Institutions or organisations wishing to conduct research on genetic material and on information collected for non-research purposes, should develop and disseminate a general policy that informs patients that such material and information may be used for future research, following research ethics committee approval, subject to the issues raised in the first and second paragraphs of section 9.4. Patients of such institutions or organisations should be informed that this policy exists, and that their privacy and confidentiality will be protected. They should be given the opportunity to refuse consent to the use of their material and information for such research.

9.5 Genetic counseling

When research may reveal information of potential importance to the future health of an identified or potentially identifiable participant's future health or to the participant's offspring, the research protocol must provide for consent procedures, counselling, support, test quality and test result confidentiality, as would apply if the participant sought such information in a clinical setting. Otherwise such research may be performed only if the genetic material has been de-identified. Counselling and information arising from the research must be provided by health professionals who have appropriate training, skills and experience.

Participants who are asked to consent to the use of their genetic material and information for future research, should be counselled about the possible consequences of doing so. In general, their genetic material and information will be used for future research in de-identified form, and feedback will not be possible. However, the research ethics committee may direct the researchers to use the genetic material and information in potentially identifiable (coded) form. In such instances, the views of participants regarding the feedback of information of potential significance to their own or their relatives' future health should be established, recorded and respected. If feedback is requested, the participant should receive information and counselling about the implications of receiving that information. This could be provided at the time of obtaining consent or in the future, prior to the provision of the feedback.

Researchers' proposals for health research to be conducted in community settings must include a clear plan on how the communities will be consulted or involved in the research process, and how, in general, they are to be kept informed.

Communication between research sponsors and ethics committees should be directed through the Principal Investigator. In some situations, particularly in the private sector, the Principal Investigator may be an employee of the sponsoring company or of a clinical research organisation. All documents and other material used to inform potential research participants should be approved by the ethics committee, including plain-language information sheets, consent forms, questionnaires, advertisements and letters.

Research ethics committees must ensure that their members receive initial and continued education in research ethics and science, and are kept aware of current issues and developments in the broad area of ethics and science

4.4 Advocacy Role and Interpreters

Advocacy: An ethics committee must consider whether persons playing an advocacy role for any participant or group of participants should be invited to the ethics committee meeting to ensure informed decision-making and understanding by these participants.

Interpreters: Where research involves the participation of persons unfamiliar with the language in which the research is to be conducted, a research ethics committee must ensure that:

- The participant information statement has been translated into the participant's language;
- It is the investigator's responsibility to ensure that the participant understands the participant information statement;
- An interpreter is present during discussions with the participants about the project. As a rule the interpreter should be independent, but when the research proposal is of minimal risk, a relevant language-speaking relative or friend of the participant may be acceptable.

4.5 Expedited Reviews for Maximal Public Benefit

A research ethics committee may establish procedures for expedited review of research when this is in the public interest, and in so doing, determine the class or classes of research to which an expedited review procedure is to apply. Expedited review and approval may be considered for research where participants have a disease that may be rapidly fatal.

In general, research with potential to cause physical or psychological harm should not be considered for expedited review. This includes drug trials, research involving invasive procedures and research involving sensitive personal or cultural issues.

4.6 Recording of Decisions

A research ethics committee shall maintain a record of all research protocols received and reviewed including the:

- Name of responsible institution or organisation;
- Project identification number;
- Principal investigator;
- Title of the project;
- Date of ethical approval or non-approval;
- Approval or non-approval of changes to the protocol;
- Approval or non-approval of changes to the information sheets and informed-consent forms;
- Approval or non-approval of changes to advertising materials, letters and notices;
- Complaints from researchers whose protocols were not approved;

- The terms and conditions of approval of any protocol;
- Whether approval was by expedited review;
- Whether the opinion of another ethics committee was considered;
- Action taken by the ethics committee to monitor the conduct of the research.

For multi-centred research proposals, the ethics committee shall also record, from information provided by the investigator:

- Details of other centres involved
- The approval status of the study at each centre;
- Details of any amendments required at other centres.

An ethics committee shall retain on file a copy of each research protocol and application submitted to it for approval. The file shall include information sheets, consent forms and relevant correspondence, all in the form in which they were approved. A list shall be kept of committee members who were present during discussion of the application and when the final decision of the committee was reached.

4.7 Monitoring

A research ethics committee has the responsibility to ensure that the conduct of all research approved by the ethics committee is monitored. The frequency and type of monitoring should reflect the degree of risk to participants in the research project.

A research ethics committee must request at regular periods, at least annually, reports from the principal investigator on matters including:

- Progress to date, or outcome in the case of completed research;
- Information concerning maintenance and security of records;
- Evidence of compliance with the approved protocol;
- Evidence of compliance with any conditions of approval.

Research ethics committees should inform the principal investigator, in writing, of decisions made after the review of progress reports.

A research ethics committee may recommend and adopt any additional appropriate mechanism for monitoring, including the random inspection of research sites, data and signed consent forms, and records of interviews, with the prior consent of research participants.

As a condition of approval of each protocol, a research ethics committee shall require that researchers immediately report anything that might warrant review of ethical approval of the protocol, including:

- Serious or unexpected adverse effects on participants;
- Proposed changes in the protocol;
- Unforeseen events that might affect continued ethical acceptability of the project.

A research ethics committee, as a condition of approval of the research proposal, may require researchers to inform the committee, giving reasons, if the research project is discontinued before the expected date of completion.

4.8 Complaints

- Each research ethics committee should establish complaints procedures.
- Any person has the right to forward a complaint to the National Health Research Ethics Council, if the response of the local Ethics Committee is considered inadequate.
- The National Health Research Ethics Council in collaboration with Ethics Committees should develop a policy to protect whistle-blowers, these are researchers who have identified unethical behaviours on the part of colleagues and divulge such information in good faith. The National Research Ethics Council will develop guidelines for "whistleblowers".

be asked whether they wish to be notified of research results that relate to them as individuals. A decision not to be notified should be respected;

- That if the research generates information that might be relevant to the health of other family members, the consent of participants will be sought before offering to disclose such information to the family members concerned;
- Whether or not information about family members, in addition to that provided by participants, is required for the research;
- That consent to approach relatives will first be obtained from the participant. In deciding to recruit relatives, researchers must consider the privacy and any known sensitivities of the relatives, accepted habits of communication within the family, and the balance of potential benefits and harms that might result from their participation in the research;
- Whether or not the research has the potential to detect non-paternity or non-maternity;
- That 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 research 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;
- Whether or not their genetic material is to be disposed of on completion of the research or after a further period of storage. Some participants or collectivities may have sensitivities regarding disposal of their genetic material. These sensitivities should be established and recorded at the start of the research and account should be taken of them at the time of disposal;
- That they are free to withdraw from the research at any time. This may involve a request that their genetic material and information be disposed of, provided the samples can be identified. Alternatively, samples and information may be retained provided they are de-identified, depending on the wishes of the participants.

When researchers propose to collect genetic material and information from individuals chosen by virtue of their membership of a particular collectivity, consent should be sought from appropriate collectivity representatives as well as from the individuals concerned, in accordance with Research Involving Collectivities.

9.4 Where the requirement for consent could be waived

As a general principle, where a researcher proposes to conduct research using stored genetic material or genetic information, consent is required from the person from whom the material was derived, or to whom the information relates.

