

Ethics in Health Research

Principles, Processes and Structures

2015



health

Department:
Health
REPUBLIC OF SOUTH AFRICA

A long and healthy life for all South Africans

FOREWORD



Health research is vital for the advancement of health care services for the people of South Africa. Because of its excellent health care and research infrastructure, skills and expertise, South Africa provides a rich arena for health and health-related research. The country is also characterised by a high burden of disease, including diseases associated with poverty and underdevelopment, along with non-communicable diseases, creating the need for a broad spectrum of health and health-related research. To ensure that South Africa's people are fairly and respectfully treated by researchers and that all research conducted in the country stands up to ethical scrutiny, South Africa's research ethics systems and infrastructure are regularly updated and strengthened. This assists with the project of ensuring that research is conducted in accordance with the highest ethical norms and standards.

The core ethical principles – respect, scientific merit and integrity, distributive justice and beneficence– apply to all forms of research that involve living persons and use of

animals, thereby placing their safety, welfare and other interests as paramount. These principles apply also to research with human biological materials and data collected from living or deceased persons.

These Guidelines, entitled '*Ethics in Health Research: Principles, Processes and Structures*', are the second edition and replace the 2004 edition. They contain the national policy for conducting research responsibly and ethically, tailored to South Africa's needs as appropriate.

- They describe the minimum national benchmark of norms and standards
- They provide detailed explication of the process of ethics review and focused guidance about specific topics and research methodologies
- They outline the expectations and standards for Research Ethics Committees (RECs) and Animal Research Ethics Committees and give guidance about standard operating procedures
- They describe the research ethics infrastructure and regulatory framework in South Africa

These Guidelines are intended for use by researchers who involve human participants in their research or who use animals, RECs, health care practitioners, health facility administrators, policy makers in government departments, and community representatives. This is consistent with the understanding that research means a systematic collection and analysis of new information undertaken with the goal of producing generalisable knowledge or improved understanding of the human condition in its environment or context.

Thank you to all who participated formally or informally in writing and producing this new edition. Your work contributes significantly to the enhancement of dignity for all South Africa's people.

A handwritten signature in black ink, appearing to be 'A. Motsoaledi', written over a faint, stylized graphic element.

DR AARON MOTSOALEDI, MP

MINISTER OF HEALTH

DATE : 1 March 2015

ACKNOWLEDGEMENTS



These guidelines '*Ethics in Health Research: Principles, Processes and Structures – 2015*' provide an updated and strengthened guide to ensure that, in South Africa, research is conducted responsibly and ethically. Mandated by Section 72 of the National Health Act 61 of 2003, the National Health Research Ethics Council (NHREC) tasked its Working Group for Norms and Standards to produce a revision of the first edition of the Guidelines issued in 2004.

Drawing on international and foreign national ethics codes and research ethics guidelines, in addition to the first edition of these Guidelines, the NHREC has endeavoured to produce a locally relevant document that fits with the matrix of research ethics guidelines available across borders.

The basic expectations of the Guidelines include that:

- Proposals to conduct research involving humans undergo independent ethics review before the research begins
- Proposed health research promote health, contribute to prevention of communicable or non-communicable diseases or disability or result in cures or alleviation of suffering
- Proposals to conduct health research stand up to scientific and ethical scrutiny appropriate to the disciplines concerned
- Harm to research participants is prevented or at least minimised and balanced against the likelihood of benefit
- The safety and welfare interests of animals used in research are promoted
- Researchers are accountable for their research activities
- Social and ethical values are promoted

The Department is also grateful for the following officials who provided secretariat support to the NHREC and in particular the NHREC's Norms and Standards Working Group as well as Ms K Nevhutalu, Mr T Molebatsi, Mr J van der Westhuizen and Mr R Maluleke from the Secretariat, the NHREC and all interested parties for their role in development of these Guidelines and for their expert and technical input.

The current NHREC comprises of Prof D du Toit (Chairperson), Prof D van Bogaert (Deputy Chairperson), Prof A Dhai, Ms K Nevhutalu (NDoH), Dr C Slack, Adv LT Nevondwe, Prof A van Niekerk, Dr NP Sithebe, Ms ET Zwane, Ms T Sebata, Prof A Pope, the late Dr L Schoeman, Dr M Sekhoacha, Dr S Ncanana, Dr NJ Ramalivhana.

A handwritten signature in dark ink, appearing to read 'M. Matsoso'.

MS MP. MATSOSO

DIRECTOR-GENERAL: DEPARTMENT OF HEALTH

DATE : 1 March 2015

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ACKNOWLEDGEMENTS

In addition to the National Health Act, 61 of 2003 (NHA), these Guidelines has drawn on the Australian National Statement on Ethical Conduct in Human Research (2007); the Canadian Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (2010); the Council of Europe Steering Committee on Bioethics: Guide for Research Ethics Committee Members (2011); the Council for International Organizations of Medical Sciences (CIOMS) (2002); the ICH Guidelines; the Nuffield Council on Bioethics: the Ethics of Research Related to Healthcare in Developing Countries (1999); the World Medical Association: Declaration of Helsinki (2013); the World Health Organization Operational Guidelines for Ethics Committees that review Biomedical Research TDR/PRD/ETHICS/2000; the World Health Organization Standards and Operational Guidance for Ethics Review of Health-Related Research with Human Participants (2011); the Montreal Statement (2013); Singapore Statement (2010); research ethics documentation and guidance of the University of Cape Town Faculty of Health Sciences Human Research Ethics Committee

<http://www.health.uct.ac.za/research/humanethics/sop/>; the University of KwaZulu-Natal at <http://research.ukzn.ac.za/Research-Ethics/Overview.aspx>; the University of Pretoria at <http://web.up.ac.za/default.asp?ipkCategoryID=2875&subid=2875&ipklookid=8&parentid=>; the University of the Witwatersrand at http://www.wits.ac.za/academic/researchsupport/19111/code_of_ethics.html.

It also draws on the South African Medical Research Council (MRC) Guidelines on Ethics for Medical Research: Use of Animals in Research and Training (2004); The South African Bureau of Standards' South African National Standard (SANS 10386:2008 or latest version) for the Care and Use of Animals for Scientific Purposes.

See Appendix 2 for bibliographic details.



Chapter 1

ETHICS IN RESEARCH

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This chapter explains ethics in research and provides an overview of the South African research context, including the remit of this document.

Introduction

- 1.1.1 South Africa is a democratic state in which human dignity, equality and the advancement of human rights are respected, promoted and protected in terms of the Constitution of the Republic of South Africa, 1996 (the Constitution). In particular, s 27(1) guarantees the right of access to health care services, while section 12(2) of the Bill of Rights in the SA Constitution, protects against research abuse by providing that
- ‘Everyone has the right to bodily and psychological integrity, which includes the right –*
- (a) to make decisions concerning reproduction;*
- (b) to security in and control over their body; and*
- (c) not to be subjected to medical or scientific experiments’ without their informed consent’.*
- 1.1.2 The National Health Act 61 of 2003 (NHA) provides statutory authority for governance of ‘health research’ and the necessary research ethics regulatory infrastructure.
- 1.1.3 ‘Health research’ per the NHA may be understood to include but is not limited to research that contributes to knowledge of
- biological, clinical, psychological, or social welfare matters including processes as regards humans
 - the causes and effects of and responses to disease
 - effects of the environment on humans
 - methods to improve health care service delivery
 - new pharmaceuticals, medicines, interventions and devices
 - new technologies to improve health and health care
- 1.1.4 In general terms, research includes a wide range of activities conducted by many different disciplines that may use different methodologies and explanatory frameworks. In the physical and biological sciences, research may be described as a systematic study or inquiry, usually using quantitative data, in seeking generalisable new knowledge. Health-related research is increasingly also using qualitative methodologies. The humanities, social and behavioural sciences use both qualitative and quantitative methods and analytic frameworks, all of which may be aimed at contributing to knowledge about the human condition in its environment and context.
- 1.1.5 The statutory definition can be interpreted as having a wide or a narrow meaning. Many researchers, especially those who work in the humanities and social and behavioural sciences, may find the statutory definition of ‘health research’ to favour biomedical research. In particular, they may perceive that the so-called ‘medical model’ for ethics review dominates and is applied frequently but inappropriately to social science, especially qualitative research.
- 1.1.6 These guidelines do not advocate the so-called ‘medical model’ of ethics review, especially not for social science, behavioural or humanities research. For purposes of this document, ‘health research’ has both a broad and narrow meaning. In the narrow sense, it refers to research carried out in a health care environment, usually with patients, whether in a hospital, clinic or home-based. In the broad sense, it refers to research conducted outside a health care environment, usually not with patients.
- 1.1.7 The core ethical principles outlined in these guidelines apply to all forms of research that involve living human participants and use of animals, placing their safety, welfare and interests of both humans and animals as paramount. The principles also apply to research that involves use of human biological materials and data collected from living or deceased persons, including human embryos, fetuses, fetal tissue, reproductive materials, and stem cells.
- 1.1.8 Research that relies exclusively on publicly available information or accessible through legislation or regulation usually need not undergo formal ethics review. This does not mean that ethical considerations are irrelevant to the research.

Note: Where ‘she’ or other version is found, ‘he’ or other version is implied and vice versa.

¹The term ‘experiments’ originates from Article 7 of the International Covenant on Civil and Political Rights - UN 1966 and echoes the Nuremberg Code; in the constitutional context, it is intended to mean ‘research’.

- 1.1.9 Research involving observation of people in public spaces and natural environments usually need not undergo formal ethics review, provided that
- the researcher does not interact directly with individuals or groups
 - the researcher does not stage any intervention
 - the individuals or groups do not have a reasonable expectation of privacy
 - dissemination of research findings does not identify individuals or groups
- 1.1.10 Research that relies exclusively on secondary use of anonymous information or anonymous human biological materials usually need not undergo formal ethics review, provided that no identifiable information is generated. See 3.3 below for further information regarding human biological materials.
- 1.1.11 Quality assurance and quality improvement studies (audits), programme evaluation activities and performance reviews usually do not constitute research and thus usually do not undergo formal ethics review. It should be noted, however, that if publication of such studies is desirable, it is prudent to obtain ethics approval before the study begins. RECs may not grant retrospective ethics approval.
- 1.1.12 These guidelines express the view that the core ethical principles apply to all forms of research that involve humans² or use of animals, insofar as the welfare and safety interests of both humans and animals are paramount. Health and safety issues include those that may arise in the environment of research e.g. viruses, parasites, bacteria, as well as the air, water and land.
- 1.1.13 This document is intended to be as inclusive as possible, so that all researchers who involve human participants or use animals in their research will find assistance in these guidelines. In other words, although this document derives its authority from the National Health Act, the National Health Research Ethics Council (NHREC) intends it to address research more broadly to achieve the specific goal of providing guidance for researchers so that all research involving human participants or animals may be conducted in accordance with the highest ethical norms and standards. This is consistent with the understanding that research means a systematic collection and analysis of new information undertaken with the goal of producing generalisable knowledge or improved understanding of the human condition in its environment or context.
- 1.1.14 This document does not deal with clinical trials which form the subject matter of the Department of Health's Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa, 2nd edition (2006) or its successor. However, this document includes guidance on insurance against research-related bodily injury, including in clinical trials.

1.2 The research context

- 1.2.1 South Africa provides a rich arena for health and health-related research because of its excellent health care and research infrastructure, skills, and expertise. The country is also characterised by a high burden of disease, including diseases associated with poverty and underdevelopment, along with non-communicable diseases, creating a need for a broad spectrum of health and health-related research. See the Department of Health's Strategic Health Plan 2014-2019 or its successor.³
- 1.2.2 South Africa is also an attractive research site for social scientists, behavioural scientists, political scientists, economists, researchers engaged in social development, education, and many more disciplines, because of its political history and current socio-economic, educational, political and social development status.
- 1.2.3 To ensure that South Africa's people are fairly and respectfully treated by researchers and that all research conducted in the country stands up to ethical scrutiny, South Africa's research ethics systems and infrastructure are regularly upgraded and strengthened.

1.3 Regulatory authority

- 1.3.1 The National Health Research Ethics Council (NHREC) was established in 2006 in terms of s 72 of the National Health Act (NHA).
- 1.3.2 In terms of the NHA, the NHREC must
- a) set norms and standards for health research involving humans and animals, as well as for conducting clinical trials
 - b) determine guidelines to facilitate best practice for research ethics committees
 - c) register and audit research ethics committees
 - d) adjudicate complaints about research ethics and Animal Research Ethics committees
 - e) refer matters concerning violations of ethical or professional rules to the relevant health professions council;
 - f) recommend disciplinary action against persons found to have violated the norms and standards set for the responsible and ethical conduct of health research
 - g) advise the national and provincial departments of health on ethical matters concerning research.
- 1.3.3 The NHREC firmly supports ethical practice of health and health-related research and asserts that research should reflect core values of respect, scientific merit and integrity, justice and beneficence. Of highest priority are refinement of ethics guidelines, establishment of research ethics and animal research ethics committees,

²Also known as 'human subjects research'; a human subject is a living individual about whom a researcher obtains (i) data through interventions or interactions; or (ii) identifiable private information.

³Available at <http://www.health-e.org.za/wp-content/uploads/2014/08/SA-DoH-Strategic-Plan-2014-to-2019.pdf>

⁴Note this list is not exhaustive.

and strengthening of review processes, to protect the rights, safety and welfare interests of individuals involved in research, particularly vulnerable participants; to protect the welfare and safety interests of animals used in research; and to protect safety and other interests of researchers.

1.3.4 The guidelines draw on prevailing international, foreign and national codes of conduct, declarations, and other documents relevant to research with humans, to strengthen processes of translational research collaboration, while taking into account the socioeconomic, ethnic and cultural diversity in South Africa. The guidelines also draw on and refer to international and national standards and guidelines for research using animals.

1.3.5 Researchers should be familiar with legislation and other binding instruments relevant to research including⁴

- Animal Diseases Act 35 of 1984
- Animal Health Act 7 of 2002
- Animals Protection Act 71 of 1962
- Basic Conditions of Employment Act 75 of 1997
- Cartagena Protocol on Biosafety May 2000
- Child Justice Act 75 of 2008
- Children's Act 38 of 2005
- Choice on Termination of Pregnancy Act 92 of 1996
- Constitution of the Republic of South Africa, 1996
- Convention on Biological Diversity
- Criminal Law (Sexual Offences and Related Matters) Amendment Act 32 of 2007
- Domestic Violence Act 116 of 1998
- Employment Equity Act 55 of 1998
- Fertilizers, Farm Feeds, Agricultural Remedies and Stock Remedies Act 36 of 1947
- Genetically Modified Organisms Act, Act No 15 of 1997
- Hazardous Substances Act 15 of 1973
- Health Professions Act 56 of 1974
- Labour Relations Act 66 of 1995
- Medical Schemes Act 131 of 1998
- Medicines and Related Substances Control Act 101 of 1965
- Mental Health Care Act 17 of 2002
- Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits,⁵
- National Environmental Management: Biodiversity Act, Act 10 of 2004
- National Health Act, Act No 61 of 2003
- National Health Laboratory Service Act 37 of 2000
- Patents Act 57 of 1978
- Performing Animals Protection Act 24 of 1935
- Promotion of Access to Information Act 2 of 2000
- Promotion of Equality and Prevention of Unfair Discrimination Act 4 of 2000
- Protected Disclosures Act 26 of 2000
- Protection of Personal Information Act 4 of 2013
- Provincial Nature Conservation Acts or Ordinances
- Rules Relating to the Practising of the Para-Veterinary Profession of Laboratory Animal Technologist. Department of Agriculture (1997) GN 1445 of 3 October 1997
- Rules Relating to the Practising of the Profession of Veterinary Nurse. Department of Agriculture (1991) GN 1065 of 17 May 1991
- Societies for the Prevention of Cruelty to Animals Act 169 of 1993
- Sterilization Act 44 of 1998
- Veterinary and Para-veterinary Professions Act 19 of 1982

1.4 Research with humans

1.4.1 The National Health Act (NHA s 72(6)(c)) gives authority to the NHREC for setting norms and standards for health and health-related research that involves humans.