An ethics committee may sometimes waive, with or without conditions, the requirement for consent. In determining whether consent may be waived or waived subject to conditions, a research ethics committee may take into account:

- The nature of any existing consent relating to the collection and storage of genetic material and genetic information;
- The justification presented for seeking waiver of consent, including the extent to which it is impossible, difficult or intrusive to obtain consent;
- The proposed arrangements to protect privacy, including the extent to which it is possible to de-identify the genetic material and genetic information;
- The extent to which the proposed research poses a risk to the privacy and wellbeing of the participant;
- Whether the research proposal is an extension of, or is closely related to, a previously approved research project;
- The possibility of commercial exploitation of derivatives of the sample, and relevant statutory provisions.

9.2 Privacy and confidentiality

Researchers must ensure the confidentiality and privacy of stored genetic information or research results relating to identified or potentially identifiable participants.

Researchers must keep information provided by participants about family members confidential. Such confidential information must not be revealed either to family members or to persons who are not family members.

The research protocol must specify whether genetic information or genetic material, and any information derived from studying the genetic material, will be stored in identified, potentially identifiable (coded) or de-identified (not identifiable, anonymous) form. (See [Section 7](#)). Researchers should be aware that the rarity of some genetic disorders might allow certain families to be identified by other researchers, and in some cases by members of the community, even where information has been communicated to others in de-identified form.

Researchers should consider carefully the consequences of storing information and material in de-identified form for the proposed research, for future research and for communication of research results to participants.

Identifying genetic information must not be released to others, including family members, without the written consent of the individual to whom the information relates, or a person or institution which may legally provide consent for that person.

A researcher must not transfer genetic material and related information to another research group unless:

- The researcher and the other research group are collaborating on research that has been approved by an ethics committee;
- The genetic material and information is provided in a form that ensures that participants cannot be identified. However, an ethics committee may approve transfer of genetic material and information, which is identified, or potentially identifiable, in certain circumstances. Where this occurs, the other research group must undertake to hold the material and related information in such a manner that there is no reduction in the protection of the privacy of the participants or of the confidentiality of the information.

9.3 Consent

The investigator or other appropriate person or organisation as specified in guidelines of this statement, must obtain a consent for human genetic research unless an ethics committee waives the requirement for consent.

When consent is sought from participants for collection of genetic material and information, they should be informed:

- That they are free to refuse consent without giving reasons. Researchers should be aware that for some genetic research, an individual's participation may be requested by, and may primarily serve the interests of, other family members and the individual may agree to participate out of a sense of obligation;
- About arrangements to ensure the privacy and confidentiality of their genetic information both with regard to other family members and persons who are not family members. Participants should be informed whether their genetic material and information will be used in an identified, potentially identifiable, or de-identified form and, if their material or information is to be de-identified, that it will not be possible to provide them with personal research results;
- Whether or not the research might reveal information of potential importance to the future health of an identified or potentially identifiable participant or the participant's offspring;
- That the researchers will endeavour to provide information about the outcome of the research. Participants should be advised when it is not intended to provide feedback. Participants should

4.9 Suspension or Discontinuation of Research

Where a research ethics committee is satisfied that such circumstances have arisen that a research project is not being conducted in accordance with the approved protocol and that, as a result, the welfare and rights of participants are not or will not be protected, the research ethics committee may withdraw approval. The research ethics committee shall also inform the researcher and the institution or organisation of its action, and shall recommend that the research project be discontinued or suspended, or that other appropriate steps be taken.

Where ethical approval has been withdrawn, a researcher must discontinue the research and comply with any special conditions required by the ethics committee.

4.10 Compliance Reports to the National Health Research Ethics Council (NHREC)

The National Health Research Ethics Council will be responsible for auditing the activities of research ethics committees to ensure their compliance with this document. All research ethics committees must be registered with the National Health Research Ethics Council, and must provide a list of their members, before considering any research protocol.

An institution or organisation and its ethics committee shall open its records to the NHREC on request.

An institution or organisation and its ethics committee shall report annually to the NHREC information relevant to its procedures, including:

- Membership and membership changes;
- The number of meetings held;
- Confirmation of participation by required categories of members;
- The number of protocols presented, the number approved and the number rejected;
- Monitoring and related problems;
- Complaints procedures and number of complaints received and handled.

5. RESEARCH REQUIRING ADDITIONAL ATTENTION

South African research ethics committees must pay special attention to protecting the welfare of certain classes of participants,¹ such as minors (this includes children and adolescents), pregnant women, prisoners, people with intellectual or mental impairment, people for whom English is not a first language, and people from vulnerable communities. Certain types of research also require special attention. Research ethics committees may impose additional measures to protect the welfare of participants. Research ethics committees may make it mandatory to conduct post-research investigations to review whether there was compliance with the additional measures imposed. If compliance was defective, research ethics committees may withdraw approval for the research investigation concerned.

Participants whose involvement needs additional attention include:

- Minors – children and adolescents
- Persons with intellectual or mental impairment
- Disabled persons
- Persons in dependent relationships
- Persons participating in research as groups (referred to as collectivities)
- Pregnant women

Types of research that need additional attention include:

- Research involving indigenous medical systems
- Emergency care research
- Innovative therapy or interventions
- Research necessitating ambiguity of information for participants.

5.1 Research involving minors²

Minors should participate in research⁴ only where their participation is indispensable to the research and where participation is not contrary to the individual minor's best interests. The research should investigate a problem of relevance to children. Where research involving minors is proposed, a research ethics committee should determine whether the research might be equally informative if carried out with consenting adults. If so, the research ethics committee should require strong justification for the inclusion of minors. Note that all types of **clinical research on minors** should be scrutinized carefully.

For purposes of these guidelines,

- 'child' means a person who has not yet reached puberty;
- 'adolescent' means a person who has reached puberty;
- 'therapeutic' means interventions that may hold out the prospect of direct health-related benefit for the participant;
- 'non-therapeutic' means interventions that will not hold out the prospect of direct health-related benefit for the participant but results may be produced that significantly contribute to generalisable knowledge about the participant's condition.

¹ For further, more detailed, discussion on special classes of participants, refer to CIOMS *International Ethical Guidelines for Biomedical Research Involving Human Subjects (2002)* Guidelines 13-17, http://www.cioms.ch/guidelines_nov_2002_blurb.htm [last visited 15 October 2004]; US Department of Health & Human Services, Office for Human Research Protections, <http://www.hhs.gov/ohrp/> [last visited 15 October 2004].

9. HUMAN GENETIC RESEARCH

Genetic research enhances our understanding of how genes and environmental factors interact to influence the health of individuals and communities. Genetic research also has the potential to generate knowledge that could improve the health of individuals and communities.

Genetic research can reveal information about an individual's susceptibility to disease and hence about the individual's future health. Such information may be of interest and benefit to research participants, especially where preventive strategies exist.

In addition to ethical considerations, which apply to all research involving humans, there are ethical issues unique to genetic research. They arise from the nature of genes and genetic information which, although personal, are also shared with other family members and with unrelated individuals in the population.

Participation of families rather than individuals is required for many genetic research studies. Research results and genetic material and information collected for research may be of significance to the health of blood relatives, including some who have not participated in the research. These family members may have an interest in their relative's genetic material or in information that the research generates, because testing that material or acquiring that information may create new options for life decisions, including those with the potential to improve health. However, some family members may prefer not to be given information that might provide knowledge of future health or health risks. In addition, other family members who are not blood relatives, such as partners and spouses, may have an interest because of concerns about the health of offspring.

Participants may be at risk of harm arising from the use of genetic information, including stigmatisation or unfair discrimination, and adoption of exclusionary policies. Researchers should recognise that special care must be taken to protect the privacy and confidentiality of genetic information. Research ethics committees should require researchers to consider whether a proposed genetic study might lead to a potential harm to participants, and what steps can be implemented to obviate such harm. The results of genetic tests, especially those that provide information about future health, could be used, potentially, by third parties such as insurance companies and employers to assist with decisions concerning research participants and their families. By participating in genetic research, people should not be put at risk of being deprived of benefits available to other members of the community.

9.1 Social significance and consequences of human genetic research

Researchers should consider the social and cultural significance of their research, especially in the areas of complex socially significant characteristics and the genetic characteristics of collectivities. When such characteristics are the subject of research, Research ethics committees should satisfy themselves that there are no contestable or dubious ethical values subsumed within the research protocol.

When assessing proposals of this type, ethics committees should consider the balance between the contribution to knowledge and the potential for harm to individuals or collectivities. One of the potential harms that may arise from genetic research is the adoption of exclusionary policies. Researchers should be asked by ethics committees whether their studies may lead to such exclusionary policies and what steps they can implement to obviate such policies.

Where it is proposed that stored human tissue samples are to be used for a research purposes different from that of the previously approved research, consent for the use of the tissue samples in the new research should be obtained.

The consent of donors should be obtained where it is proposed to use tissue samples that have been:

- Held in storage following, or in association with, clinical investigations;
- Held in archives or banks; or removed in the course of a clinical procedure and not required for any clinical purpose, in research that may lead to harm, benefit or injustice to a donor of such tissue.

8.5 Where the requirement for consent might be waived

A research ethics committee may sometimes waive, with or without conditions, the requirement for consent. In determining whether consent may be waived, or waived subject to conditions, a research ethics committee may take into account:

- 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.

8.6 Confidentiality

Where human tissue samples or related information are gathered in the course of a professional relationship, professional confidentiality must be observed. Identification of samples must be limited to the minimum necessary to achieve the stated objectives of the study. If the study may produce information relevant to the health and wellbeing of the person from whom the sample was derived, the ethics committee may request procedures to identify participants to facilitate appropriate follow-up.

8.7 Human tissue repositories

Human tissue is collected, stored and distributed for research purposes by a human tissue repository. The three components of repository activities are:

- Collection of samples;
- Storage and data management in an appropriate repository;
- Investigation of recipients.

The research ethics committee (REC) should oversee the operation of the repository and its data management centre. Supervision would include:

- REC review and approval of a protocol specifying conditions under which data and specimens may be collected and shared;
- Ensuring adequate provisions are made for the protection of the privacy of the donors and the maintenance of the confidentiality of the data;
- REC review and approval of a sample collection protocol and the informed consent document for the distribution to tissue collectors and their local RECs;

5.2 Research involving a child should be approved only if:

- The research, including observational research,⁴ places the child at no more than minimal risk (that is, the risk commensurate with daily life or routine medical or psychological examinations – referred to as 'negligible risk' in some guidelines); or
- The research involves more than minimal risk but provides possible benefit for the child participant. The degree of risk must be justified by the potential benefit; or
- The research, including observational research,⁵ involves greater than minimal risk, with no prospect of direct benefit to the child participant, but has a high probability of providing significantly generalisable knowledge; that is the risk should be justified by the risk-knowledge ratio. The risks must represent no more than a minor increase over minimal risk.

Consent for minors to participate in research must be obtained from:

- The parents or legal guardian in all but exceptional circumstances (such as emergencies); and
- The minor where s/he is competent to make the decision; and
- Any organization or person required by law, eg the National Health Act 61 of 2003.
- Where the minor is not competent, assent from the child (where appropriate) and permission from the parent(s) or legal guardian must be sought. No other caregiver can act on behalf of a child in providing consent to participate.
- A minor's refusal to participate in research must be respected, ie such refusal settles the matter.
- In all cases, the protocol must provide sufficient information to justify clearly why children should be included as participants.

5.2.1 Child assent:

The research ethics committee must ensure that adequate steps are outlined in the protocol to obtain the child's assent when, in the judgement of the research ethics committee, the child is capable of providing such assent. When the research ethics committee decides that assent is required, it must also indicate whether and how such assent must be documented.

² The Constitution (Act 108 of 1996) provides that a child is a person younger than 18 years. This is potentially confusing because, currently, minority ends at 21 years of age (in terms of the Age of Majority Act 57 of 1972, which was not repealed by the Constitution). Furthermore, the Child Care Act 74 of 1983 confers power on (but does not compel) minors to consent to medical treatment in two age categories, viz those who are 18 years and older may consent to a surgical operation, while those who are 14 years and older may consent to medical treatment, which, though not defined in the Act, is interpreted generally as non-invasive interventions, but including blood or blood product transfusion and excluding tooth extraction (see *Van Heerden et al Boberg's Law of Persons and the Family* 2nd ed. 1999: 853 n58). The Child Care Act specifically states that 'child' does not have the same meaning as 'minor' in terms of the Age of Majority Act. Considerable confusion exists regarding whether the provisions in the Child Care Act (to be repealed by the Children's Bill [B 70 – 2003 Reintroduced]) extend to consent to participation in medical research. The National Health Act 61 of 2003 refers to 'minors' rather than 'children' in s 72 which deals with research with human subjects. Impliedly, therefore, consent to medical treatment differs from consent to participation in medical research. This latter Act also refers to 'therapeutic' and 'non-therapeutic' in connection with research with minors. In particular, the Act requires that research or experimentation may be conducted on a minor only if it is in the minor's best interests. The age of majority may be lowered to 18 years when the Children's Bill (currently before Parliament) is promulgated. These guidelines use 'minor' to indicate the current law, ie majority begins at 21 years of age.

³ Section 6 of the Children's Bill stipulates various factors that must be considered when applying the best interest of child standard. Research ethics committees should familiarise themselves with these factors.

⁴ Of a non-invasive nature that involves no interference with the bodily or psychological integrity of the child.

⁵ Of an invasive nature that may involve interference with the bodily or psychological integrity of the child, eg questions about sensitive matters that could cause emotional upset for the child. The consequences of reporting obligations on health care workers in cases of suspected abuse must be taken into consideration too.

5.2.2 Parental permission:

Where the research does not involve greater than minimal risk to the child, or involves greater than minimal risk but presents the likelihood of direct benefit to the child, the research ethics committee may find that the permission of one parent is sufficient. Permission from both parents is necessary where the research involves greater than minimal risk, is of no direct benefit to the child but is likely to produce generalisable knowledge. Where only one parent is available for reasons including the death, incompetence or disappearance of the other, or where a court has placed the child in the sole custody of one parent, then the permission of that one parent is sufficient for participation in the latter type of research. In the event of conflicting views between the parents, the child's best interest settles the matter.⁶

5.3 Adolescents

In terms of section 39(4) of the Child Care Act 74 of 1983 and in the absence of specific legislative provisions to the contrary, adolescents who have attained the age of 14 years are legally capable of consenting to medical treatment of themselves and their children. Adolescents who have attained the age of 18 years are legally capable of consenting to surgical operations upon themselves provided in all cases the adolescent is competent, i.e. sane and sober. Conversely, the consent of a parent or legal guardian is required for medical treatment or an operation if the adolescent is under the age of 14 or 18 years respectively. Note, however, that an unmarried mother who is herself a minor may not consent to the participation of her child in research investigations. Her guardians (usually her parents) are also the guardians of her child and must thus consent to the child's participation as set out above.⁷

The Children's Bill will repeal the Child Care Act, amongst other legislation. The Children's Bill makes no provision for age categories and consent to treatment. Instead it states that '[e]very child capable of participating meaningfully in any matter concerning that child has the right to participate in those proceedings in an appropriate way and views expressed by the child must be given due consideration'.⁸ The National Health Act does not distinguish between minors who are children and minors who are adolescents and requires the consent process to be the same for both groups, subject to the distinction between 'therapeutic' and 'non-therapeutic' research. As discussed above (see n 2), research is not the same as medical treatment. It is rarely arguable that participation in medical research is necessary.