1.4.2 Every organisation/institution, health agency and health establishment at which health and health-related research involving human participants is conducted, must establish or have access to a registered Human Research Ethics Committee (REC) (NHA s 73(1)).

1.4.3 RECs that review research involving human participants must register with the NHREC (NHA s 73(1)).

1.5 Research using animals

1.5.1 The National Health Act (NHA) gives authority to the NHREC for setting norms and standards for health research that uses animals (NHA s 72(6)(c)).

1.5.2 Every organisation/institution, health agency and health establishment at which health research using animals is conducted, must establish or have access to a registered Animal Research Ethics Committee (AREC) (NHA s 73(1)).

⁴Ratified by South Africa on 11 May 2011. For further information, see <http://www.cbd.int/abs/>

- 1.5.3 ARECs that review health research using animals must register with the NHREC (NHA s 73(1)).
- 1.5.4 The South African Bureau of Standards' South African National Standard (SANS 10386:2008 or latest version) for the Care and Use of Animals for Scientific Purposes and MRC Guidelines on Ethics for Medical Research: Use of Animals in Research and Training (2004) provide the minimum benchmark to ensure ethical and humane care of animals used for scientific purposes as well as for teaching activities, in line with the fundamental principles of Replace, Reduce and Refine animal use. ARECs and researchers are expected to familiarise themselves with the content of both documents in addition to these Guidelines, as appropriate.
- 1.5.5 International and foreign codes for animal research include the Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes and the Australian Code for the Care and Use of Animals for Scientific Purposes (8th Edition) 2013.

1.6 Ethical research review

- 1.6.1 The NHA (s 72(1)) requires that proposals to conduct 'health research' must undergo independent ethics review before the research is commenced.
- 1.6.2 Ethics review of proposed 'health research' must be conducted by an REC or AREC that is registered with the NHREC (s 73(2) of the NHA).
- 1.6.3 RECs must review 'health research' proposals and protocols to ensure that the research will promote health, contribute to prevention of communicable or non-communicable diseases or disability or result in cures or alleviation of suffering caused by communicable or non-communicable diseases or disability (NHA s 73(2)(a)).
- 1.6.4 RECs must ensure that research proposals stand up to scientific and ethical scrutiny appropriate to the disciplines concerned.
- 1.6.5 RECs must review research proposals and protocols prospectively to ensure that they meet the accepted ethical norms and standards before research commences, using these Guidelines as a minimum benchmark (NHA s 73(2)(b)).
- 1.6.6 The review process entails an independent and objective assessment of the potential effect of the proposed research on potential participants and on the general day-to-day functioning of the infrastructure that provides the site or context for the research. Ethics review is not about obstructing scientific progress or innovative research. Promoting ethical conduct of research entails co-operation between RECs and researchers to ensure a comprehensive and frank assessment of the ethical implications of proposals so that participants (and researchers) can be protected appropriately.⁶
- 1.6.7 The review must ensure that ethical and scientific standards are maintained to
 - protect participants from harm by weighing the risks of harm against the likelihood of benefit by minimising risks of harm to the extent possible and then by balancing the risk of harm relative to the likelihood of benefit
 - protect the safety and welfare of animals used in research by ensuring close adherence to the expected benchmarks
 - hold researchers accountable for the research activities
 - promote important social and ethical values.
- 1.6.8 In weighing risk of harm against likelihood of benefit, the analysis is concerned not only with current participants or research animals themselves but also with societal interests and future hypothetical beneficiaries.
- 1.6.9 Retrospective review and approval or clearance is not permitted.

1.7 Glossary and resources

- 1.7.1 A Glossary of terms used in these Guidelines appears in Appendix 1.
- 1.7.2 A list of resources appears in Appendix 2.
- 1.7.3 Templates appear in Appendix 3.

⁶Wassenaar 'Ethical issues in social science research' in Terre Blanch, Durrheim & Painter (2006) 60-79.

1.8 Purpose and status of these Guidelines

- 1.8.1 These Guidelines is intended to provide the minimum national benchmark of norms and standards for conducting responsible and ethical research.
- 1.8.2 The minimum benchmark for research that uses animals is found in the South African Bureau of Standards SANS 10386:2008 or later version. These Guidelines endorses the ethical principles laid down in the South African Bureau of Standards SANS 10386:2008 (or later version) and MRC Guidelines on Ethics for Medical Research: Use of Animals in Research and Training (2004).
- 1.8.3 These Guidelines further endorses the ethical principles laid down in
- The Belmont Report: www.edu/irb/pdfs/BelmontReport.pdf
 - Declaration of Helsinki 2013: www.wma.net/e/policy/pdf/17c.pdf
 - Medical Research Council: Guidelines on Ethics for Medical Research: HIV Preventive Vaccine Research: www.sahealthinfo.org/ethics/ethicsbooks5.pdf
 - The Singapore Statement on Research Integrity www.singaporestatement.org
 - Human Heredity and Health in Africa (H3Africa) Initiative <http://h3africa.org/>
- 1.8.3 This document should be read in conjunction with other guidelines such as the DoH Guideline for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa (2006); the Human Sciences Research Council Research (HSRC) Ethics Guideline; and international guidelines such as the Declaration of Helsinki (2013); the Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines for Biomedical Research involving Human Subjects (2002); the ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6 (R1) 1996; the ICH Harmonised Tripartite Guideline: Clinical Investigation of Medicinal Products in the Pediatric Population E11 2000.

1.9 Structure of these Guidelines

- 1.9.1 Chapter 2 discusses the principles that inform the procedures and decision-making processes for ethics review of research proposals.
- 1.9.2 Chapter 3 provides detailed explication of the process of ethics review, and focused guidance about specific human participants, specific types of research or specific research contexts. Discussion is provided also about storage and use of biological samples and related data for research purposes, human genetic research and insurance against trial-related harm.
- 1.9.3 Chapter 4 outlines the expectations and standards for RECs; and describes standard operating procedures for ethics committees as well as the responsibilities of researchers.
- 1.9.4 Chapter 5 describes the 'health research' ethics infrastructure for South Africa.



Chapter 2

GUIDING PRINCIPLES FOR ETHICAL RESEARCH

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This chapter sets out the broad principles underpinning research that inform the norms and standards, as well as the procedures and decision-making processes for ethics review in all disciplines of research proposals to involve human participants.

2.1 Ethical principles

The broad ethical principles are

- beneficence and non-maleficence

This refers to the ethical obligation to maximize benefit and to minimize harm, and requires that the risks of harm posed by the research must be reasonable in light of anticipated benefits; that research design must be sound, and that researchers must be competent to carry out the proposed research activities. Beneficence prohibits deliberate infliction of harm on persons; sometimes expressed as a separate principle: non-maleficence (do no harm). Research that involves human participants should seek to improve the human condition. If the research cannot do this, then it is unlikely to be ethical.

- distributive justice (equality)

This means that there should be a fair balance of risks and benefits amongst all role-players involved in research, including participants, participating communities and the broader South African society. In this way the principle of equality is expressed in the research context. 'No segment of the population should be unduly burdened by the harms of research or denied the benefits of knowledge derived from it.'⁷ There should be a reasonable likelihood that the population from which participants are drawn will benefit from the research results, if not immediately, then in the future.

- respect for persons (dignity and autonomy)

This principle requires that persons capable of deliberation about their choices must be treated with respect and permitted to exercise self-determination. Further, persons who lack capacity or who have diminished capacity for deliberation about their choices must be protected against harm from irresponsible choices. Respect for persons recognises that dignity, well-being and safety interests of all research participants are the primary concern in research that involves human participants. Respect for persons includes 'the dual moral obligations to respect autonomy and to protect those with developing, impaired or diminished autonomy'.⁸ Autonomy includes the ability to deliberate about a decision and to act on that decision. Interests of participants should usually outweigh the interests of science and society. Consequently, involvement of persons or particular categories of people in the research should be justified in research proposals. Respect for persons means also that the interests of researchers must be considered. These include welfare and safety interests, authorship and intellectual property interests, and collegial and professional interests.

2.2 Role of ethical principles

Ethical principles assist RECs to identify and protect the interests of research participants in a variety of research contexts and to promote development of high-quality knowledge that may benefit future generations. These ethics principles are articulated in national and international research ethics guidelines. Persons who conduct research in South Africa are expected to adhere to these principles which underscore responsible and ethical research conduct.

Note: Detailed discussion about how to apply these principles is in Chapter 3.

2.3 Key norms and standards

The key ethical norms and standards are:

- Relevance and value

- Scientific integrity
- Role-player engagement
- Fair selection of participants
- Fair balance of risks and benefits
- Informed consent
- Ongoing respect for participants, including privacy and confidentiality
- Researcher competence and expertise

Note that the fundamental principles for research that uses animals are Replace, Reduce and Refine animal use in research. (See SANS 10386:2008 (or later version); see 1.5.4.)

2.3.1 Relevance and value

Research should be relevant and responsive to the needs of the people of South Africa. The proposal should explain the anticipated contribution to knowledge generation and, ideally, how the findings might be translated into products, interventions, processes or services likely to improve living standards and well being of South Africans.

2.3.2 Scientific integrity

The study's design and methodology are vital for research integrity, regardless of the discipline. Sound design and methodology are likely to result in reliable and valid data and outcomes that address the research objectives. Poor design and inappropriate methods may expose participants to unnecessary risk of harm and burden with little or no compensating benefit in the form of useful knowledge gained.

2.3.3 Role player engagement

Researchers should engage key role players at various stages of planning and conducting research to improve the quality and rigour of the research, to increase its acceptability to the key role players, to harness role player expertise where possible, and to offset power differentials where these exist. Engagement efforts may comprise of various activities, including awareness-raising initiatives for role players, including but not limited to participating communities.

2.3.4 Favourable risk-benefit ratio

A risk-benefit analysis should precede carrying out the research. A desirable ratio is one where, at minimum, the potential risk of harm to a participant is outweighed by the likelihood of benefit, for participants or to society, from the knowledge to be gained from the research. In other words, the likelihood of benefit should outweigh the anticipated risk of harm to participants. However, this does not mean that participants should be exposed to unacceptable risks of harm on the basis that the participants are likely to benefit from the research. In assessing the risk of harm, both the magnitude or seriousness of the harm and the probability of its occurrence should be addressed.

Usually, participants who might face undue risk of harm should not be included in the study, even if they represent a category of person that may benefit from the research. On the other hand, research with such persons may nevertheless be approved after careful review and acceptable justification that demonstrates the anticipated importance and value of the research for society. In such cases, a carefully phased approach should be adopted.

2.3.5 Fair selection of participants

This means recruitment, selection, exclusion and inclusion of participants for research must be just and fair, based on sound scientific and ethical principles. Persons should not be excluded unreasonably or unfairly on the basis of any of the prohibited grounds for discrimination: race, age, sex, sexual orientation, disability, education, religious belief, pregnancy, marital status, ethnic or social origin, conscience, belief or language (s 8 of the Constitution). Similarly, persons should not be unfairly targeted for research merely on the basis of one or other of these grounds.

2.3.6 Informed consent

In general, participation in research must be voluntary and predicated on informed choices. Voluntariness and informed choices are evidenced by the informed consent process which must take place before the research commences, in principle, and be affirmed during the course of the study, as part of the commitment to an ongoing consent process. In some circumstances, research may not require prior consent (see 3.2.5 & 3.3)

2.3.7 Ongoing respect for enrolled participants

A research participant has the right to privacy and to confidentiality. This requires that a proposal must explain how these constitutionally protected rights will be managed and protected in the course of the research. Simply stated, privacy is concerned with who has access to personal information and records about the participant; including clinical health care records. On the other hand, 'confidentiality' is about ensuring that appropriate measures will be implemented to prevent disclosure of information that might identify the participant (inadvertently or not) either during the course of the research or afterwards. The Protection of Personal Information Act 4 of 2013 (partially in effect) has increased the need to ensure computer safety, locked record storage facilities and careful gate keeping about access to raw data including completed informed consent documents (see also 3.1.8). Researchers should take measures to ensure privacy and confidentiality interests throughout the research period, including when disseminating results or findings.

⁷Tri-Council Policy Statement (Canada) 2010, 10.

⁸Tri-Council Policy Statement (Canada) 2010, 8.

2.3.8 Researcher Competence and Expertise

Researchers must be suitably qualified and technically competent to carry out the proposed research. The principal investigator (PI) or research leader has primary responsibility to ensure the safety and well-being of participants, the scientific integrity of the protocol and responsible implementation of that protocol. For international multi-centre research, at least one (co-) PI must be South Africa-based.

Competence is demonstrated mainly by academic qualifications, credentials, scientific and technical competence as evidenced in previous publications or testimonials. Competence includes research competence, which is assessed in terms of education, knowledge, certification and experience. In addition, researchers should produce evidence of appropriate research ethics training within the previous three years.

Principal investigators or research leaders must disseminate research results or findings, whether positive or negative, in a timely, accessible, responsible and competent manner. This includes reporting back to participant communities where appropriate, in accordance with the norm of role player engagement and collaboration.

This chapter describes the substantive norms and the operational processes and procedures that Research Ethics Committees (RECs) are expected to adhere to when reviewing and engaging in decision-making about the ethics of research proposals. In what follows, the minimum benchmark for promoting responsible, ethical and safe research involving human participants is described and discussed.

Note that while the norms and procedures apply also to research with animals as appropriate, this chapter is aimed more at research with human participants. Details regarding norms and operational processes for research using animals may be found in The care and use of animals for scientific purposes SANS 10386:2008 or its successor.

The aim of this chapter is to

- provide descriptions of best ethical practices in research involving human participants;
- guide compliance with national and international ethical and regulatory requirements;
- outline a framework within which South Africa-based research can be evaluated and conducted with confidence; and
- facilitate consistent deliberative processes and decision-making about ethical issues in research involving participants or animals.

The chapter is organized into sections that address, first, the substantive norms that inform ethics review; and secondly, the processes and procedures that ensure procedural and administrative consistency and transparency. Thirdly, guidance is provided about specific types of research or groups of research participants that require meticulous treatment in light of particular sensitivities or vulnerabilities. Finally, a series of special topics is discussed, including biological materials, genetic research issues and insurance against research-related bodily injury.



Chapter 3

SUBSTANTIVE NORMS AND OPERATIONAL PROCESSES FOR ETHICS REVIEW

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3.1 Ethical basis for decision-making in the review process

RECs should use the principles outlined in Chapter 2 and articulated in international human rights and research ethics guidance documents as the basis for evaluating research proposals. RECs should make clear which specific ethical guidelines are relied on in making their decisions; the guidelines should be readily accessible to researchers and other interested persons, including the general public.

Key criteria for the review and evaluation processes include

3.1.1 Scientific design, aims and objectives

The ethical implications of the methodology and design of a research proposal must be reviewed. This means that the ethical acceptability of the chosen methodology and the design must be assessed as well as the relevant disciplinary

scholarly standards, where appropriate. Sound and valid scientific methods must be evidenced by prior scientific review or the REC must engage specifically in scientific review that shows not only whether the selected design and methodology are sound but also that the study is worth doing. In other words, that the stated aims and objectives are achievable and will likely produce valid outcomes. In the case of qualitative research, the theoretical paradigm and methodology chosen must be assessed for suitability in light of the stated aims and objectives (see also chapter 6). The ethical implications of the selected design, methodology and research plan must also be analysed. Even if scientific review has occurred, the REC must assess how the research will be conducted, whether the researchers are suitably qualified, that adequate monitoring and safety measures are in place and achievable, that the site is suitably resourced, and so forth.