It is arguable, however, that adolescents may be capable of consenting themselves to certain types of research participation and that, for particular types of research, it may be desirable that they do so unassisted.

5.3.1 Research involving adolescents who may consent unassisted should be approved only if:

- The research, including observational research,⁹ places the adolescent at no more than minimal risk; **and**
- The nature of the research is such that, in the opinion of the research ethics committee, the parents or legal guardians or community at large are unlikely to object to the adolescent consenting him or herself to participation in the investigation. The opinion of the research ethics committee must be informed by information gathered from the community concerned and by contributions from the lay members of the committee.
- In all cases, the protocol must provide sufficient information to justify clearly why adolescents should be included as participants.
- In all cases, the protocol must justify clearly why the adolescent participants should consent unassisted.

⁸ Section 10 of the Children's Bill. Section 17 of the Bill stipulates the age of majority as 18 years.

⁹ Of a non-invasive nature that involves no interference with the bodily or psychological integrity of the adolescent.

8.2 Respect for persons

The fundamental ethical principle to be observed in the use of human tissue samples for research is respect for the person. This is reflected in:

- Provision to the donor of full information about the purposes of the sampling, or and 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 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.

If research using human tissue samples will require access to medical records of donors, consent for permission to use information in the donors' medical records should be obtained.

It is important for institutions or organisations, in conjunction with their ethics committees, to determine when consent should be sought for the use of tissue in research or when a waiver of the requirement for consent may be considered.

8.3 Institutional responsibility

Institutions or organisations at which research involving the use of human tissue samples is conducted, should develop policies regulating the conduct and ethical approval of such research. All research must conform to the National Health Act, 2003 (Act No 61 of 2003) and other relevant legislation and also be consistent with this statement. These policies must provide guidance to researchers and ethics committees in relation to soliciting or accepting voluntary donations of, and specifying conditions for, the use of human tissue samples in research. In their development, relevant considerations should include:

- The nature and cultural or religious sensitivity of the person who was the source of the sample;
- The original reason for its collection;
- The purpose of the research.

It is the responsibility of the institution or organisation at which research involving human tissues samples is conducted, to ensure that all uses of human tissue samples are in accordance with the consent given by the donors. It is also the responsibility of such institutions or organisations to maintain proper records of all uses of the human tissues samples in their custody. These records should include copies of ethics approval obtained for all uses. Research ethics committees and regulatory authorities should be given access to these records.

Samples that are no longer required should be disposed of safely and sensitively.

8.4 Where consent would be required

Where human tissue samples are collected for purposes including research, consent for their use in research is generally required. Consent should:

- Be voluntary;
- Be specific to the purpose for which the tissue is to be used;
- Be honoured by the provision of full information about the project, including advice as to whether tissue samples are to be stored after completion of the research for which consent is given.

8. USE OF HUMAN TISSUE SAMPLES

8.1 National Health Act, 2003 (Act No. 61 of 2003) Section 68

Section 68 of the National Health Act, 2003 (Act No.61 of 2003) make provision for the minister to make regulations relating to tissue, cells, organs, blood, blood products and gametes:

- (1) The Minister may make regulations regarding-
- (a) the post-mortem examination of bodies of deceased persons;
 - (b) the preservation, use and disposal of bodies, including unclaimed bodies;
 - (c) the removal of donated tissue or cells from persons, tissue or cells obtained from post-mortem examinations and the procurement, processing, storage, supply and allocation of tissue or human cells by institutions and persons;
 - (d) tissue transplants;
 - (e) the production, packaging, sealing, labelling, storage and supplying of therapeutic, diagnostic and prophylactic substances from tissue;
 - (f) the supply of tissue, organs, oocytes, human stem cells and other human cells, blood, blood products or gametes;
 - (g) the importation and exportation of tissue, human cells, blood, blood products or gametes
 - (h) the withdrawal of blood from living persons and the preservation, testing, processing, supply or disposal of withdrawn or imported blood;
 - (i) the administering of blood and any blood product to living persons;
 - (j) the production, packaging, sealing, labelling and supplying of blood and blood products;
 - (k) the bringing together outside the human body of male and female gametes, and research with regard to the product of the union of those gametes;
 - (l) the artificial fertilisation of persons;
 - (m) the appointment and functions of inspectors of anatomy and investigating officers;
 - (n) the records and registers to be kept by persons and institutions;
 - (o) the returns and reports, including extracts from registers, to be submitted to specified persons and institutions;
 - (p) the acquisition, storage, harvesting, utilisation or manipulation of tissue, blood, blood products, organs, gametes, oocytes or human stem cells for any purpose;
 - (q) the appointment and functions of inspectors of the national blood transfusion service and progenitor cell transplant institutions; and
 - (r) any other matter relating to regulating the control and the use of human bodies, tissue, organs, gametes, blood and blood products in humans.
- (2) The Minister, with the concurrence of the Cabinet member responsible for finance, may make regulations concerning the payment of persons or institutions in connection with procurement, storage, supply, import or export of human bodies, tissue, blood, blood products or gametes.
- (3) The Minister may, if it is consistent with the objects of this Act and upon such conditions as the Minister may deem fit, by notice in the *Gazette* exempt any person or category of persons from any or all of the regulations made under this section.

The principles of ethical conduct and review described in the above statement should govern all research using human tissues or bodies within the prescribed regulations of the National Health Act, 2003 (Act No. 61 of 2003) (also see Appendix E).

Where human tissue is to be used in research, researchers and research ethics committees must be satisfied that the research proposal conforms to the guidelines. The additional ethical issues that arise in genetic research using human tissue need to be addressed in conformity with human genetic research (Reproductive Biology and Genetic Research [MRC Book 2]).

Approval must be obtained from accredited research ethics committees for collecting samples of human material for research. New research ethics committee approval must be obtained for all research projects not specifically mentioned when consent was originally obtained.

5.3.2 Research involving adolescents who assent assisted by parents or legal guardians should be approved only if:

- The research involves more than minimal risk but provides possible direct benefit for the adolescent participant. The degree of risk must be justified by the potential benefit; or
- The research, including observational research,¹⁰ involves greater than minimal risk, with no prospect of direct benefit to the adolescent participant, but has a high probability of contributing to generalisable knowledge. In addition the risk must represent no more than minor increase over minimal risk. (See 5.2).
- In all cases the protocol must provide sufficient information to justify clearly why adolescents should be included as participants.
- In all cases, assent from the adolescent and permission from the parent(s) or legal guardian must be sought. No other caregiver can act on behalf of an adolescent in providing consent to participate.

5.3.3 Adolescent assent: The research ethics committee must ensure that adequate steps are outlined in the protocol to obtain the adolescent's assent when, in the judgement of the research ethics committee, the adolescent is capable of providing such assent. When the research ethics committee decides that assent is required, it must also indicate whether and how such assent must be documented.

5.3.4 Parental permission: Where, in the judgement of the research ethics committee, the adolescent should not consent unassisted, or where the research involves greater than minimal risk but presents the likelihood of direct benefit to the adolescent, the research ethics committee may find that the permission of one parent is sufficient. Permission from both parents is necessary where the research involves greater than minimal risk, is of no direct benefit to the adolescent but is likely to produce generalisable knowledge about the adolescent's condition. Exceptions would include situations as set out in 5.2.2.