Scholarly disciplines and fields of research vary considerably in regard to their traditions for scholarly review, including the stage at which the review takes place. These disciplinary variations must be taken into account by RECs. Duplication of scholarly peer review should be avoided if possible. To this end, researchers should provide clear evidence of previous scholarly assessments and the outcome where appropriate. RECs may request full documentation of scholarly reviews.

Note that a risk of harm is unlikely to be justifiable if the research lacks scientific or scholarly merit.

3.1.2 Inclusion and exclusion criteria

The selection of participants must be appropriate for the research question. The rationale for the planned number of participants must be reasonable in light of the aims and objectives and proposed methodologies. Underpowered studies may be futile. An explanation of how the sample size is to be determined should be provided. For qualitative research, the method for sample selection must be clear and complete. The rationale for the inclusion and exclusion criteria must be clear, explicit and reasonable. If vulnerable participants are to be included, an adequate justification should be provided; protective safeguards and measures should be explained. Exclusion criteria should be based on sound reasons. Inclusion and exclusion criteria have ethical implications (e.g. fairness of selection) and are not just of scientific relevance.

3.1.3 Selection of study population and sampling

The principle of distributive justice requires that particular groups or categories of persons should not bear more than a fair share of the burden of research participation. But, equally, groups or categories of persons should not be deprived of a fair opportunity to participate in research. In other words, all persons should be able to contribute to the advancement of knowledge that research aims to achieve. RECs should assess whether the selected study population that will bear the risks associated with participation is likely to benefit from the research, if not immediately, then at least in the foreseeable future or, at least, whether the group represented by the participants is likely to benefit from the research. In other words, the risk-benefit ratio can include that risk of harm to participants might be offset against likelihood of benefit to others, in some circumstances.

3.1.4 Recruitment and enrolment

Recruitment strategies should be neutral, and should describe the purpose of the research, the anticipated risks of harm and potential benefit of participation and other relevant details. Recruitment methods should be properly described in the proposal and the recruitment materials should be included with the proposal e.g. posters, flyers, and advertisements. Recruitment and enrolment processes should endeavour to avoid perceptions of selection bias. The location, context and timing of recruitment and enrolment should be appropriate for protection of privacy and confidentiality interests. If potential participants are in a dependent relationship with the researchers or recruiter, e.g. student/lecturer, patient /doctor, employee/employer, the proposal should explain the measures that ensure that the potential participant's ability to make a voluntary choice is unrestricted. Where the researcher will recruit personally, the possibility of perceptions of undue influence or therapeutic misconception must be managed. The REC should enquire also whether the selected sample group has been or is currently involved in previously approved research so as to assess the possibility of excessive burden or risk exposure.

3.1.5 Research procedures

The research procedures should be described in a manner that ensures the rationale and details are clear to the REC. Procedures that are standard of care should be differentiated from procedures necessary only for research purposes, to assist with weighing the risk of harm against the likelihood of benefit. The proposal should explain whether specific results of data collection, e.g. incidental findings, clinical test results and other clinically relevant findings, will be made known to participants.

The appropriate expertise and qualifications of researchers,⁹ study and project leaders to perform procedures should be assured, e.g. paediatric training is required for paediatric research procedures. Research procedures should not adversely affect routine treatment and management of patients or the functioning of health care facilities. In the case of research conducted in other settings, care should be exercised not to disrupt routine practices without the parties involved having made prior arrangements.

3.1.6 Risks of harm and likelihood of benefit

The ratio of risk of harm to likelihood of benefit should be favourable, i.e. the likelihood of benefit, at least to the category of person involved, should outweigh the risk of harm to the participants as well as to the community or society as a whole. In weighing risk of harm against likelihood of benefit, the analysis is concerned not only with the participants themselves but also with community or societal interests.

The ratio may be analysed by considering whether

- the harms and benefits are adequately identified, evaluated and described;
- the harms stated in the proposal match those stated in the informed consent documentation;
- the risk of harm is reasonable in relation to anticipated benefit;

- the risk of harm is reasonable in relation to the importance of the anticipated knowledge to be gained;
- counselling and support services will be made available if appropriate.¹⁰

Anticipated harms should be minimised by preventing occurrence as far as possible and by implementing appropriate remedial interventions should the harm occur. The nature of harms will vary in accordance with the type of research under consideration and may include physical, psychological, legal, social (including stigma) and financial harms. The REC should also assess the possibility of harm to the researcher, study or project personnel e.g. safety concerns.

3.1.7 Reimbursements and inducements for participants

Participants should not have to incur expenses to take part in research. Consequently, researchers should budget to reimburse expenses incurred by participants for travel, refreshments and also for inconvenience, depending on the circumstances. If no travel or other expenses are incurred, reimbursement is not required unless an inconvenience reimbursement is justifiable.

A fair rate of reimbursement should be calculated using the Time, Inconvenience and Expenses (TIE) method to determine the cost to participants for time expended, inconvenience and refreshments associated with research participation. This method costs expenses at the current hourly rate for unskilled labour in the market place, regardless of whether the participant is employed. See NHREC (2012) *Payment of trial participants in South Africa: ethical consideration for Research Ethics Committees*.¹¹

Researchers must submit planned payment schedules and amounts together with a justification to the REC when making application for ethics review. RECs should exercise caution against taking an unreasonably paternalistic view of the rate of reimbursement. The proposal and the informed consent documentation should indicate whether reimbursements are pro rata if the participant does not complete the study; i.e. whether only some of the offered reimbursement is available if participation is stopped before the anticipated end of the study.

Where minors are the participants, their accompanying parent or guardian should also receive reimbursement for travel costs and refreshments.

Inducements encourage participation. They may be offered in some circumstances where e.g. recruitment, especially of healthy participants, is anticipated to be difficult. However, a justification for this tactic should be provided and the inducement should not unduly influence an informed choice about participation. In particular, an inducement should not undermine a potential participant's assessment of risk of harm. All inducements should be clearly explained and justified to the REC. Input from community members on the REC or other role players may be constructive.

3.1.8 Participants' privacy and confidentiality interests

The principle of respect for persons requires careful attention to privacy and confidentiality interests. Privacy describes the person's interest in controlling access to her personal information. Confidentiality is about whether and how research data might be disclosed carelessly or inadvertently, thus revealing the participant's identity or category, making him vulnerable to harm. (See also 2.3.7)

The proposal should explain how data records (written, audio or visual) are to be secured, the length of time they will be retained¹² and who will be responsible for storage and/or final disposal. The proposal should explain why particular identifying information is required for the study that purports to collect data anonymously. RECs should assess whether notifiable activities might occur amongst participants, e.g. abuse of minors or notifiable diseases and, consequently, whether appropriate measures are in place and are explained in the research proposal. Furthermore, the REC must ensure that the required notification or reporting and its management are explained in the consent documents.

Where focus groups are planned, RECs should check that the information for participants explains clearly that researchers cannot guarantee confidentiality because members of the focus group may disclose information outside the research setting, despite agreeing not to do so. For this reason, consent documentation should advise potential focus group participants not to disclose personally sensitive information, as the researcher cannot guarantee confidentiality, even if other participants are urged to respect confidentiality.

The Protection of Personal Information Act 4 of 2013 was assented to on 19 November 2013.¹³ This Act provides guidance on how the right to privacy regarding personal information is protected. It stipulates that the right to privacy includes 'protection against unlawful collection, retention, dissemination and use of personal information' (Preamble to Act). A tension between the right to privacy and the need for free flow of information in a society that seeks to make progress on economic, social, health care and educational fronts, is immediately evident. The Act does not appear to hold out negative implications for research activities that record personal information about research participants. However, special attention should be given to ensuring that computers and electronically stored data are protected from unauthorised access, inadvertent or accidental dissemination and distribution in form of a 'data dump', etc.

Research activities are a legitimate purpose, provided that protective measures are adhered to. Thus researchers and RECs should pay careful attention to measures that will protect privacy and confidentiality interests. In general terms, a person should know what information is being collected, why it is being collected, what will happen to it, how long it will be retained, whether it will identify the person, whether it will be shared with others and why, whether it will be sent outside South Africa and why. The person should agree to these terms.

¹⁰Researchers' includes PIs and research assistants and others who will do the work of research.

¹¹E.g. if emotional distress is a likely side effect of research procedures, arrangements to facilitate access to assistance should be made.

¹²Available at <http://nhrec.org.za> – the current rate (2014) for unskilled construction workers is approximately R15 - R25 per hour depending on the tasks (see Department of Labour's sectoral determinations).

¹³Storage requirements may vary according to institutional requirements; usually between five and fifteen years.

¹⁴Some parts came into effect on 11 April 2014: s 1 (definitions); part A of Chapter 5 (establishment of Information Regulator); s 112 (about making Regulations); and s 113 (procedures for making Regulations) by Proclamation in GG 37544 R.25, 2014.

Some specific terms are summarised:

- in the case of a child (person under the age of 18 years), a parent or guardian¹⁴ must give permission for the information to be collected (s 35(1)(a));¹⁵
- if the information is to be sent outside the Republic, the recipient must assure that the level of protection afforded in that country is commensurate with that expected in South Africa (s 18(1)(g));
- information about a person's race or ethnic origin must be necessary (s 29(a)) or for affirmative action purposes (s 29(b));
- information about a person's health or sex life must be necessary for the research activity (s 27(1)(d));
- information about a person's inherited characteristics must be necessary for the research activity (s 32(5)(b));
- biometric¹⁶ information about a person must be necessary for the research activity (s 27(1)(d)).

In effect, the Act outlines and requires the usual requirements for ethical and responsible informed consent procedures. The provisions underpin the importance of comprehensive SOPs and rigorous adherence thereto. It should be remembered that research records including informed consent documentation may be solicited by interested parties via application in terms of the Promotion of Access to Information Act 2 of 2000.

3.1.9 Obtaining informed consent

The principle of respect for persons underpins the requirement that a person must choose voluntarily whether to participate in research on the basis of information that allows an informed choice to be made. The process of providing the necessary information and of engaging with the person before a decision is reached is known as the informed consent process. It should be noted that informed consent is a necessary but insufficient element of ethical research, i.e. that a person voluntarily chooses to participate does not mean that the research proposal is ethical. All the other elements should also stand up to ethical scrutiny.

An important element of making an informed choice is the nature and quality of information made available to the potential participant. See below for expectations regarding information disclosure.

Adults, i.e. persons over the age of 18 years, may make independent decisions. However, they may wish to consult with family members or others in keeping with personal preference or cultural practices. Consequently, the process should permit sufficient time for consultation between the recruitment approach and the point of decision-making. No person should be required to make an immediate decision. The informed consent process for adults with diminished or no decision-making capacity (factually incapacitated) and for minors (legally incapacitated) is described at 3.2.4.3 and 3.2.4.2 respectively.

RECs should assess the proposed process for informed consent as well as the information that potential participants will be given and the measures to facilitate understanding. Considerations for assessment include whether

- the setting will
 - minimise the possibility of undue influence
 - be sufficiently private and appropriate
- the person who will conduct the process
 - will be appropriately trained, independent and bias-free
- the text
 - is in plain language and appropriate to the participants' level of understanding¹⁷
 - is free of jargon and unexplained acronyms
 - is clear and explains technical terminology e.g. randomisation
 - is translated into language(s) appropriate to the context
 - states that participants may contact the REC at the contact details provided if they have queries or complaints about their rights and welfare as research participants
 - states that participants may contact the researcher at the contact details provided if they have queries about the research project
 - conforms to the proposal
- the information explains
 - that the person is being asked to participate in research
 - that the choice whether to participate is voluntary
 - that refusal to participate will not be penalised
 - that choosing to participate can be reversed, i.e. the person may decide to terminate participation at any time without explanation or prejudice
 - the purpose and nature of the research procedures and components

¹⁴Note a caregiver, a foster parent, and a schoolteacher or principal are not guardians.

¹⁵This requirement is compatible with the consent requirements for minors as described elsewhere in these Guidelines (see 3.2.2).

¹⁶Biometrics means a technique of personal identification that is based on physical, physiological or behaviour characterisation including blood typing, fingerprinting, DNA analysis, retinal scanning and voice recognition' (s 1 of the Act). ¹⁷The Flesch-Kinkaid readability tool should be used to assess the complexity of text. This tool is built into MS Word's spelling & grammar check tool as 'readability statistics'. No more than Grade 8 equivalency should be the target complexity level.

- the research-related activities and procedures that the participant is being asked to consent to
- the expected duration of participation
- the nature of the participant's responsibilities
- the nature of the researcher's responsibilities
- the anticipated risks of harm or discomfort
- the measures to minimise risk of harm
- the extent to which confidentiality is possible
- whether reimbursement for expenses is available
- that sponsors of the research and regulatory authorities may inspect research records
- who the researchers are and the nature of their expertise
- the potential benefits, if any, for participants both during and after the research
- that the research may be terminated early in particular circumstances
- that the research has been approved by a registered REC (include identifying details)
- a measure to probe understanding and comprehension of the information is planned and how it proposes to do so especially for very vulnerable potential participants

Where a clinical trial is proposed, additional information for prospective participants is required.¹⁸

3.2 Vulnerability and incapacity

Vulnerability is not an absolute condition but rather occurs on a sliding scale. In South Africa, arguably, the majority of potential research participants are vulnerable when compared to those in North America or Europe, from whence much funding is sourced.¹⁹ Whether vulnerability is present is a matter of fact and degree. However, certain groups of participants²⁰ require careful consideration to ensure that, where appropriate, additional precautions are put into place. For example, advanced age, very young age, personal or environmental factors like extreme poverty and ordinarily poor access to health care may increase vulnerability

3.2.1 Contextual circumstances

Personal circumstances, such as mental or intellectual impairment, acute illness, advanced age, and pregnancy and childbirth may increase vulnerability. Persons may be factually incapable or less capable of understanding information and processing it to reach a decision e.g. about whether to participate in research. Environmental circumstances may also increase vulnerability such as very poor socio-economic conditions, low levels of formal education and literacy, or restricted access to health care services. Such persons may be more easily persuaded to agree to participate without a properly considered understanding of the implications.

It is important to note the difference between legal incapacity and factual incapacity. No person may claim that, because a minor is factually capable, the legal incapacity should be waived. On the other hand, no adult may be assumed to be incapable unless incapacity is established factually. Consequently, mental incapacity must be established by a factual assessment of the individual's abilities to understand and to communicate that understanding. Legal incapacity prevails notwithstanding the existence of factual capacity.

South Africa is home to a number of vulnerable communities. Where factors usually associated with vulnerability are integral to the research, the proposal should demonstrate how vulnerability would be managed. Particular caution should be exercised before undertaking research involving participants in such communities, and RECs should ensure that

- persons in these communities are not being involved in research merely because they are expediently accessible, while the research could be carried out in a less vulnerable community;
- the research is relevant to the health needs and priorities of the community in which it is to be carried out; and that
- research participants know they will take part in research; and that the research will be carried out only with their consent.²¹ Particular attention should be given to the content, language(s) and procedures used to obtain informed consent.

¹⁸See Department of Health (2006) Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa or its successor.

¹⁹UNAIDS defines 'vulnerable community' 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 and understanding of scientific research; limited access to health care and treatment options; limited ability of individuals in the community to provide informed consent.