5.4 Research involving persons in dependent relationships or comparable situations

Persons whose proposed involvement in research arises from dependent or comparable relationships need additional attention and the research ethics committee must be satisfied that their consent is both adequately informed and voluntary.

It is not possible to define such relationships exhaustively, but they include persons who are in junior or subordinate positions in hierarchically structured groups and may include relationships between:

- older persons and their caregivers;
- persons with chronic conditions or disabilities and their caregivers;
- wards of State and guardians;
- patients and health-care professionals;
- students and teachers;
- prisoners and prison authorities;
- persons with life-threatening illnesses;
- employees and employers, including farm workers and their employers, including members of the uniformed services and hospital laboratory staff and their employers.

¹⁰ Of an invasive nature that may involve interference with the bodily or psychological integrity of the adolescent, e.g. questions about sensitive matters that could cause emotional upset for the adolescent. The consequences of the reporting obligations on health care workers in cases of suspected abuse must be taken into consideration too.

5.5 Research involving women

Exclusion of women as research participants has led to a lack of data needed to promote women's health. Research ethics committees should consider whether the exclusion of women is justified in terms of research priorities and the specific research question under consideration. As part of advocating improved health for women, researchers have ethical obligations to conduct research that does not perpetuate discriminations against women by unfairly or unjustifiably excluding them from study protocols.

Research ethics committees must give extra attention to research that involves women who are, or may become pregnant, because of the additional health concerns during pregnancy and the need to avoid unnecessary risk to the foetus. Reasons for excluding women from research should be adequately justified both from the point of protecting the health of a foetus and from the perspective of whether such exclusion is scientifically supportable.

Guidelines for inclusion of "special populations" as participants in research (The IRB Policy and Procedure Manual [1997])

No research activities involving pregnant women and fetuses may be undertaken unless:

- Appropriate studies on animals and non-pregnant individuals have been completed
- The purpose of the activity is to meet the health needs of the mother of the particular foetus, the risk to the foetus is minimal and, in all cases, presents the least possible risk for achieving the objectives of the activity.

Individuals engaged in the activity will have no part in:

- any decision as to the timing, method and procedures used to terminate the pregnancy,
- determining the viability of the foetus at the termination of the pregnancy.
- No procedural changes, which may cause greater than minimal risk to the foetus or the pregnant woman, will be introduced into the procedure for terminating the pregnancy solely in the interest of the activity.

5.6 Pregnant women as participants.

No pregnant woman may be involved as a participant in any research activity unless¹¹:

- The purpose of the activity is to meet the health needs of the mother and the foetus will be placed at risk only to the minimum extent necessary to meet such needs, or
- The risk to the foetus is minimal.

Any activity permitted above may be conducted only if the mother is legally competent and has given informed consent after having been fully informed about the possible impact on the foetus.

The father's informed consent need not be secured if:

- the purpose of the activity is to meet the health needs of the mother;
- his identity or whereabouts cannot reasonably be ascertained;
- he is not reasonably available; or

¹¹ Clinical trials involving pregnant women or nursing mothers should ideally involve products where the toxicology in adults is established and is acceptable. In the case of pregnant women the potential risks associated with using a substance whose short term and long term effects on a foetus and developing infant are unknown, should be outweighed by the benefits. An example of a positive risk benefit ratio would be the use of anti-retrovirals in mother to child HIV transmission studies. For nursing mothers, the amount of drug passing into breast milk should be established and the potential impact on a breast fed infant anticipated, and the mother so advised.

7.11 Disclosure of research results

Researchers should not inform the Press about the findings of research unless the findings have been subjected to some form of peer review - that is, presented and discussed at a conference or have been published. Only for good reasons, such as emergency or epidemic, may this be waived. For example, investigators may discover health hazards that demand correction, and become advocates of means to protect and restore health. In this event, their advocacy must be based on objective scientific data only

Researchers should not exaggerate their results with the aim of increasing the likelihood of obtaining future research funding or making their paper more attractive to editors.

compromise the potential participant's ability to make independent informed decisions. While the nature of incentives in epidemiological research is very different to those existing in clinical studies, the principle applies equally that incentives should not result in undue influence on the participation of individuals, particularly those from vulnerable groups. In most public health studies participants have many opportunities to refuse participation and this should be clear in all aspects of research.

7.8 Obligations on epidemiologists

Where epidemiological research identifies the presence of a risk to the health and safety of particular participants or populations, the researchers should ensure that this information is not withheld from the populations or participants affected. Feedback to individual participants and, if necessary, family members and the community, of information relating to health risks should be included as part of the protocol and be required for a protocol to gain ethical approval.

Epidemiologists should also take into account the risk of publishing analyses that may stigmatize the group or groups in question.

Because epidemiologists are frequently occupied in research involving communities and groups with high disease burdens or risks, particular attention should be paid to ensuring that epidemiological research does not exploit the vulnerability of such groups (see Section 5). Rather, epidemiological research should seek to strengthen the capacity of vulnerable groups to reduce their vulnerability. Approval by a research ethics committee should be contingent on a consideration of the extent to which such responsibilities have been considered by the researcher, and where reasonably feasible, suitable actions incorporated into the research protocol.

7.9 Validity and ethical standards

Sound ethical practice demands that epidemiological research be conducted according to a rigorous scientific protocol to ensure that respondents are not asked to take part in a study that is fatally flawed in its design.

7.10 Conflict of interest

Researchers should have no undisclosed conflict of interest with their collaborators, sponsors or participants. Researchers must disclose actual, apparent or potential conflicts of interest to the research ethics committee and must publicly acknowledge all sponsorship of research. The research ethics committee is obliged to consider whether the apparent conflict of interest might compromise the scientific integrity of the study, and it must recommend appropriate remedial action and standards to be met in order for the study to be approved.

Results of a study, whether government- or industry-sponsored, should be the intellectual property of the investigators, not the sponsor, and all results should be published if they have scientific merit. Requests to withhold findings, to change or tone down the content of a report are not acceptable to good ethical epidemiological practice. However, sponsors or stakeholders should be afforded the opportunity to provide comment on research findings prior to publication, without any entitlement to veto, change the conclusions, or delay publication of results unreasonably.

Preferably, such considerations should be formalised by contract at the start of negotiations with the sponsor, whether private or governmental. There should be a written document stating that the results will be published regardless of outcome and that the independence of the investigator is acknowledged and will be maintained throughout the study.

5.7 Research involving foetuses

No foetus in utero may be involved as a participant in any research activity unless:

- the purpose of the activity is to meet the health needs of the particular foetus and foetus will be placed at risk only to the minimum extent necessary to meet such needs, or
- The risk to the foetus imposed by the research is minimal and the purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means.

Any activity permitted above may be conducted only if the mother and father are legally competent and have given their informed consent.

The father's informed consent need not be secured if:

- His identity or whereabouts cannot reasonably be ascertained;
- He is not reasonably available;
- The pregnancy resulted from rape.

5.8 Research involving indigenous medical systems

Researchers must respect the cultures and traditional values of all communities. Participants involved in research of indigenous medical systems must be accorded the same degree of respect and protection from harm as participants in scientific medical research. The research must be submitted for ethics review. Any substance that is used on participants must be subjected to stringent toxicology testing. Researchers should furnish proof of safety to the research ethics committee.