²⁰For further, more detailed, discussion on special classes of participants, see CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects (2002) Guidelines 13-17, http://www.cioms.ch/publications/guidelines/guidelines_nov_2002_blurb.htm; US Department of Health & Human Services, Office for Human Research Protections, <http://www.hhs.gov/ohrp>.

²¹Note that this requirement does not mean that a REC may not approve a waiver of personal informed consent for types of research into e.g. record reviews or such like.

²²Section 28 of the Constitution; and s 17 of the Children's Act 38 of 2005.

Note, however, that RECs should avoid patronising assumptions about a community's ability to make responsible decisions. Factual information is required before deciding that a community is too vulnerable to be invited to choose whether to participate in research.

In order to ensure optimal protection of vulnerable participants, the REC may impose additional protective measures for the informed consent process; or require increased monitoring and interim reporting on participants' welfare; or require post-recruitment reviews of the effectiveness of the protective measures imposed. Other measures may also be appropriate.

Note that the decision to impose additional measures should flow from an assessment of the nature of the research and the circumstances of the potential participants. In other words, additional protective measures should not be automatic just because a vulnerable group will be recruited; rather, the decision should be based on the particular circumstances of the proposal before the REC. For example, an automatic assumption that impoverished people cannot choose responsibly whether to participate in research is disrespectful because it denies their autonomy.

If compliance with the additional measures is poor and participants' welfare is negatively affected, approval for the study may be withdrawn, temporarily or permanently, as the case may be.

Groups of participants discussed here include

- minors (children and adolescents)
- women
- adults with incapacity to provide informed consent
- persons in dependent relationships
- persons highly dependent on medical care
- persons with physical disabilities
- prisoners
- collectivities

Note this list is not exhaustive but provides an indication of the types of consideration to be applied

3.2.2 Minors (children and adolescents)

Below the age of majority, the law protects young people from their own emotional, cognitive and physical immaturity and limited life experience through the legal status of minority. In other words, minors, i.e. persons under 18 years of age,²² are legally incapable of performing legal transactions without assistance from a parent or guardian. In the research context, this means that, in principle, anyone under the age of 18 years may not choose independently whether to participate in research; a parent or guardian must give permission for the minor to choose. This is because young persons' understanding of key aspects of the research initiative may be compromised and, consequently, they may be exposed to increased risk of harm from particular research procedures. Exceptions to the requirement for parental permission are discussed at 3.2.2.4.

Tension exists between the views that, in general, children and adolescents should not bear the burden of research unnecessarily, on the one hand, and that children and adolescents are entitled to improved health care based on findings drawn from rigorous research conducted in the child population of South Africa, on the other. The solution lies in the approach that minors should participate in research only where their participation is indispensable to the research; i.e. the research cannot deliver the desired outcomes if adult participants were to be used instead.

Because of their status of legal incapacity, in principle, minors may not choose independently whether to participate in research. A parent or guardian must give permission for the minor to choose. It should be noted that the parent or guardian does not choose for the minor who is capable of choosing;²³ rather, the parent or guardian gives permission for the minor to choose. Where a minor is very young or is factually incapable of exercising a choice, then the parent or guardian chooses whether the minor should participate.

The best interest of a child should be paramount in decisions that affect the child.²⁴ This principle is difficult to apply in the research context because research participation is unlikely to be in the best interest of a minor. Good research design does not accommodate a best interest analysis easily. Rather, the design draws on aggregates of information. This means that, in the research context, the best interest principle should be understood to mean that participation in the research should not be contrary to the individual minor's best interest. Further, the research should investigate a problem of relevance to minors.

Where research can be done with consenting adults but nevertheless proposes also to include minors, the researchers must provide strong justification for the inclusion of minors. The REC should not make assumptions on behalf of the researchers. It should require all relevant information to be provided by the researchers. Note that all types of clinical trial research on minors should be scrutinized carefully in case extra precautions or conditions are necessary.

For purposes of these guidelines

'Adolescent' means a child between the ages of 12 and 17 years of age (ICH Topic E 11 Clinical Investigation of Medicinal Products in the Paediatric Population. 2000 [<http://www.emea.eu.int/pdfs/human/ich/271199EN.pdf>])

'Caregiver' means a person who factually cares for a child (s 1 Children's Act, 38 of 2005; a caregiver is obliged (in terms of s 32(1)) to safeguard the child's health, well-being and development; and to protect the child from abuse and other harms. Further a caregiver may exercise the parental right to consent to medical examination or treatment of the child (in terms of s 32(2))

'Child' means a person under the age of 18 years (s 28 Constitution; s 1 Children's Act 38 of 2005)

²²Section 10 of the Children's Act 38 of 2005. Note that a caregiver, a foster parent and a schoolteacher or principal are not guardians. Note that legal incapacity is not the same as factual incapacity. Minority is a legal incapacity status.

²⁴See also s 9 of the Children's Act 38 of 2005.

'Child-headed household' means a household per s 137 Children's Act 38 of 2005

'Guardian' means a person appointed by a court to look after the financial and welfare interests of a minor, or a person appointed by a parent with sole responsibility for the minor in terms of the parent's Will

'Harm' means physical, emotional, psychological, social or legal harm

'Minor' means a person (child) less than 18 years (s 17 Children's Act 38 of 2005)

'Neonate' means a newborn child, including an infant less than a month old

'Orphan' means a child who has no surviving parent caring for him or her (s 1 Children's Act 38 of 2005)

'Parent' includes an adoptive parent (s 1 Children's Act 38 of 2005)

'Therapeutic research' means research that includes interventions that may hold out the prospect of direct health-related benefit for the participant (Regulation 135)

'Non-therapeutic research' means research that includes interventions that will not hold out the prospect of direct health-related benefit for the participant but may produce results that contribute to generalisable knowledge (Regulation 135)

3.2.2.1 Minimum conditions for research involving minors

The following considerations are critical when RECs review proposals to involve child participants:

- a) Children should participate in research when their participation is scientifically indispensable to the research. In the case of interventional clinical research, equipoise²⁵ should exist. Research should investigate a problem of relevance to children. The protocol should provide sufficient information to justify clearly why children should be included as participants.
- b) Children should participate in research only where such research poses acceptable risks of harm. That is, research involving minors should be approved only if:
 - i. The research, including observational research, is not contrary to the best interest of the minor;
 - ii. The research, including observational research, places the minor at no more than minimal risk of harm (i.e. the 'everyday risks standard' which means the risk of harm is commensurate with daily life in a stable society or routine medical, dental, educational or psychological tests or examinations – referred to as 'negligible risk' in some guidelines); or
 - iii. The research involves greater than minimal risk of harm but provides the prospect of direct benefit for the minor. The degree of risk of harm should be justified by the potential benefit; or
 - iv. The research, including observational research, involves greater than minimal risk of harm, with no prospect of direct benefit to the minor, but has a high probability of providing significant generalizable knowledge. The degree of risk of harm should be justified by the risk-knowledge ratio.
 - v. Greater than minimal risk of harm should represent no more than a minor increase over minimal risk.
 - vi. Where appropriate, the minor will assent to participation.
- c) Research involving children must be reviewed appropriately. The National Health Act distinguishes research with children as 'therapeutic' and 'non-therapeutic' research. The intention is to place special emphasis on deliberation by the REC about the degree of risk of harm posed by a proposal and the likelihood of benefit to the child-participant. This distinction is of little practical import since most research involves a mix of 'therapeutic' and 'non-therapeutic' interventions or components and reviewers usually assess the proposal as a whole.
- d) The degree of risk of harm should be evaluated against the likelihood of benefit to the child-participant as outlined in b) above. Furthermore, registered RECs that have been granted permission in writing to exercise the Minister's delegated power to approve research with children that includes non-therapeutic components must ensure that their deliberations on these components are properly minuted and recorded as required by the Regulations. RECs that review research with child participants must include members with appropriate paediatric research experience.
- e) Children should participate in research only where the proper written permissions have been obtained. The general principle is that minors cannot agree to research participation without assistance of a parent or guardian (exceptions to the general principle are discussed in 3.2.2.4). This principle holds notwithstanding the exceptions created in the Children's Act 38 of 2005 for consent to medical treatment and surgical operations (s 129); consent to HIV-testing (s 130); and the exception for female minors created in the Choice on Termination of Pregnancy Act 92 of 1996 (s 5(2)). Consequently, in principle, the consent process for a minor's participation in research requires
 - Permission in writing from parents or legal guardian for the minor to be approached and invited to participate (in accordance with s 10 of the Children's Act 38 of 2005);
 - Assent from the minor in writing (i.e. agreement to participate) if he or she chooses to participate.

Note that an unmarried minor mother may not agree to the participation of her child in research without assistance. Her guardian (usually her parent) is also the guardian of her child while she is a minor and must consent to the child's participation. In other words, pregnancy and childbirth do not change the legal status of the minor mother. When the mother reaches the age of majority (18 years), she may consent to her child's participation in research.

- f) Children should participate in research that takes cognisance of their privacy interests. Although children are legally dependent, they have significant privacy interests. Their genetic privacy interests, in particular, may be more important than those of adults who manifest a particular genetic condition.

²⁵ 'Equipoise' literally means a state of balance or equilibrium; in the research context it means that, amongst health care experts, uncertainty prevails about whether a particular treatment or intervention is better than another. This principle forms the basis for conducting clinical research.

- g) When parents or a guardian give permission for their minor child to choose whether to participate in research, this permission is given based on a detailed description of all diagnostic and therapeutic interventions that will affect the child in the study. However, this does not mean that parents are entitled to know the outcome of all diagnostic and therapeutic interventions, especially as regards older minors (adolescents). The informed consent documentation must explain whether results of tests will be made known to child-participants and their parents. Whether this happens, depends to an extent on the socio-cultural context and the best interest standard.
- h) The minor's interest in confidentiality, i.e. being identified or identifiable without permission of the minor and her parent or guardian must be respected.
- i) Research involving children must respect their evolving capacity to give consent. Minors who turn 18 years old during the course of a study should be approached at the time of their birthday to re-consent. This is because they must now provide independent consent to continue to be a participant. In cases where minors are permitted to decide independently whether to participate,²⁶ the consent process should address how re-consent will be managed when they change status from minority to majority. Similarly, in the case of large and longitudinal studies, attention must be given to how the change from minority to majority will be managed. Where a study is no longer in active interaction with participants, re-consent procedures may be less important.
- j) Researchers must familiarise themselves with the legal obligations to report child abuse and neglect. See 3.2.2.5.

3.2.2.2 Parental permission

The Children's Act 38 of 2005 emphasises the right of a child to participate in any matter concerning that child, provided he or she has sufficient maturity to participate appropriately and meaningfully (s 10), notwithstanding legal incapacity. This means that parents or guardians may not decide whether their minor child should participate in research without the minor's contribution to the decision. The choice of whether to participate is not a legal decision but rather a factual choice. Consequently, the process should be that the parent or guardian is requested to give permission for the minor to be approached to be invited to participate in the study. The factual decision whether to participate is the minor's and not the parent's.

Parental permission and minor's decision must be consistent, i.e. if the minor decides not to participate, the parent may not override this decision. If the parent is reluctant for the minor to participate but the minor wants to do so, the matter must be managed carefully to establish what the concerns are and whether they may be resolved. The minor cannot choose to participate if the parent withholds permission for that minor to choose. Researchers are unlikely to be able to intervene where the suspicion is that the parent is withholding permission unreasonably, since a best interest analysis in this context is irrelevant.

3.2.2.3 Orphans without guardians

i. Introduction

Many minors in South Africa do not have parents and very few have court-appointed guardians. These minors are often described as 'orphans and vulnerable children' or OVC. The absence of a legally appropriate parental substitute poses a problem for researchers because of the lack of clear guidance as to an acceptable substitute in the informed consent process for research participation. (Note that for treatment purposes, substituted consent occurs on the basis of necessity, which is not applicable to the research context.)

ii. Justification

Important research that seeks to understand and improve psychosocial, economic and educational conditions for orphans and vulnerable children to improve their future well being generally involves no more than minimal risk of harm. Other research including clinical research that may involve a minor increase over minimal risk of harm may also be justified on the basis that it would be unjustifiable to exclude a significant segment of the child population from research on the basis of their legal status. Consequently, it is ethical and reasonable to designate parental substitutes in these circumstances.

iii. Pragmatic parental substitutes²⁷

In the interest of fostering consistency as well as compliance with the spirit of the legal provisions that protect minors' interests, especially the Constitution and the Children's Act, pragmatic guidance is provided here to deal with situations where no biological parent or legal guardian exists. The permissible level of risk is limited (see 3.2.2.1).

Note this guidance does not permit expedient substitution e.g. where a parent is temporarily unavailable.

This guidance takes its lead from the Constitution, the Children's Act, the National Health Act, the Criminal Law (Sexual Offences) Amendment Act; the South African Good Clinical Practice Guidelines (2006) available at www.doh.gov.za/docs/factsheets/guidelines/clinical/2006/index.html.

The guidance is premised on three conditions, all of which must be satisfied:

1. The risk standards set out in 3.2.2.1 b) must be adhered to; and
2. It is not possible to do the research with adult participants; and

²⁶See 3.2.2.4.

²⁷This pragmatic guidance is provided to temper the chilling effect of a literal interpretation of s 71 of the National Health Act 61 of 2003, which otherwise might prevent important ethical research.

²⁸Note a caregiver, a foster parent and a schoolteacher or principal are not guardians.

3. The research proposes to investigate a problem of relevance to minors.

Note that if the proposed research holds out more than a minimal risk of harm, there must be a compelling justification for why orphans should be included as participants, e.g. the research focus has particular relevance for OVC and cannot be studied without their enrolment.

The parental substitutes should be used in descending order, as listed.

- i. The minor chooses whether to participate and thus expresses her will AFTER
- ii. The parent gives assistance with understanding (so the minor makes an informed choice)
- iii. If no parent, then guardian: either court-appointed OR as indicated by the parent in a Will (s 27 Children's Act)
- iv. If no guardian, then foster parent (per order of Children's Court) (Note that social workers should request that the authority to give permission should be included expressly in the court order authorising foster care)²⁸
- v. If no foster parent (per iv. above), then caregiver (s 1 Children's Act: defined as '...any person other than a parent or guardian, who factually cares for a child and includes – a) a foster parent; b) a person who cares for the child with the implied or express consent of a parent or guardian of the child; c) a person who cares for the child whilst the child is in temporary safe care; d) the person at the head of a child and youth care centre where a child has been placed; e) the person at the head of a shelter; f) a child and youth care worker who cares for a child who is without appropriate family care in the community; and g) the child at the head of a child-headed household')
- vi. If minor is caregiver in child-headed household and no supervisory adult (s 137 Children's Act), then trusted adult nominated by minor, including but not limited to social worker, community worker or teacher.

3.2.2.4 Minors' independent consent

In particular circumstances, e.g. for reasons of sensitivity, like discussion about sexual activities, substance abuse etc., it may be desirable and ethically justifiable for minors (especially older minors i.e. 16 years and older) to choose independently i.e. without parental assistance, whether to participate in research. Generally, only minimal risk research is suitable for independent consent by minors. Reasons supporting the desirability of independent consent may include recruiting sufficient numbers of minors who otherwise would be unwilling to participate if they must tell their parents about the nature of the research in order to obtain parental permission.

An ethical justification for independent consent by minors may be made in the following manner:

- By prior engagement with participating community role players, the PI can request (and justify explicitly) REC approval of a waiver of the parental (or substitute) permission requirement. Engagement could include outreach to relevant role players such as canvassing the opinion of a representative body of parents e.g. via schools.
- Factual evidence of such engagement must form part of the PI's justification in the protocol. Factual evidence may be in the form of a letter from a relevant role player (like a community leader, school principal or a CAB) that confirms the view that independent consent is acceptable to the parents.
- If the REC accepts the ethical justification and the factual evidence of parental support for independent choice by their minor children, then the REC may grant a waiver of the requirement of written parental permission and must document the process carefully.