5.9 Emergency care research

The benefits of emergency care research include improved effective treatment for life-threatening conditions and improving therapies for survival and quality of life. Research into emergency medical treatment needs to involve participants who are experiencing medical emergencies. There are circumstances in which it is not possible to obtain consent for inclusion in emergency care research. In these circumstances, participants are vulnerable.

Accordingly, ethics committee approval of such research should be granted only if the ethics committee is satisfied that the following criteria will be met:

- After a protocol has been presented by a researcher giving clear reasons to justify the initiation of the emergency care research without consent, a research ethics committee in a hospital with an acute care facility may approve the research without consent provided it is satisfied that:
- reasonable steps are being taken to ascertain the religious and cultural sensitivities of patients experiencing medical emergencies;
- The condition of the patient precludes the giving of consent;
- Inclusion in the trial is not contrary to the interests of the patient;
- The research is intended to be therapeutic and poses no more risk than is inherent to the patient's condition or would be caused by alternative methods of treatment;
- The patient and the patient's next of kin or legal representatives will be informed as soon as is reasonably possible of the patient's inclusion in the study and of the option to withdraw from the research project at any time;
- The patient will be informed, and consent obtained, once the patient has regained consciousness;
- The research is based on valid scientific hypotheses and offers a realistic possibility of benefit over standard care.

5.10 Research involving innovative therapy or intervention

Research, which must be considered by a research ethics committee, includes the use of any innovative therapy or intervention that is being tested on one or more patients.

A research ethics committee must ensure that appropriate provision is made for the long-term care and observation of participants and for the maintenance and security of records, before commencing new therapeutic or innovative procedure.

5.11 Research involving prisoners

Ethical review must take cognisance of the impact of a prisoner's incarceration on their ability to make a voluntary decision, without coercion, on whether or not to participate in research.

In addition, when reviewing research involving prisoners, ethics committees must meet the following requirements:

- a majority of the research ethics committee, other than prison members, shall have no association with the prison(s) involved, apart from their membership of the research ethics committee.
- at least one member of the ethics committee shall be a prisoner, or a prisoners' representative with appropriate background and experience to serve in that capacity. Where a research project is reviewed by more than one ethics committee, only one research ethics committee need satisfy this requirement of a prisoners' representative.

Research studies in South Africa may involve prisoners as participants only where the research has been registered with the National Health Research Ethics Council, and where, in the opinion of the MCC and the relevant research ethics committee, the clinical trial involves:

- study of the possible causes, effects, and processes of incarceration, and of criminal behaviour, provided that the study presents no more than minimal risk and no more than inconvenience to the participants;
- study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the participants;
- research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on diseases that may be more prevalent in prisons and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults) only after appropriate experts have been consulted;
- research on practices, both innovative and accepted, that have the intent and probability of improving the health or wellbeing of prisoners. Where some prisoners may be assigned to control groups that may not benefit from the research, the research may proceed only after appropriate experts have been consulted. Research that could be conducted on a population other than prisoners should not be permitted, unless cogent motivation is presented to the research ethics committee, and the committee is satisfied that the motivation does not represent exploitative research. Research ethics committees should take into consideration the extent to which research facilitates the empowerment of prisoners as a vulnerable group.

7.5 Record review

Consent is not required for use of information in the public domain, although guidance may be needed concerning definition of what type of information about citizens is regarded as public.

Data gathered for administrative purposes or audit does not require the participants' consent if obtaining the consent could cause undue concerns, be impractical or too expensive. However, where publication of audited results may have potentially adverse consequences for study participants or for particular social groups, consent to use such data must be sought. Researchers should always seek the advice of a research ethics committee to decide whether record review requires individual consent.

A research ethics committee may approve the collection of data from records, either retrospectively or prospectively, that is identified or potentially identifiable if:

- It is satisfied that the scientific validity of the study would be compromised by de-identifying the data (i.e. that the objectives of the study could not be attained by de-identifying the data), or that
- An alternative study design which allowed for the use of de-identified data to meet the same objective was not possible, and that confidentiality of data collected could be assured.

Where data is collected from records, either retrospectively or prospectively, a research ethics committee may approve access to identified or potentially identifiable data without seeking the consent of those whom the data identifies, where the ethics committee is satisfied that:

- The procedures required to obtain consent are likely either:
 - to cause unnecessary anxiety for those whose consent would be sought; or
 - to prejudice the scientific value of the research;
- There will be no disadvantage to the participants, their relatives or any collectivity involved that will compromise their rights and dignity to an extent unreasonable and unjustified in terms of the benefits of the research;
- It is impossible in practice, due to the quantity, age or accessibility of the records to be studied, to obtain consent; and public interest in the research outweighs to a substantial degree the public interest in privacy.

7.6 Limited disclosure

For some epidemiological studies, non-disclosure of all the aims of the study may be permissible where full disclosure might bias the investigation or invalidate the hypothesis under investigation. In these circumstances, an independent research ethics committee may grant permission for such limitations, but only where based on careful considerations of the evidence that:

- Limited disclosure is justified in terms of the relative balance of benefits and harms;
 - the validity of the study clearly depends on non-disclosure;
 - the research is likely to yield considerable benefits to participants or other parties;
 - harm or potential for harm to participants are non-existent or minimal, and are outweighed by benefits;
- Respect for the autonomy of the participants is not unduly compromised;
 - there are no reasonable alternatives to meeting the study objectives that might better maintain participant autonomy;
 - that the extent to which participants' autonomy would be undermined by partial disclosure is not unreasonable.

7.7 Incentives

Research ethics committees should be satisfied that the conditions under which participants agree to participate in proposed epidemiological studies do not constitute undue influence that could

- **De-identified (not re-identifiable, anonymous)**

The process of de-identification can be irreversible if the identifiers have been removed permanently or if the data has been de-identified. It should be recognised that the term 'de-identified' is used frequently in documents other than this statement, to refer to sets of data from which only names have been removed. Such data may remain 'potentially identifiable'.

7.2 Approval by research ethics committee

All epidemiological research must be approved by a research ethics committee and should be conducted according to written protocols that state the aims of the study, the data that is required and how the data will be collected, used and protected.

When a research ethics committee considers a protocol for epidemiological research it must be satisfied that:

- The research complies with relevant South African legislation or approved policies dealing with the privacy and confidentiality of data;
- Researchers have the necessary facilities and skills in epidemiology to conduct the research;
- access to medical or other records for research should be restricted to properly qualified researchers;
- There is a scientifically acceptable process for the disclosure of information and dissemination of research results and, where there is to be selective disclosure of information, that there are scientifically justifiable reasons for so doing.

7.3 Consent

Informed consent of participants should generally be obtained for the use of identified or potentially identifiable data for all epidemiological research.

Special precautions should be taken to ensure that participants understand the information provided as part of informed consent, especially when research is conducted in cross-cultural settings, or in vulnerable communities.

Exceptions to this rule may be considered as indicated in Sections 7.5 and 7.6 below. Research participants have the right to refuse to take part in a study but they also have the right to accede. As a general rule only research ethics committees may deny participants the right to choose for themselves.

7.4 Data privacy

Privacy is concerned with protecting or limiting access to personal records containing confidential information. (See also Sections 2.7 and 9.2).

Data collected in epidemiological studies should preferably be in de-identified form. Data should be stored with personal identifiers (identified or potentially identified data) only if absolutely necessary and where approved by a research ethics committee in terms of sound justification. (See Section 7.5 below)

Identifiable personal data should never be stored in computers outside research establishments and the files containing personal identifiers should be stored in locked cabinets or rooms separately from the data used for analysis. Back-up copies must be subject to the same degree of data security and personal data should be sent only by secure methods.

Anyone who has a legitimate right to view the data must sign a promise of secrecy and may seek individual data only for legitimate research purposes.

5.12 Research involving vulnerable communities

South Africa is home to a number of vulnerable communities.¹² Where factors relating to vulnerability are an aspect of the research, the researchers should demonstrate how they will seek to redress that vulnerability. Particular caution must be exercised before undertaking research involving participants in such communities, and ethics committees must ensure that:

- persons in these communities will not ordinarily be involved in research that could be carried out in non-vulnerable communities;
- the research is relevant to the health needs and priorities of the community in which it is to be carried out;
- research participants should know that they are taking part in research and this research should be carried out only with their consent. This requires that particular attention be paid to the content, languages and procedures used to obtain informed consent.

The research protocol should not adversely affect the routine treatment of patients, nor should it disrupt routine management protocols.

5.13 Research involving collectivities

A collectivity is an expression used to distinguish some distinct groups from informal communities, commercial or social groups.

Collectivities are groups distinguished by:

- common beliefs, values, social structures and other features that identify them as a separate group;
- customary collective decision-making according to tradition and beliefs;
- the custom of leaders expressing a collective view;
- members of the collectivity being aware of common activities and common interests.

Researchers must seek research ethics committee approval for research involving a collectivity when any of the following conditions apply:

- property or information private to the group as a whole is studied or used;
- the research requires the permission of people occupying positions of authority, whether formal or informal, or involves the participation of members acknowledged as representatives.
- arrangements to address these issues should follow a process of respectful negotiation, and may include:
- the manner in which anticipated or actual disagreements between the researcher and the collectivity will be resolved;
- the seeking of informed consent from both the collectivity and individual participants;
- resolution of the ownership of data and the rights of publication of research findings;
- the fair distribution of direct benefits and harms of the research among affected participants.

Research ethics committees should require that researchers provide a plan for consultation of community representatives, community involvement and feedback of results.

¹² UNAIDS define vulnerable communities as having some or all of the following characteristics: Limited economic development; Inadequate protection of human rights and discrimination on the basis of the health status; Inadequate community/cultural experience with the understanding of scientific research; Limited availability of health care and treatment options; Limited ability of individuals in the community to provide informed consent.

5.14 Research involving persons highly dependent on medical care

The involvement in research of participants who are highly dependent on medical care raises ethical issues that deserve special attention. The gravity of their medical condition may require invasive measures carrying increased risk. Researchers need to acknowledge that informed consent may be compromised by the effect of the medical condition on the participant's capacity to form an opinion or to communicate. Additionally, there may be a perception of coercion if a participant is reluctant to refuse consent for fear that it may compromise his or her medical treatment. Researchers need to consider whether an unfair burden of participation is being placed on groups such as those referred to below.

- **Emergency care research (see 5.9)**

The distinguishing features of emergency care research is that consent to commence a project usually has to be obtained rapidly, when the vulnerability of patients and families is likely to be greatest. Because of their extreme vulnerability, such persons should be excluded from all but minimally invasive observational research. Moreover, the circumstances surrounding emergency care research are such that it may not always be possible to obtain consent for inclusion without delaying the initiation of treatment, and so risking a reduction of potential benefits.

- **Intensive care research**

Characteristic features of intensive care research are the difficulties in communicating with patients receiving ventilatory assistance and the impairment of cognition in heavily sedated individuals.

Whenever possible, information regarding intensive care research should be obtained from potential participants before their admission to that care. Because of their extreme vulnerability such persons should be excluded from all but minimally invasive observational research.

- **Neonatal intensive care research**

Research involving infants receiving neonatal intensive care should be conducted in strict accordance with the principles set out in Research Involving Children (see 5.1) These principles do not permit research that is contrary to the child's best interests.

The small size and vulnerability of some infants are unique features of this research, which renders all but minimal intrusion likely to be contrary to the child's best interests. The collection of even small blood samples additional to those required for diagnostic purposes, or the handling of a low birth-weight infant to make observations, will demand careful scrutiny.

- **Terminal care research**

Research in terminal care is distinguished by the short remaining life expectancy of participants and potential vulnerability to unrealistic expectations of benefits.

Researchers must take care that the prospect of benefit from research participation is neither nor used to justify a higher risk than that involved in the patient's current treatment.

Researchers must respect the needs and wishes of participants to spend time as they choose, particularly with family members

7. EPIDEMIOLOGICAL RESEARCH

Epidemiology is the study of the distribution and determinants of health-related states or events in specified populations, and the application of the study to control health problems. "Study" includes surveillance, observation, hypothesis testing, analytic research and experiments. "Distribution" refers to analysis by time, place and class of persons affected. "Determinants" are all the physical, biological, social, cross-cultural and behavioural factors that influence health. "Health related states and events" include diseases, causes of death, behaviours such as use of tobacco, reactions to preventative regimens and provision and use of health services. "Specified populations" are those with identifiable characteristics such as precisely defined numbers. "Application of study to control health problems" makes explicit the aim of epidemiology - to promote, protect and restore health." The Dictionary of Epidemiology (2001).

Epidemiological research is thus concerned, through the collection of data related to health, with the description of health and welfare in populations, and with the goal of improving health. Some epidemiological research may require a study of entire populations and go beyond an individual institution or organisation.

Epidemiological research is part of wider public health and health services' research. It is concerned with improvements of health and welfare in human populations and with improving the efficiency and performance of human health services. Public health and health services' research are often carried out with human participants, or data or biological samples from them, and such research provides important new knowledge that is not readily obtainable in other ways.

Public health surveillance should be distinguished from public health and epidemiological research. Its role is to monitor the health status of the community, known risk factors and emerging threats to community health. Its purpose is to facilitate a prompt, effective and corrective response. It may be carried out for reasons of disease surveillance, provision of information to government health services or to guide the development of health policy. Public health agencies generally are required or authorised by law to conduct health surveillance. However, under certain circumstances, public health surveillance data may be used for research purposes. Under such circumstances, considerations pertaining to data privacy and record review (Sections 7.3 -7.5 below) should be seen to apply.

In epidemiological research, medically relevant information about individuals and groups is accumulated. Features of groups of persons may be investigated whether or not the information was originally obtained for research purposes.

7.1 Categories of personal information

Epidemiological research includes the use of the following types of data:

- **Identified**

Data that allows the identification of a specific individual is referred to as 'identified data'. Examples of identifiers may include the individual's name, date of birth and address. In particularly small sets of data even information such as a postal code may be an identifier.

- **Potentially identifiable (coded, re-identifiable)**

Data may have identifiers removed and replaced by a code. In such cases it is possible to use the code to re-identify the person to whom the data relates so that the process of de-identification is reversible. In these cases the data is referred to as 'potentially identifiable'.

In pre-registration clinical trials all adverse events need to be reported, as the safety of products is yet to be established.

Ethics Committees have a duty to check all research protocols for suitable procedures for reporting adverse events.

- **Ethics of providing (access to) participant data**

While reporting suspected adverse events or reactions, care should be taken to ensure privacy of participants' data. Health professionals should have permission from participants to report such data. However, health professionals have an ethical obligation to report serious adverse events in the interest of future patients. Health professionals should be allowed and even obliged to provide such data, even if the participant withholds permission. ADR committees should ensure that data is anonymised when reported to others.

- **Ethics of risk or benefit decisions**

Health professionals have a duty to fairly assess risks and benefits before and while treating patients. If they are not sure of reaching a risk or benefit decision, they should consult colleagues or relevant literature.