3.2.2.5 Mandatory reporting obligations

There is no general obligation to report either the commission of or the intention to commit a crime. However, if a researcher has information indicating that direct harm to another person may occur as a result of the intention to commit harm (e.g. a participant says 'I'm going to kill her...'), then there may be an obligation, especially when the third person is known to the researcher. For specifically designated persons, there are statutory reporting obligations. (See Appendix 3 for SOP Template.)

- i. Reporting obligations for abuse and neglect

The Children's Act requires anyone who reasonably believes a child to be suffering physical abuse causing injury, deliberate neglect and sexual abuse to report this to a child protection agency, the provincial social development department, or to a police official.

- ii. Reporting obligations for under-age sexual activity

The age at which minors can lawfully consent to sexual activity is 16 years, in terms of the Criminal Law (Sexual Offences and Related Matters) Amendment Act 32 of 2007 (Sexual Offences Act). Anyone with knowledge of a sexual offence against a minor is required to report this to a police official. In effect, any adult or person >16 years who engages in sexual activity with a minor <16 years commits a crime and may be prosecuted. The Act describes a broad range of sexual offences, including rape, sexual assault, sexual grooming, sexual exploitation, and use of children in pornography including photographs. This means that the range of activities that may constitute a sexual offence is extensive.

The Sexual Offences Act differentiates between adolescents (12 - <16 years) and older minors (16 and 17 years). In the case of children younger than 12 years, sexual activity is unlawful even with consent. For

²⁹The *Teddy Bear Clinic for Abused Children v Minister of Justice and Constitutional Development* (CCT 12/13) [2013] ZACC 35; 2014 (2) SA 168 (CC); see also *J v NDP* [2014] ZACC 13.

³⁰See Draft Criminal Law (Sexual Offences & related matters) Amendment Act Amendment Bill [B-2014]

³¹Clinical 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 fetus 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.

adolescents, the situation is as follows. The Teddy Bear Clinic case²⁹ found criminalisation of consensual sexual acts between adolescents aged 12 – <16 years to be unconstitutional, on the basis that adolescents should not be subjected to criminal sanctions when they exercise their entitlement to determine their personal relationships in light of their rights to autonomy, dignity and privacy. The Constitutional Court imposed a moratorium on action against adolescents in terms of ss 15 and 16 of the Sexual Offences Act. This moratorium of 18 months is to give Parliament time to revise the offending legislative provisions by April 2015.³⁰

Consensual sexual acts between adolescents aged 12 - <16 years are not criminal and are not reportable. Sexual acts with adolescents aged 12 - <16 years by an adult or a person >16 years, even if consensual, are criminal and reportable. Sexual acts with children <12 years are criminal and reportable.

iii. Sexual and reproductive health research with minors

Research with minors that focuses on their sexuality and reproductive health is likely to encounter instances of abuse and underage sexual activity. The dilemma for researchers is whether to ignore the strict letter of the law or to report as indicated in terms of the Sexual Offences Act and the Children's Act. The matter is not simple.

The clash of interests is obvious, e.g. using the law to protect the minor from abuse may have the unintended consequence of increased harm (physical and social) for that child. Further, thoughtless reporting may violate privacy and confidentiality interests of the minor e.g. in terms of the Choice on Termination of Pregnancy Act, the Children's Act and the Child Justice Act. Whether a researcher, who has but a research interest in the life of the child, but no further right of access or duty of intervention ought to take on the responsibility of a social worker is unclear. Consequently, researchers should think very carefully about the anticipated consequences of reporting in light of the legal context. The proposal submitted for ethics review should explain fully the approach to be adopted, and justify how reporting obligations will be managed, so that the REC can deliberate effectively. The consent documents should clearly inform the minor (and proxy consent providers where necessary) about when reporting obligations arise and how they will be addressed, so that an informed choice can be made about whether to participate. Appropriate engagement with role-players such as child rights and child care organizations may assist researchers to make appropriate and meaningful referrals.

3.2.3 Women

Exclusion of women as research participants has led to a lack of data needed to promote women's health. Any proposed exclusion of women participants must be justifiable in light of research priorities as well as the specific research question under consideration. For example, women are appropriately excluded from prostate cancer research because the relevant population is male. In particular, systematic class exclusion must be guarded against to avoid unfair participant selection.

Additional health concerns arise during pregnancy, including the need to avoid unnecessary risk to the fetus. Consequently, researchers and RECs should exercise extra caution when women participants are or may become pregnant. Exclusion of women from research may be justifiable

- a) to protect the health of the fetus; and
- b) if exclusion is scientifically supportable.

Note that the informed consent documents must explain carefully and fully what the possible effect of the research activities on the fetus might be.

Usually, research involving pregnant women should be undertaken when

- the purpose of the proposed research is to meet the health needs of the mother of the particular fetus;
- appropriate studies on animals and non-pregnant individuals have been completed;³¹
- the risk of harm to the fetus is minimal; and
- in all cases, inclusion poses the least risk of harm possible for achieving the objectives of the research.

3.2.4 Adults with factual incapacity to provide informed consent

Adults who are factually incapable of giving informed consent should participate in research only where their participation is indispensable to the research; i.e. the research cannot deliver the desired outcomes if capable adult participants were to be used instead. Further, the research should investigate a problem of relevance to incapacitated adults. Where research can be undertaken with capable adults but nevertheless proposes also to include incapacitated adults, strong justification for their inclusion must be provided.

The primary difficulty for informed consent in this context is whether proxy consent is permissible. The best interest principle is often used in connection with decisions relating to whether incapacitated adults should be enrolled in research. However, similarly to the case of minors, this principle is difficult to apply in the research context because research participation is unlikely to be in the best interest of an incapacitated adult. Good research design does not permit a best interest analysis easily. Rather, the design draws on aggregates of information. This means that, in the research context, the best interest principle should be understood to mean that participation in the research should not be contrary to the individual's best interest.

Note that all types of clinical trial research on incapacitated adults should be scrutinized carefully in case extra precautions or conditions are necessary.

³² Georgetown University Informed Consent and Limitations on Decision making Capacity Chapter 2 <https://bioethicsarchive.georgetown.edu/nbac/capacity/Informed.html>

3.2.4.1 Capacity and communication

Decision-making incapacity may result from a variety of causes and take various forms. The most important insight is that incapacity to decide is a question of fact to be determined on a case-by-case basis. Even if for other purposes, a person has been declared legally incompetent, she may retain the capacity to make decisions. It is thus vital that researchers bear this in mind because to ignore this fact is to seriously violate the person's constitutional right to dignity as well as the ethical principle of respect (autonomy).

When recruiting participants, the crucial elements are whether the person retains the capacity to decide whether to participate and whether he is able to communicate that decision. The first point to note, therefore, is the difference between the capacity to decide and the ability to communicate the decision. The capacity to decide necessarily includes the capacity to understand the information that is communicated to him. The ability to communicate includes the ability to hear and to speak or otherwise signal or express her wishes. For example, deafness should never be mistaken for incapacity to decide. Similarly, the inability to speak should not be mistaken for a lack of capacity to decide whether to participate.³²

3.2.4.2 Minors and decision-making incapacity

Parents or guardians of minors with intellectual or mental impairments should give permission for their minor children to choose whether to participate in research. If the minor is unable to communicate at all or lacks the capacity to choose, then the parent or guardian should choose whether the minor may be enrolled. In other words, the parent acts as a proxy decision maker. In the case of a minor who remains intellectually or mentally impaired after reaching the age of majority, the situation changes because the person becomes an adult with decision-making incapacity (see 3.2.4.3 below).

3.2.4.3 Adults incapable of giving adequate informed consent

Proxy decision makers are not permitted for adult persons who lack capacity unless the proxy is a court-appointed curator. Neither the National Health Act 61 of 2003 nor the Mental Health Care Act 17 of 2002 makes provision for proxy decision makers for research purposes but they provide clear lists of proxy decision makers for treatment purposes.

Since it would be unethical to exclude a category of persons from research participation without adequate justification, arguably, an ethical argument can be made for using the statutory treatment proxies to provide permission for participation in research that complies with the stipulations set out below. However, RECs must be careful not to confuse the distinction between treatment and research. In unusual circumstances, e.g. major incident research (see 3.4.1), it may be ethically permissible to permit proxy consent also in a situation where no statutory proxy is available but the risk of harm to knowledge ratio justifies it.

In particular circumstances, the REC may approve delayed consent.

Note *this does not mean that informed consent is waived.*

RECs should ensure that a clear and full justification for the proposed delay accompanies the research proposal. The individual circumstances of the patient must be carefully considered to prevent inadvertent violation of personal or cultural values.

The REC may approve a delay in obtaining informed consent for emergency care research if

- the research is based on valid scientific hypotheses that support a reasonable possibility of more benefit than that offered by standard care; **and**
- participation is not contrary to the medical interests of the patient;
- the research interventions pose no more risk of harm than that inherent in the patient's condition or alternative methods of treatment;
- the participant and her relatives or legal representatives will be informed of the participant's inclusion in the research as soon as reasonably possible, and advised of her right to withdraw from the research without any reduction in quality of care.

3.2.4.4 Minimum conditions for research involving incapacitated adults

Research involving incapacitated adults should be approved only if

- i. The research, including observational research, is not contrary to the best interest of the individual;
- ii. The research, including observational research, places the incapacitated adult at no more than minimal risk (i.e. the 'everyday risk standard' which means the risk is commensurate with 'daily life or routine medical, dental or psychological examinations and in social or education settings activities' – referred to as 'negligible risk' in some guidelines); or
- iii. The research involves greater than minimal risk but provides the prospect of direct benefit for the incapacitated adult. The degree of risk must be justified by the potential benefit; or
- iv. The research, including observational research, involves greater than minimal risk, with no prospect of direct benefit to the incapacitated adult, but has a high probability of providing generalizable knowledge; i.e. the risk should be justified by the risk-knowledge ratio;
- v. Greater than minimal risk must represent no more than a minor increase over minimal risk;
- vi. The legally appropriate person (treatment proxies as stipulated in NHA s 7 or s 27(1)(a) of the Mental Health Care Act 17 of 2002) gives permission for the person to participate; and
- vii. Where appropriate, the person will assent to participation. Note that the incapacitated person's refusal or resistance to participate, as indicated by words or behaviour, takes precedence over permission by a proxy.

The National Health Act specifies the sequence of legally appropriate treatment proxies as spouse or partner; parent; grandparent; adult child; brother or sister. The Mental Health Care Act provides, in no particular sequence, that legally appropriate proxies are spouse; next of kin; partner; associate (defined as 'a person with a substantial or material interest in the well-being of a mental health care user or a person who is in substantial contact with the user'); and

parent or guardian.

3.2.5 Persons in dependent relationships

This class of persons includes persons in junior or subordinate positions in hierarchically structured groups and may include relationships between older persons and their care-givers; persons with chronic conditions or disabilities and their care-givers; persons with life-threatening illnesses; patients and health care professionals; wards of state and guardians; students and teachers (including university teachers); employees and employers, including farm workers, members of the uniformed services and hospital staff and their respective employers.

Particular attention should be given to ensuring that participants are adequately informed and can choose voluntarily whether to participate in research.

3.2.6 Patients highly dependent on medical care

Patients who are highly dependent on medical care deserve special attention when considering research participation. The gravity of their medical condition may require invasive measures that carry increased risk of harm. The quality of informed consent may be compromised by the effect the medical condition has on the participant's decision-making or communication abilities. A patient may be reluctant to refuse consent for fear that this may compromise his medical treatment. Adequate provision must be made for informing patients and their relatives about the research, to ensure that stress and other emotional factors do not impair their understanding. The dependency of patients and their relatives on caregivers should not unduly affect research participation decisions.

In particular circumstances, the REC may approve delayed consent.

Note this does not mean that informed consent is waived.

RECs should ensure that a clear and full justification for the proposed delay accompanies the research proposal. The individual circumstances of the patient must be carefully considered to prevent inadvertent violation of personal or cultural values.

The REC may approve a delay in obtaining informed consent for research participation by patients highly dependent on medical care if

- the research is based on valid scientific hypotheses that support a reasonable possibility of more benefit than that offered by standard care; and
- participation is not contrary to the medical interests of the patient; and
- the research interventions pose no more risk of harm than that inherent in the patient's condition or alternative methods of treatment; and
- the research is based on valid scientific hypotheses that support a reasonable possibility of more benefit than that offered by standard care; and
- as soon as reasonably possible, the participant and her relatives or legal representatives will be informed of the participant's inclusion in the research; be requested to give delayed consent; and advised of the right to withdraw from the research without any reduction in quality of care.

3.2.7 Persons with physical disabilities

Recruitment strategies for research participation in general should be sensitive to the possibility that persons with physical disabilities may wish to volunteer and therefore should ensure that there are no unintended barriers to such participation; e.g. the absence of ramps or a lift for wheelchair-bound potential participants. Research involving participants with physical disabilities should anticipate possible barriers and include measures to minimise them.

3.2.8 Prisoners

The chief reason to consider prisoners as a vulnerable class of persons is the potential effect of incarceration on the voluntariness of the decision to participate in research. Neither coercion (direct threat of negative sanction) nor undue influence is acceptable in the informed consent process. Researchers should pay attention to whether their intended participants are awaiting trial prisoners or convicted prisoners. Quite obviously, different ethical issues arise for the former group who remain innocent until proven guilty, notwithstanding being incarcerated. The recruitment strategy design must pay careful attention to how coercion and undue influence will be avoided. Similarly, persons administering questionnaires or conducting interviews must be conscious of environmental factors that may influence voluntariness.

The REC should include, at least on an ad hoc basis, a member with experience and knowledge of working with prisoners when deliberating on the protocol. The researchers must comply also with the requirements of the Department of Correctional Services as listed at <http://www.dcs.gov.za/services/Research.aspx>.

Research should be conducted amongst prisoners only if

- their participation is indispensable to the research
- the research cannot be conducted with non-prisoners
- the research concerns a problem of relevance to prisoners
- sound informed consent processes can be ensured
- engagement with relevant role players about the proposed research has occurred.

In the case of minor prisoners, the limitations and restrictions on independent consent must be remembered. In general terms, it is unlikely that independent consent by the minors will be justifiable.

³³Tri-Council Policy Statement (Canada) 2010, 169. ³⁴Human biological materials means 'material from a human being, including DNA, RNA, blastomeres, polar bodies, cultured cells, embryos, gametes, progenitor stem cells, small tissue biopsies and growth factors from the same' (Regulation 177 GG 35099 2 March 2012); blood and blood products are also included (Regulation 180 GG 35099 2 March 2012).

3.2.9 Collectivities i.e. persons participating in research as groups

'Collectivity' is a term 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 that leaders express a collective view
- members of the collectivity being aware of common activities and common interests.

Research involves a collectivity when

- property or information private to the group as a whole is studied or used
- permission of people occupying positions of authority, whether formal or informal, is required
- participation of members acknowledged as representatives is involved.

Research involving collectivities should include measures to ensure

- dispute resolution mechanisms for anticipated or actual disagreements between the researcher and the collectivity
- respectful negotiation with the collectivity or its leaders
- permission is sought from appropriate representatives of the collectivity to approach individual participants
- an informed consent process for individual participants
- fair distribution of research-related benefits and harms among affected collaborating parties
- agreement about ownership of data and rights of publication of research findings;
- agreement about feedback to the collectivity about the findings.

3.3 Data and biological materials for research purposes

3.3.1 Introduction

Researchers often wish to collect data, including images, or human biological materials from participants for research purposes or to use previously collected diagnostic or therapeutic biological material for research. Once collected, biological material may be stored in repositories as a future research resource (see 3.5.2 below). Although data and biological material are separate from their source (e.g. a particular patient), they symbolise that person. Hence, ethical considerations concerning their use involve how to access, and use them appropriately, how to manage potential privacy concerns that may arise from information management, as well as how to address the special status some segments of the population ascribe to the human body and its parts. RECs and researchers must demonstrate sensitivity to the values, beliefs and attitudes of the persons from whom the materials are derived.³³

Use of data and human biological materials³⁴ causes an inevitable and unavoidable overlap between clinical and research domains. For this reason, RECs should have comprehensive SOPs to guide review of research that proposes use of human data or biological materials; be meticulous in their deliberations, and should ensure the integrity and comprehensiveness of the informed consent documentation. In particular, consent documentation must distinguish clearly between biological materials or data collected for clinical purposes and those collected for research purposes.

For purposes of this section

'Anonymous data or specimen' means data or material without any overt identifying information or link to a specific participant or donor

'Biological specimen' means material from a person including blood and blood products, DNA, RNA, blastomeres, polar bodies, cultured cells, embryos, gametes, progenitor stem cells, small tissue biopsies and growth factors

'Broad consent' means the donor donates materials with permission to use them for a broad range of future studies, subject only to further prior ethics review and approval

'Coded data or specimen' means a number, a symbol or other method provides a coded substitute for identifiers; and a key to the code exists so that the specimen can be linked to its original source

'Donor' means the person (living or deceased) from whose body a biological specimen has been removed or withdrawn

'Identifier' means information such as a name, initials, address, folder number, or biometric identifier (e.g. finger print) that can identify a particular donor

3.3.2 Permitted usage of biological materials

Biological material may be removed from living and deceased persons (NHA ss 55 and 62) for diagnostic, therapeutic and health research purposes (NHA s 64(1)).

³³See World Health Organization. Informed Consent Templates. Consent for Storage and Future Use of Unused Samples http://www.who.int/rpc/research_ethics/informed_consent/en/

³⁴See also Human Heredity and Health in Africa (H3Africa) Guidelines for Informed Consent. August 2013. <http://h3africa.org/ethics/17-ethics/71-informed-consent>

³⁷Human Heredity and Health in Africa (H3Africa) Initiative <http://h3africa.org/>

3.3.3 Identifiability of biological materials and data

RECs must assess the extent to which human biological materials or data could be used to identify a donor. Materials with direct identifiers can directly identify a donor. Coded materials may identify a donor if security and confidentiality measures are not adequate. Anonymised materials without any linkage to donors are unlikely to identify a donor. Materials collected without identifiers of any kind are unlikely to identify an individual donor. Genetic markers make it possible to identify groups rather than individuals. RECs must pay attention to eliminating or at least minimising risks to privacy and autonomy as a result of re-identification.

RECs must also consider the implications for donor welfare of complete anonymisation: it prevents disclosure of material findings, an offer of benefits of research findings, and withdrawal of material from research use. Informed consent documentation must be carefully scrutinised to ensure that the proposed approach and its implications are adequately disclosed and explained.

3.3.4 Collection of biological materials and data

Biological materials and data are collected in a variety of ways

- specifically for research purposes
- incidentally to diagnostic or therapeutic procedures
- for a combination of purposes, including the intention of possible future research use

Collection of materials or data specifically for research use requires prospective informed consent, usually from the living donor (see 3.3.6). Where a donor is unable to provide informed consent, a proxy may be permissible (see 3.2.4.3 above). Where materials or data from a deceased person are sought, permission from an authorised person is required (see 3.3.6).

3.3.5 Restrictions on collection of biological materials

Certain persons are specially protected: without Ministerial permission, biological materials may not be taken from mentally ill persons; biological materials that are not naturally replaceable may not be taken from a minor; no gametes may be taken from a minor; and no fetal biological material except for umbilical cord progenitor cells may be collected from anyone. These restrictions are absolute which means that research with the categories of person mentioned requires special permission. RECs must satisfy themselves that the necessary special permission has been obtained, where appropriate.

3.3.6 Informed consent

Written informed consent is required prior to removal of biological material from a living donor (NHA ss 56 and 62).

In the case of a deceased person, consent to removal and use of biological materials may be found in the Will of the person, in a written statement or in a witnessed oral statement (NHA s 62(1)(a)) or may be provided by 'the spouse, partner, major child, parent, guardian, major brother or major sister of that person in the specific order mentioned' (NHA s 62(2))

Because biological specimens may be collected for diagnostic, therapeutic or health research purposes, RECs should assess whether the nature of the planned usage is explained adequately so that the purpose for which consent is being requested is completely clear.

RECs must also consider the circumstances under which re-consent from donors would be sought, bearing in mind specific local or national needs.

Different forms of consent are implicated:

- i. Narrow (restrictive) consent: the donor permits use of the biological specimen for single use only; no storage of leftover specimen; and no sharing of data or specimen. This form necessitates new consent if further use is desirable.
- ii. Tiered consent: the donor provides consent for the primary study and chooses whether to permit storage for future use, sample and data sharing.
- iii. Broad consent: the donor permits use of the specimen for current research, for storage and possible future research purposes,³⁵ even though the precise nature of future research may be unclear at present. The nature of the further usage should be described as fully as possible and should stipulate that further prior ethics review of the new study is necessary. Permission may be sought to re-contact the person if intended future use is outside the scope of the current consent.³⁶

RECs should also bear in mind the vision of the H3Africa Initiative and its recommendation that consent should be

'broad enough to allow for future and secondary uses of data, in line with the opportunities to use such data in advancing knowledge to improve health. The consent processes need to be appropriate for the cultural contexts in which the research takes place and tailored accordingly'.³⁷

RECs should be aware that 'blanket' or unrestricted consent is not recommended for the reason that it becomes difficult to implement and sustain fundamental ethical principles especially that of respect for persons. In South Africa's multicultural society, different views prevail about the use of biological materials. RECs should bear in mind that careful deliberation is always necessary when considering future use of materials. One reason is that biological materials cannot be completely anonymised. The presence of hereditary elements implies that any sample can be re-identified, albeit only to a group rather than an individual. This has implications for the consent process insofar as participants should understand clearly what is being requested.

³⁸The Human Heredity and Health in Africa (H3Africa) Initiative <http://h3africa.org/about/vision>.

³⁹Previously known as disaster research.

3.3.7 Secondary use of materials or data

Secondary use means use in research of materials or data originally collected for other purposes. Biological materials collected for diagnostic or therapeutic purposes are usually stored for future use, e.g. pathology samples. Ordinarily informed consent for removal has not anticipated such use to include research purposes. Other researchers may have banked surplus samples in a tissue bank. The importance of stored biological material as a research resource cannot be overstated. The dilemma is whether unanticipated research usage necessitates fresh informed consent and, if so, what should be done when a donor is no longer available.

In the absence of broad consent to future use of material or data, including images, for research purposes, the following is recommended

- i. Use of existing or archived material collected for clinical or diagnostic purposes, including waste and surplus samples, requires expedited review. The nature of the previously obtained consent should be determined to ascertain whether subsequent usage was envisaged and whether it falls within the scope of the current proposal. If so, new consent is not required.
- ii. If the scope of the current proposal is different, then new consent may be required.
- iii. If samples are anonymous and the results of research would not place any individual, family or community at social, psychological, legal or economic risk of harm, then new consent is not required.
- iv. If the link to identifiers exists but is not provided to the research team and the results of research will not place any individual, family or community at social, psychological, legal or economic risk of harm, then new consent is not required.
- v. The person who holds the code or link should sign an explicit written agreement not to release the identifiers to the research team. This agreement should accompany the submission to the REC.
- vi. If the samples can be linked to identifiers, the REC must decide on a case-by-case basis whether expedited or full review is necessary.

3.3.8 Genetic research

Genetics refers to the study of genes (human DNA), heredity and variation as well as how they affect inheritance of traits and conditions between generations of people, especially regarding human health and disease. A gene is the unit of heredity.

From an ethical perspective, genetic research may hold out positive and negative implications. While its purpose may be to shed increasing light on causes of diseases and how to prevent or combat them, participants in such research may experience negative effects like stigmatisation, unfair discrimination and so on. Furthermore, genetic information is not specific to one individual but reveals much about that person's relatives and others with a shared ancestry.

When assessing the ethics of proposed genetic research, RECs must pay particular attention to multiple considerations, including the proposed social value of the research; consent, privacy, confidentiality as well as the potential effect of the research on families, communities and other groups. The proposal must include a plan that outlines how information revealed by the genetic research will be managed. This plan must be explained to potential participants. Plans to share findings with participants must include opportunities for participants to choose whether they wish to receive the information personally, and whether the information may be shared with biological relatives. Genetic counselling must be available if findings will be disclosed to participants.

3.3.9 Genomics research

Genomics research refers to the study of all of a person's genes (the genome) and how they interact with each other and with the person's environment. Genomics research permits investigation into diseases at a population level to take into account not only genetic, but also environmental factors.

The stated goal of the H3Africa initiative is to

enhance the capacity of African researchers to undertake cutting edge research to advance understanding of the genetic and environment determinants of common diseases and use this knowledge to improve the health of African populations.³⁸

Collection and storage of data and human biological materials should balance the need for adequate participant safeguards with optimal advancement of such research in line with the stated goal expressed above.

Special or additional protections for participants' interests may be necessary, e.g. in instances where identifiable samples or data are collected; where findings in genetic studies may pose social, psychological, legal or economic risks for a participant, his family or his community. Most data and biological material can be de-identified after collection or can be collected without identification of the donor.

3.3.10 Commercially available cell lines

Biosafety and ethical issues may arise from use of commercially available cell lines depending on the nature of the planned research work. For example, if cells are to be infected, biosafety and hence also ethical issues, arise for researchers rather than participants. If cells will undergo genetic modification, there may also be ethical implications.

Whether REC review is required, depends on whether institutions have properly functioning research review and biosafety infrastructures. Where these do not yet exist, RECs should be part of the process to ensure biosafety and ethical standards are maintained.

³⁸Sections 30 and 31 of the Constitution.

³⁹In terms of s 12(2)(c) of the Constitution and s 71 of the National Health Act.

⁴⁰Ratified by South Africa on 11 May 2011. For further information, see <http://www.cbd.int/abs/>.

⁴¹Informed by a series of international conventions such as the Berne Convention of 1967, Universal Declaration of Human Rights (1948), Declaration on the Rights of Indigenous Peoples (2007) (Art. 13), International Covenant on Economic, Social and Cultural Rights, WIPO-UNESCO World Forum on Protection of Folklore, and the Marrakesh agreement of 1994

Note that 'blanket approval' for use of commercially available cell lines is not permitted. At minimum, a researcher is expected to liaise with the REC about the biosafety and ethical implications of the planned work. RECs should draw up a SOP and query template to assist establishing the implications.

3.4 Considerations specific to research methods or contexts

Particular types of research require careful scrutiny in case additional precautions or monitoring procedures are required.

Types of research discussed include:

- Major incidents³⁹ and research
- Intensive care research
- Terminal care research
- Innovative therapy or interventions
- Indigenous medicines research
- Deception, concealment or covert data collection

Note this list is not exhaustive, merely illustrative.

3.4.1 Major incidents and research

Major incidents include any sudden event that occurs where local resources are constrained, so that responding urgently and appropriately is difficult. Major incidents include acute disasters – natural or man-made – such as floods, tornados, earthquakes, outbreaks of deadly disease, or political violence and armed conflict with resultant injuries to humans. They may also take the form of an unusual and sudden demand on local resources or other emergency with consequent ethical implications for patient care. Research in these contexts is important for advancing emergency health care interventions and treatments, and for refining resource allocation policies. The potential benefits of major incident research include improved triage methods and procedures, effective treatment for life-threatening conditions and improving therapies for survival and quality of life.

Although patients in a major incident context face extreme vulnerability, RECs should be cautious about being overly restrictive about the type of research that may be conducted. The development of new drugs and procedures to treat emergency patients safely depends on being able to conduct research, including carefully designed randomised controlled trials.

In order to carry out research in such contexts, planning of the research and ethics clearance processes usually must occur very rapidly. From the REC perspective, proposals for major incident research usually demand expedited processing, which means that the time for deliberation is curtailed.

When research is not actually dependent on a major incident context, the proposal should be approached cautiously. RECs should consider carefully whether sufficient justification is presented for expedited processing. In the same way that research involving minors should be done only when adult participants cannot provide the necessary data, so major incident research should take place about matters that are unlikely to or do not occur in 'ordinary' contexts.

Informed consent usually has to be obtained rapidly and at a time when vulnerability of patients and families is likely to be extreme. Patients may be incapacitated (i.e. unconscious or on a ventilator), which points to the likelihood of difficulties with the usual approach to informed consent. Consequently, RECs may consider alternative approaches such as proxy consent or delaying consent in particular circumstances. (See 3.2.4.3, 3.2.4.4 & 3.2.6.)

3.4.2 Intensive care research

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

Whenever possible, informed consent for planned intensive care research should be obtained from potential participants before admission to that care. See 3.2.4.3, 3.2.4.4 & 3.2.6.

Research involving infants receiving neonatal intensive care should be conducted in strict accordance with the principles set out for minors (see 3.2.1 above). These principles do not permit research that is contrary to the child's best interest. The small size and extreme vulnerability of some infants are unique features of this class of participants. This means that all but minimally intrusive interventions are likely to be contrary to the child's best interest. Collection of even small blood samples for research in addition to those required for diagnostic purposes, or additional handling of a low birth-weight infant to make research-related observations, requires very careful justification and skill, especially in assessing the risk-benefit ratio. Input from neonatal intensive care experts should be sought.

3.4.3 Terminal care research

Terminal care research is distinguished by the short remaining life expectancy of participants and their potential vulnerability to unrealistic expectations of benefits from participation in research. In principle, because of their extreme vulnerability, terminally ill patients should not participate in research that is more than minimally invasive without adequate justification.

The prospect of any direct benefit from research participation must not be overstated or used to justify a risk of harm higher than that involved in current treatment. Research participation must not be used to prevent or devalue the needs and wishes of participants rather to spend time as they choose, particularly with family members.

3.4.4 Traditional medicines research

In line with the constitutional guarantees for cultural and language rights,⁴⁰ indigenous cultures and traditional values of all communities must be respected. However, since fundamental rights do not trump each other without careful justification, participants in research involving traditional medical systems and beliefs must be accorded the same respect and protection as any other human research participant.⁴¹ The context of the research activity, interaction or intervention is important for determining whether, how and when to incorporate traditional values and their cultural expression in research.

In terms of the Traditional Health Practitioners Act 22 of 2007,

‘Traditional medicine’ means an object or substance used in traditional health practice for-

- (a) the diagnosis, treatment or prevention of a physical or mental illness; or
 - (b) any curative or therapeutic purpose, including the maintenance or restoration of physical or mental health or well-being in human beings,
- but does not include a dependence-producing or dangerous substance or drug.

‘Traditional health practice’ means the performance of a function, activity, process or service based on a traditional philosophy that includes the utilisation of traditional medicine or traditional practice and which has as its object-

- (a) the maintenance or restoration of physical or mental health or function; or
 - (b) the diagnosis, treatment or prevention of a physical or mental illness;
- or
- (c) the rehabilitation of a person to enable that person to resume normal functioning within the family or community;
- or
- (d) the physical or mental preparation of an individual for puberty, adulthood, pregnancy, childbirth and death,

but excludes the professional activities of a person practising any of the professions contemplated in the Pharmacy Act 53 of 1974, the Health Professions Act 56 of 1974, the Nursing Act 50 of 1974, the Allied Health Professions Act 63 of 1982, or the Dental Technicians Act 19 of 1979, and any other activity not based on traditional philosophy.