Professionals in ADR committees who receive reports of possible adverse reactions, should fairly assess the causality of the event. Where uncertainty exists, or if the event is of a serious nature, further information should be requested.

- **Ethics of the communication of risk**

Participants have a right to know about benefits and risks of treatments, including the possibility of adverse effects. Health workers have an ethical duty to present fairly both positive and negative aspects of treatments. Participants should receive written information about such risks, either as part of informed-consent documents or as information leaflets specifically designed to inform participants.

- **Research involving persons with impaired capacity to communicate**

The distinguishing features of research involving persons with impaired capacity to communicate includes acute impairment states requiring medical care, as well as non-acute states. In the former, the condition and medical care may mask the person's degree of cognition and require different means of expression. In the latter, the condition may be such as to prevent the person expressing wishes at all.

- **Research involving unconscious persons**

The distinguishing feature of research with unconscious persons is that, because of their incapacity for cognition or communication, it is impossible for them to be informed about the research or for a researcher to determine their wishes about it. Consent to participation in research by an unconscious person must be given by others, including relevant statutory authorities, on that person's behalf. Because of their extreme vulnerability unconscious persons should be excluded from all but minimally invasive observational research.

- **Human Research Ethics Committee consideration of research proposals involving persons highly dependent on medical care**

When research procedure precludes conformity to the principle of consent, and neither the prospective participant nor the participant's representative is able to give consent in advance, a research ethics committee may approve a research project without prior consent if it is satisfied that:

- inclusion in the research project is not contrary to the interest of the patient;
- the research is intended to be therapeutic and the research intervention poses no more of a risk than that inherent in the patient's condition and alternative methods of treatment;
- the research is based on valid scientific hypotheses which support a reasonable possibility of benefit over standard care;
- as soon as reasonably possible, the participant and the participant's relatives or legal representatives will be informed of the participant's inclusion in the research, and will be advised of their right to withdraw from the research without any reduction in quality of care.

In the case of research proposals in which it is practicable to obtain consent before including in the research a participant who is highly dependent on medical care, an Ethics Committee must be satisfied that:

- adequate provision will be made for informing patients and their relatives about the research, to ensure that stress and other emotional factors do not impair their understanding of it;
- the dependency of patients and their relatives on the medical personnel providing treatment does not affect any decision to participate.

5.15 Other special groups

The discussion on special groups should not be limited to those already mentioned. Other special groups include: traumatised and comatose patients, terminally ill patients, elderly or aged patients, minorities, students, and employees. Research ethics committees must ensure special consideration is given to all these groups, especially with regard to informed consent. For a more detailed discussion on informed consent please refer to Section 2.5 of this document.

6. CLINICAL TRIALS

This section must be read in conjunction with Sections 2 and 5 of the Guiding Principles.

A clinical trial is a study involving humans to find out if a treatment or diagnostic procedure, which is believed to benefit a patient, actually does so. A clinical trial may involve testing a drug, a surgical or other procedure, or a therapeutic or diagnostic device (Other clinical or related disciplines also conduct research, which involves ethical considerations similar to clinical trials).

In pharmaceutical trials there are established codes of good clinical research practice that define clearly what is meant by a clinical trial. This section has principal application in the context of clinical drug trials but should also apply to other interventions claiming therapeutic benefit, wherever provided or conducted.

Protocols of studies involving the administration of substances to healthy human volunteers must be submitted to and approved by ethics committees.

An ethics committee must consider all aspects of the design of the trial and be satisfied that:

- The clinical trial is directed to answering a specific question, that the hypothesis is scientifically valid and that the trial medication offers a realistic possibility of benefit over standard treatment;
- The methodology provides a rationale for the selection of appropriate participants, an appropriate method of recruitment, adequate understandable information for the purpose of obtaining participants' informed consent, a clear description of the interventions and observations to be conducted, and statistical validation of sample size and outcome.

When a research ethics committee reviews a protocol for a clinical trial it must be satisfied that the protocol conforms to the spirit of these guidelines and the international documents:

- The World Medical Association Declaration of Helsinki;
- The International Conference for Harmonisation Guideline for Good Clinical Practice (ICH Guideline for GCP);
- The Association of the British Pharmaceutical Industry (ABPI) Guidelines for Medical Experiments in healthy volunteers if the study intends involving such volunteers.
- Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa and other guidelines as may be required. 17

The aims of every trial should be precisely stated and every trial should be conducted by competent researchers with suitable experience and qualifications.

The use of a placebo in a clinical trial is ethically unacceptable where the use of a therapy or intervention is available, which has been demonstrated to be effective for a particular condition (also see Placebo-Controlled Trials in Appendix C). Research ethics committees should examine the costs of each trial relative to its proposed benefits and the costs relative to the use of placebo.

A research ethics committee should examine those aspects of the budgets of clinical trials that raise ethical issues, particularly capitation fees, payments to researchers or institutions or organisations involved in the research, current and consequential institutional or organisational costs, and costs that may be incurred by participants.

The research ethics committee must be satisfied that:

- No payments in money or kind could influence the findings of the research;
- There will be proper disclosure of the above aspects to the research participants.

¹⁷ For further information refer to the Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants, in South Africa, 2000, Department of Health, Pretoria

An ethics committee must be satisfied, before approving a clinical trial, that arrangements exist to ensure adequate compensation to participants for injury suffered as a result of participation in the trial.

It is recommended that ethical acceptability of a clinical trial should include a research ethics committee's evaluation of the likelihood of implementation of study findings.

Once a research ethics committee has approved the clinical trial, the researchers must:

- Conduct the trial in accordance with the agreed protocol;
- Inform the research ethics committee if amendments to the protocol become necessary, detailing – with rationale – the changes required, and seeking approval to incorporate them in the protocol;
- Inform the research ethics committee of the occurrence, during the trial, of serious or unexpected adverse effects that are likely to affect the safety of the participants or the conduct of the trial;
- Provide a report of the progress of the trial to the research ethics committee at least annually, but more frequently if requested.

It may be unethical to continue a trial for the intended period if:

- There are or have been substantial deviations from the trial protocol;
- Side effects of an unexpected type or frequency are encountered;
- As the trial progresses, one of several treatments or procedures being compared proves to be so much better, or worse, than others that adherence to the approved protocol disadvantages some of the participants.

In a clinical trial, data should be recorded accurately in a durable and appropriately referenced form and:

- Data management should comply with relevant privacy protocols;
- Data management should include levels of access and should preclude, as far as possible, the risk of tampering with the data;
- Where data is confidential, confidentiality must be observed and researchers must not use such information for their own personal advantage or for that of a third party.

The research ethics committee should ensure procedures for the continuing review and approval of each trial and determine the frequency of review appropriate to the degree of risk to participants. Such review should occur at least once a year, after which the principal researcher will be informed of the research ethics committee's decisions. A research ethics committee should require a researcher to report promptly:

- Deviations from the protocol, so that immediate hazards to trial participants may be eliminated;
- Changes that increase the risk to participants or affect significantly the conduct of the trial;
- All adverse drug reactions that are serious or unexpected;
- New information that may affect adversely the safety of all participants of the trial.

6.1 Adverse reactions and events

In South African health workers report annually an estimated 500 suspected adverse reactions of marketed medicines to the MCC ADR (Adverse Drug Reaction) centre. This means that, on average, each doctor reports only one suspected ADR in his professional career. This is in stark contrast to the fact that in several countries up to 10% of hospital admissions are due to adverse drug reactions.

Reporting suspected adverse reactions to a competent authority is an ethical duty of health professionals, especially in instances of serious adverse reactions or unknown suspected adverse reactions.