‘Traditional philosophy’ means indigenous African techniques, principles, theories, ideologies, beliefs, opinions and customs and uses of traditional medicines communicated from ancestors to descendants or from generations to generations, with or without written documentation, whether supported by science or not, and which are generally used in traditional health practice.

RECs should pay attention to indications that intellectual property may be intended to be acquired by non-South Africans and should advise that appropriate advice be sought. Intellectual property in indigenous flora, fauna and medicines is a particularly sensitive matter currently and not easily regulated. Protection of intellectual property relating to South African medicinal plants is a cross-cutting issue, responsibility for which is spread amongst several government departments, including the Department of Health; Trade and Industry; Science & Technology; Environmental Affairs; Tourism; Agriculture, Forestry & Fisheries; and Rural Development & Land Affairs. International and domestic legislation, policies and regulatory guidelines applicable in these departments must be taken in account when conducting research on traditional medicinal plants and genetic material, to ensure compliance.

Current legislation that governs intellectual property relating to traditional knowledge and genetic material includes

- The Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits,⁴² which advances Articles 15 & 8(j) of the Convention on Biological Diversity
- The National Environmental Management: Biodiversity Act 10 of 2004 and its Regulations
- The Patents Act 57 of 1978
- The Department of Trade & Industry’s policies on Intellectual Property including the Intellectual Property Amendment Bill 2008.⁴³

Prior ethics review of the proposed research is required to ensure that norms and standards for health research in South Africa are being upheld. Toxicology tests must be performed on substances to be used on or ingested by participants; and equivalent rigour must apply to such research. Researchers should furnish proof of safety of the substances to the REC. The practice of requiring a randomised controlled trial may not be appropriate in all circumstances for indigenous treatments and interventions. However, RECs must consider methodology carefully and make decisions on a case-by-case basis.

3.4.5 Research involving deception or withholding information

Sometimes, to ensure validity of research, researchers withhold certain information in the consent process. This may take the form of withholding information about the purpose of specific procedures. In most such cases, the prospective participants are asked to consent to remain uninformed as to the purpose of some procedures until the research is completed. After conclusion of the study, participants are given the omitted information. In other cases, participants are not told that some information is being withheld until the research has been completed. The latter approach must receive the explicit approval of the REC.

Active deception of participants is considerably more controversial than simply withholding certain information. Deception is not permitted where the deception itself would disguise the possibility of a participant being exposed to more than

⁴⁴ The National Health Act 61 of 2003 regulates tissue banks for transplantation purposes in Regulation 182 GG 35099 2 March 2012. The focus primarily appears to be on compliance with the Declaration of Istanbul on Organ Trafficking and Transplant Tourism of 2009 and WHO guiding principles. Stem cell banks are regulated by Regulation 183 GG 35099 2 March 2012.

⁴⁵ See <http://health.uct.ac.za/research/humanethics/forms/> FHS020 as an example.

minimal risk. RECs should be satisfied that deception is indispensable; that no other research method would suffice; that significant advances could result from the research; and that nothing has been withheld that, if divulged, would cause a reasonable person to decline to participate. The REC should consider the consequences for the participant of being deceived, and whether and how deceived participants should be informed of the deception upon completion of the research. Participants who disapprove of having been deceived should be offered the opportunity to request that their information be excluded from the research.

3.5 Special topics

3.5.1 Novel, innovative and unproven therapies

i. The context

Innovative treatment and research are both experimental in nature. However, the purpose of each is different. The aim of research is to accumulate a body of generalizable knowledge using a standardized protocol for the benefit of future patients. By definition, the therapeutic best interest of the individual patient is not the focus in a research study. Rather, the benchmark is that participation in research should not be contrary to the best interest of an individual patient.

The aim of novel therapy is to address the best interest of a specific individual patient or a unique circumstance on an ad hoc basis. Information gathered during delivery of novel therapy may be useful for future research projects, but is not gathered with research purposes in mind. Experimental therapy necessarily focuses on the best interest of the individual patient.

ii. Definition

'Experimental treatment' means a therapy, intervention or procedure (not standard of care) delivered to a specific individual patient for therapeutic purposes in an attempt to cure or alleviate symptoms.

'Novel, innovative and unproven therapies' means

- a newly introduced or locally untested treatment or procedure; or
- a modification to an existing treatment, intervention or procedure where no systematic research profile or side effect profile about the modification exists; or
- an experimental treatment, intervention or procedure; or
- a treatment, intervention or procedure not included in the usual package of care

which is sought to be used on an experimental or compassionate basis in circumstances where it is thought, on reasonable grounds, that a theoretical justification exists for such use, despite the absence of a systematic research profile or side effect profile.

'Research' means a systematic investigation or study designed to produce generalizable knowledge on the basis of conventional scientific and ethical standards appropriate for the context.

iii. The treatment context

The wish to use a novel, innovative or unproven treatment usually arises in a context suffused by the rule of rescue. In other words, a health care worker may face a situation where all standard options have been exhausted, the desire to provide further rescue interventions exists and the patient (or the patient's family) is willing to risk the unknown. While the health care worker takes primary responsibility to act in the best interest of the patient, in these circumstances, the health care worker should not make unilateral decisions. Responsibility and accountability should be shared in accordance with these Guidelines.

Ethical principles must inform the process of deciding whether a novel, innovative or unproven therapy is appropriate in the circumstances. And, importantly, the decision-making should be predicated on a deliberative process undertaken by well-informed people. Although innovation is often the driving force in the advancement of new knowledge in health care, when time and emotional pressures prevail, especially at the individual level, deliberate objective thinking may be undermined, which can lead to decision-making that is not appropriately responsible. In light of s 27 of the Constitution, which guarantees the right of access to health care services to all, elevation of one individual's claim to more than standard of care necessarily has implication for accountability and responsible decision-making in health facilities.

iv. The legal and ethical context

Use of locally novel, innovative or unproven therapy involves legal, ethical and practical considerations.

The National Health Act 61 of 2003 (NHA) makes provision for 'health services for experimental or research purposes' (s 11) and requires that, prior to treatment, the patient must be informed of the experimental or innovative status of the intended treatment.

The Act further stipulates that institutional authorities responsible for oversight of treatment must give written permission for the treatment. This means that the decision whether the proposed therapy is experimental treatment or research must precede the decision whether to permit its use for the patient. Where the intended novel therapy is classed as research, the REC must review and approve the research proposal before therapy begins.

The Declaration of Helsinki (2013) indicates that 'unproven interventions in clinical practice' (par 37) may be used, subject to obtaining expert advice, and appropriate informed consent from the patient. All information about the intervention must be recorded and made publicly available as appropriate. Further, the intervention should subsequently be researched formally so that safety and efficacy can be evaluated.

⁴⁶See H3Africa's data sharing and access policy (August 2014) <http://h3africa.org/consortium/documents>

⁴⁷Detailed guidance for conducting clinical trials is provided elsewhere – see DoH SAGCP 2006 or its successor. However, because insurance cover is relevant also to other interventional clinical research, the topic is addressed here too.

⁴⁸(12285/08) [2013] WCHC 7 May 2013; and on appeal (A11/2014) 22 October 2014. ⁴⁹South African Department of Health (2006) 'Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa' 2nd ed (or its successor)

v. Clinical ethics versus research ethics

Clinical and research ethics considerations must be distinguished: each form of ethical scrutiny performs an important but different role in academic medicine. Clinical ethics considerations include the likely efficacy and risk of harm of the proposed therapy, intervention or procedure to the patient; the clinical information that supports its use; whether a research profile regarding its use exists; the availability and cost implications of the therapy, intervention or procedure; and whether other patients might also benefit from the therapy, intervention or procedure. On the other hand, research ethics considerations require a research study to be planned and conducted in accordance with the highest scientific and ethical standards. This means that prior review of the proposal is conducted by peers and by persons with expertise in research ethics.

In the context of considering motivations for novel, innovative or unproven therapy, the roles of the two committees complement each other directly. In other words, whether use of a therapy, intervention or procedure that is not standard of care is clinically ethical may require consideration also of whether a research study is called for in order to answer the clinically ethical question. If so, then research ethics considerations are triggered.

Current biomedical research ethics guidelines indicate that a single case report (≤ 3 patients) is usually exempt from research ethics approval. This is because a single case report does not generate sufficient generalisable knowledge. However, journal editors may require evidence of patients' written consent as a condition of publication. In social sciences, however, a case study ($n=1$) is a fully valid research activity. For example, documenting an exception to a rule, theory and so on is a particularly powerful research finding. Exemption from ethics scrutiny is thus unlikely. A biomedical case series (>3 cases) usually triggers the need for research ethics review, since generalizable knowledge can be generated.

3.5.2 Databases, registries and repositories

Databases, registries (data banks) and repositories (tissue banks) may be created for research, diagnostic or clinical purposes.⁴⁴ They constitute a valuable research resource and allow researchers to pursue questions that were not anticipated at the time of collection of either data or material.

3.5.2.1 Terminology

From a regulatory and ethics point of view, the three forms of data or specimen storage are treated similarly. Consequently, in these Guidelines, references to repositories apply also to databases, registries or tissue banks.

'Database' means a collection of information including images (data) arranged to facilitate swift search and retrieval. It may be electronic or paper-based.

'Registry' means a collection of information (data) from multiple sources, maintained over time with controlled access through a gatekeeper organizer.

'Repository' means a collection, storage and distribution system for human biological materials for research purposes including blood, urine, faeces, bone marrow, cell aspirates, diagnostic specimens, pathology specimens and so on. Usually demographic and medical information about the donors is included in the repository as are codes that link the material to the donors.

'Virtual Repository' means a digitised system that manages distributed bar-coded electronic versions of material, data or images through shared data systems.

3.5.2.2 REC oversight of repositories

Institutions and researchers that maintain repositories (biobanks or tissue banks) must have appropriate facilities, equipment, policies and procedures to store human biological materials and data safely and in compliance with accepted standards. Appropriate safeguards, including physical, administrative and technical, must exist to protect against unauthorised handling. Institutional repositories created, maintained and used for present or future research purposes should preferably have prior institutional REC approval. New repositories must have prior REC approval. An existing research database or non-research database may be converted into a repository. RECs should establish procedures to guide this process and to guide use of the repository.⁴⁵

3.5.2.3 Informed consent

The consent documentation for donors should explain clearly

- the purpose and nature of a repository, including the specifics for which consent is being sought, how a repository works and the types of research it supports
- the conditions and requirements under which data or material will be shared with other researchers
- how privacy and confidentiality interests will be protected
- the nature and extent of specific risks of harm related to use and storage of material or data, especially if identifiers are retained
- in the case of genetic or genomic research, information should be provided about the implications of genetic testing (e.g. paternity determinations, insurance risks, reproduction decisions) and associated confidentiality risks
- potential benefits (if any)
- where applicable, that material may be

⁴⁴Also known as Research Ethics Policy in some institutions. Note that usually an Institutional Research Ethics Policy is the institutional document that authorizes the creation of an REC & SOPs, rather than the SOPs themselves.

⁴⁵Diversity of REC membership refers mostly to ethnicity, culture and gender of members.

- used for future research not yet identified
- shared with or transferred to other institutions
- the freedom to withdraw consent at any time and to request withdrawal of data and that unused identifiable material be destroyed. If this is not possible, the information should clearly indicate this
- information about the length of storage time
- when the current consent to use material or data will expire
- information about possible secondary use of stored material
- information about possible creation of an immortalised cell line based on the specimen
- the REC may approve a waiver of consent for secondary use of material or data where no more than minimal risk of harm is likely; and the donor's rights and welfare interests are unlikely to be adversely affected; and the research cannot be conducted if the waiver were not approved

Where data or materials are shared with researchers in other institutions, the recipient institution should agree to comply with the requirements of the donor institution. Furthermore, use of the data or material should comply also with any additional requirements of the recipient institution. Inter-institutional sharing agreements should be confirmed in writing.⁴⁶

3.5.3 Insurance against research-related bodily injury⁴⁷

Research participants should not have to bear the financial cost of rectifying harms that occur when something goes wrong during the study. Consequently, it has become standard practice in most countries to encourage or even to require researchers, institutions or sponsors to assure participants that medical costs necessitated as a result of a research-related bodily injury will be paid by an insurer.

Note that insurance is not a requirement for all research but, when it is foreseeable that research-related bodily injury might occur, researchers and RECs must give careful consideration to whether insurance cover is available. For example, NIH-sponsored research does not include any insurance cover, which may raise ethical concerns at an institutional level. This is because, were a research-related bodily injury to occur, the necessary consequent medical treatment is likely to have resource allocation implications for the health facility. It is possible also that researcher-initiated studies could lead to research-related bodily injuries as a result of interventions or investigational drugs. In the absence of pharmaceutical company sponsorship, no commercially sponsored insurance cover is available.

RECs must pay careful attention to the measures proposed for dealing with research-related injury in this context. In order to address this potential problem, some academic institutions provide insurance cover themselves to address research-related bodily injury that eventuates in a non-commercially sponsored interventional study.

Where insurance cover is offered, commonly the documentation explains that the insurance policy will pay for medical expenses in the event of a research-related bodily injury. However, most protocols do not explain clearly in simple terms the exact nature and scope of the insurance cover offered. This section explains the relationship between research-related injuries and insurance cover.

3.5.3.1 Scope of insurance cover

The lay understanding seems to be that insurance against research-related bodily injury covers reasonable medical expenses and also pain and suffering, loss of income, and related claims. This view is not correct. The recent case of *Venter v Roche Products (Pty) Ltd*⁴⁸ highlighted the need for clarification so that clinicians, research ethics committee members, researchers and participants all understand the scope of insurance cover when the protocol and consent documents are developed and approved.

The Department of Health's 'Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa' (known as SA GCP 4.11)⁴⁹ requires a clinical trial sponsor to take out insurance cover. If a trial-related serious bodily injury of an enduring nature occurs as a result of participation in the trial, then the sponsor's insurer pays the medical costs of necessary treatment to restore the participant to his previous position, if possible.

This offer of payment has a moral rather than a legal basis. SA GCP follows the lead of the Association of the British Pharmaceutical Industry (ABPI), which recommends that sponsors adopt the morally right position of paying for treatment in the event of trial-related injury. This recommendation is followed in many countries. In South Africa, it is mandatory to have this insurance cover for clinical trials and RECs should assess whether it is in place and valid.

Payment for medical expenses is made without acknowledgment of any liability and is thus to be understood as an *ex gratia* payment.

'The MCC, ethics committees and other relevant regulatory authorities require that all participants in clinical trials are covered by comprehensive insurance for injury and damage. Notwithstanding the absence of legal commitment, the sponsor should pay compensation to patient-volunteers suffering bodily injury, including death, in accordance with these Guidelines.'

3.5.3.2 What a participant agrees to

By choosing to participate in research, a participant agrees to the violation of bodily integrity necessitated by receiving investigative medication or undergoing procedures and to the possible risk of harm outlined in the consent documentation. This means that, in law, when one accepts the risk of harm (by consenting to the invasion of bodily integrity), then there is no claim for damages (compensation) if that harm materialises. This is known as voluntary acceptance of risk of harm.

Thus, in the absence of an offer to pay for the necessary treatment and an acceptance of the offer by a participant,

no claim for payment of treatment costs exists in law. This is why the SA GCP requires a clinical trial sponsor to take out insurance cover: it is morally right that the sponsor (responsible for causing the bodily injury) should assist the participant by paying for the reasonable medical expenses needed to treat the bodily injury that materialises through participation in the research. The possible risk of loss of income or other losses was also foreseeable and agreed to, but no moral argument is made for this voluntary assumption of risk to be subsidised by a sponsor. The same reasoning applies to researcher-initiated studies and an institutional insurance policy (see 3.5.3).

In *Venter v Roche Products (Pty) Ltd*, Mr Venter argued that the sponsor owed more than necessary medical expenses to him. The High Court disagreed, pointing out that what was offered and accepted by the participant was as described in the consent documentation. Venter accepted the risk of harm as described in the consent documentation and during the consent discussions, and accepted the offer of payment of treatment costs, as described, in the event that harm occurred. More recently, in an appeal, the Western Cape High Court has confirmed this view by dismissing Venter's appeal. These cases show that RECs must pay careful attention to the statements in consent documentation that explain the nature and scope of insurance cover offered.

3.5.3.3 'You do not give up your legal rights'

The state of affairs described above does not, however, preclude separate litigation, based in negligence, to claim compensation in a South African court for e.g. loss of income. This is what the frequently used statement 'you do not give up any of your legal rights' means. If a claim is instituted against either a sponsor company or a researcher, this is an entirely separate matter and has nothing to do with the insurer. The cost of medical treatment of the research-related injury previously paid by the insurer would not form part of the subsequent claim.

The argument that pain and suffering, loss of income and other possible claims should be paid for by a sponsor is not sound in South African law. Similarly, professional malpractice (negligence) insurance of health care practitioners is separate from the sponsor's offer of payment for necessary medical costs to treat a research-related bodily injury. A sponsor's insurer is unlikely to pay if a health care practitioner has been professionally negligent and caused harm.

(See Appendix 3 for insurance cover for research-related injury Template.)



Chapter 4

RESEARCH ETHICS COMMITTEES

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Note REC includes AREC unless otherwise indicated

4.1 Introduction

A registered REC must review proposals to do health research. If all standards are met, then the REC may approve the proposal, with or without additional conditions (NHA s 71(1)(a) read with s 73(2)).

Independent ethics review by a registered REC is a basic requirement to engender confidence in the ethical character of research. 'Independent' means that the members of the REC are encouraged to be objective, informed and to act without fear or favour in their scientific and ethical reviews. Concerns should be raised and deliberated on by the committee; and decisions to impose additional conditions to protect human participants, animals or researchers should be taken where necessary.

This chapter describes the legislative framework; the role of RECs; REC membership composition; operational procedures; and standard operating procedures for RECs. Note that detailed information about ARECs is to be found in SANS 10386:2008 South African National Standard The care and use of animals for scientific purposes or its successor and in MRC Guidelines on Ethics for Medical Research Book 3: Use of animals in research and training (2004).

4.2 Legislative Framework

Section 73 of the National Health Act (NHA) requires every institution, health agency and health establishment at which health research is conducted, to establish or have access to an REC, which is registered with the National Health Research Ethics Council (NHREC).

Researchers without affiliation to an institution or organisation with an REC should approach a registered REC to request it to review their health research proposals. If the REC is willing to review external applications, a fee for service may be levied.

4.3 Role of Research Ethics Committees

The primary role of the REC is to protect the interests (rights and welfare) of the research participants who volunteer to take part in scientifically sound research. Consequently, the primary responsibility of each REC member is to decide independently whether the proposed research protects the interests of participants adequately and keeps to exemplary standards in research activities. In the case of research with animals, the primary role of the AREC is to protect the welfare interests of animals used or to be used in research.

The role and function of an Animal Research Ethics Committee (AREC) are set out in SANS 10386:2008 South African National Standard The care and use of animals for scientific purposes or its successor and in MRC Guidelines on Ethics for Medical Research Book 3: Use of animals in research and training (2004).

4.3.1 Terms of Reference and Standard Operating Procedures

Each REC should have Terms of Reference (ToR)⁵⁰ and Standard Operating Procedures (SOPs).

The Terms of Reference (ToR) describe the formal character of the committee and usually combine institutional requirements with the statutory requirements. The ToR should include the scope of the REC's responsibilities, its relationship to non-affiliated researchers, its accountability responsibilities, the mechanisms for reporting and remuneration, if any, for members.

Standard Operating Procedures (SOPs) set out in systematic detail how to review proposals, the various procedures and considerations that should be taken into account and adhered to, as well as provide information or references to

additional materials to assist with the process of review and application for ethics approval. The ToR and SOPs should be accessible to the institutional members, researchers and other interested persons, usually via internet or intranet sites. (See also 4.5.1.)

4.3.2 Code of Conduct

The institution should have a Code of Conduct for REC members, which details conduct and integrity expectations of REC members, including regular and punctual attendance at meetings, diligent performance of responsibilities, maintenance of confidentiality, and consideration of potential conflicts of interest.

4.4 Membership

RECs should be independent, multi-disciplinary, multi-sectoral and pluralistic.⁵¹In general terms, membership should include

- as many disciplines, sectors and professions as possible, appropriate to the remit of the particular REC
- members drawn not only from the senior ranks
- ethnically and culturally diverse members and an appropriate mix of males and females
- lay persons, preferably from communities in which research is conducted
- researchers who do not do human participant research and
- members from other disciplines.

Collectively, the committee should include sufficient members with the necessary qualifications and experience, including research ethics training, to be able to review and evaluate the science, the health aspects, the ethics of the proposed research, as well as to assess the anticipated layperson's perspective. REC members and researchers are expected to familiarise themselves with the institutional documentation as well as national and international research ethics guidelines and should have documented proof of such familiarity.

Training of all REC members is critical, especially for RECs that review high risk research. This means that training and refresher courses should be available; that members should be expected, **at least once during a term of appointment, to produce evidence of recent training**; and that membership should be managed to ensure an optimal mix of experienced and new members to promote good succession planning. The term of office of members may vary according to institutional requirements. Consideration should be given to succession planning and accumulation of institutional memory for RECs. A reasonable term of office is between two and four years, renewable twice, after which the person should stand down for at least one term. This ensures that both expertise and responsibility are fairly distributed and encouraged in a range of members, and that institutional memory is accumulated.

4.4.1 Formal membership requirements for RECs and ARECs

4.4.1.1 General

Subject to institutional requirements, a Chairperson could be appointed or elected at the first meeting of the REC, and thereafter confirmed annually. Alternately, the Chairperson, suitably qualified, could be appointed by the institutional leadership for a period of two to four years, renewable if so specified. The Chairperson should be assisted by at least one Deputy Chairperson, depending on the size of the committee. The Deputy Chairperson should be elected by the members and be expected to assist the Chairperson with responsibilities and inter-meeting matters, as well as to step into the role of Chairperson when necessary.

4.4.1.2 Research Ethics Committees

All REC members should have documented proof of research ethics training, refreshed at least once within the period of appointment.

REC membership should consist of

- i. at least nine members with a quorum being a simple majority
- ii. where the number of members is more than 15, the quorum may be 33%
- iii. at least one layperson
- iv. at least one member with knowledge of, and current experience in, the professional care, counselling or health-related treatment of people. Such a member might be e.g. a medical practitioner, psychologist, social worker or nurse
- v. at least one member with professional training and experience in qualitative research methodologies
- vi. members with professional training and experience in quantitative research methodologies
- vii. a member with expertise in bio-statistics
- viii. a member with expertise in research ethics
- ix. at least one member who is legally qualified

4.4.1.3 Animal Research Ethics Committees

Various categories of members are dictated by international and national standards including the SABS SANS 10386 (2008 or later version).

Four categories of member are required:

- A: Veterinarians
- B: Scientists with substantial and recent experience in the use of experimental animals
- C: Animal welfare organization representatives
- D: Representatives not involved in animal experimentation

The size of the committee may depend on the number of animal users in the institution.

Quorum rules should be adjusted to reflect the size of the committee but should always include at least one member from each category of member.

4.4.2 Expectations of institutions regarding RECs and ARECs

- i. Institutions should ensure that adequate administrative support and resources are provided so that the work of the REC can be done in compliance with these minimum standards.
- ii. Procedures and criteria for recruitment and appointment of REC members should be in place, transparent and accessible.
- iii. REC and AREC members should be given a formal appointment letter that sets out, at a minimum, the term of office; where to find the necessary information for new members; and the assurance that members are indemnified from personal liability against claims that may arise in the course of ordinary business of the REC or AREC.
- iv. Opportunities for training and refresher courses in research ethics (human and animal) and Good Clinical Practice (GCP) should be made available or accessible for committee members and researchers. Committee members should receive research ethics training and orientation on appointment and should refresh at least once every three years. REC members who review clinical trial proposals should have GCP training, evidenced by a certificate issued not more than 2 years previously.
- v. Institutions should indemnify committee members from personal liability and should ensure that adequate public liability insurance exists. The institution should take legal responsibility for the decisions and advice of the REC and AREC, provided that members act in good faith.

4.5 Standard Operating Procedures

- i. RECs and ARECs should have written standard operating procedures (SOPs) to ensure
 - standardised best practices for health research
 - compliance with national and international ethical and regulatory requirements
 - consistent processes about ethical issues in health research
 - declarations regarding confidentiality and conflict of interest for each meeting.
- ii. Ethical issues in research often require case-by-case deliberation. The ethics review process should not be mechanical. Although consistency of review outcomes for similar studies may be desirable, it is not always possible or appropriate in light of the details of an application.
- iii. REC members and researchers should be encouraged to
 - be mindful of the basic ethical principles that should inform planning, designing and conducting health research
 - be open-minded and not allow personal biases to cloud their application of these guidelines
 - accept that consensus about how ethical principles should be balanced is difficult to achieve and that divergence enriches deliberations
 - be mindful of the influence that the context (social, cultural and economic) has on how to prioritise principles
 - be deliberate, reflective and thoughtful in discussions about how to balance ethical considerations.
- iv. SOPs should be regarded as living documents, to be reviewed, revised and updated at regular intervals.
- v. REC members and researchers should ensure that they use the most recent versions of documents.

4.5.1 Written Standard Operating Procedures.

SOPs should cover topics including but not limited to

- ethical and regulatory requirements for research with humans and research using animals
- definitions as appropriate
- institutional lines of authority and responsibility
- REC activities and processes, including frequency of meetings, preparation of agenda and minutes (minutes should be detailed and include dissenting views), registers for meetings, expectations and time-lines for reviewers
- guidance and specification of REC procedures required for expedited and full REC review; if the REC reviews US federally funded research proposals, the procedures must comply with the US Common Rule (45 CFR 46)
- quorum requirements
- decisional analysis guidance
- conflict of interest and of confidentiality regarding researchers
- the protocol review process
- continuing review and re-certification procedures

⁵²Available at <http://www.gov.za/documents/download.php?f=70285>

⁵³Available at <http://www.health-e.org.za/wp-content/uploads/2014/08/SA-DoH-Strategic-Plan-2014-to-2019.pdf>

⁵⁴Available at <http://www.doh.gov.za>; South African National Standard 'The care and use of animals for scientific purposes SANS 10386:2008 (or later version) www.sabs.co.za.

⁵⁵Like the Declaration of Helsinki (2013) <http://www.wma.net>; see Appendix 2 for further examples.

⁵⁶See <http://www.nhrec.org.za> for documentation.

- protocol amendment procedures
- adverse events and unanticipated problems
- protocol deviations and protocol violations
- non-compliance consequences
- suspension and termination
- compliance checks and audits
- informed consent
- privacy and confidentiality regarding participants and their health care information
- research involving minors
- research involving vulnerable persons
- data collection and storage
- biological materials collection and storage
- databases, registries and repositories
- complaints procedures
- whistleblower protection

4.5.1.1 Applications for ethics review

- Each research proposal should include a description of the ethical considerations implicated in the research.
- The protocol should reflect adequate consideration of participants' welfare, rights, beliefs, perceptions, customs and cultural heritage.
- All documents and other material to be used to inform potential participants should be included in the ethics review application, such as information sheets, consent forms, questionnaires, advertisements, videos, dramatisations and letters.
- Researchers should ensure that plain language adapted to anticipated literacy levels is used in the participant documentation. An indication of the readability level should be included (see also 3.1.9).
- Where research is to be conducted in community settings, evidence of consultation and plans for ongoing involvement should be included.
- Animal research protocols should explain comprehensively how the welfare interests of the animals will be attended to.
- Animal research protocols should include monitoring schedules listing the responsible persons and their contact numbers, the schedule and indicators for analgesia delivery and so forth.
- Protocols for clinical trials and studies involving a moderate increase over minimal risk should include monitoring schedules, the responsible persons and their contact numbers.
- Researchers should disclose conflicts of interest, financial interests and information that may result in perceptions of conflict of interest.

4.5.1.2 Decision making and feedback to applicants

- After the deliberative review process, the REC should approve, require amendment to, or reject a research proposal.
- In considering a research protocol, the REC may seek assistance from experts, but such experts may have no conflicts of interest in relation to the application.
- Decisions of the REC should be recorded in writing.
- A decision to approve should include the conditions, e.g. the duration of the approval, the reporting requirements, etc.
- A decision to require amendment or to reject, should record reasons for the decision.
- Outright rejection should be avoided if a researcher can be advised to improve the proposal.
- The educative role of RECs should be fostered, which means that, where possible, researchers should be encouraged to engage with the concerns and seek to improve their protocols.
- Feedback should be instructive to assist the researchers to improve the application if appropriate.
- Feedback should be sufficiently detailed so that the concerns of the REC are understandable to the researchers.
- RECs should require researchers to report immediately anything that might warrant reconsideration of ethical approval of the protocol, including but not limited to
 - Serious or unexpected adverse effects on participants
 - Proposed changes in the protocol
 - Unforeseen events that might affect continued ethical acceptability of the project.
- RECs should require researchers to report immediately if a project is terminated or suspended before the anticipated date of completion.

4.5.1.3 Review and consultation

- RECs may consult with experts outside of the committee, provided they are not conflicted in relation to the study under consideration and subject to confidentiality assurances.
- RECs may consult with other RECs if appropriate, bearing in mind confidentiality constraints.

4.5.1.4 Reciprocal recognition of review decisions

- RECs may, at their own discretion, recognize prior review and approval of a research proposal by another registered REC to avoid duplication of effort.
- Reciprocal recognition means that two or more registered RECs decide to recognize each other's prior review.
- RECs that recognize prior review in this manner must determine the nature of the documents to be filed locally, which must, at minimum, include a copy of the approval letter from the other REC.

- iii. RECs that recognize prior review in this manner may revise their decision to do so if justifying circumstances arise. The reasoning supporting a reversal of recognition should be documented.

4.5.1.5 Expedited review

- i. RECs may establish procedures for expedited review. The nature of research that may be expedited should be described in the procedures.
- ii. Expedited review should apply, in principle, only to research that poses no more than minimal risk of harm.

4.5.1.6 Record keeping

- i. RECs should keep written records of all research protocols received for review, including information sheets, consent forms and relevant correspondence, in the form in which they were approved. Note that electronic records are acceptable, provided that signatures, especially on the finally approved documentation, are properly documented and included in the record.
- ii. REC records must provide a reliable and authoritative record of the business of the REC that will stand up to scrutiny in the event of queries, conflict and audit.
- iii. The record should include at least the following:
 - Name of principal investigator
 - Protocol identification number
 - Title of the project
 - Date of approval or rejection
 - Conditions of approval, if applicable
 - Whether approval was expedited
 - Copy of the signed final proposal or protocol approved
 - Whether and how consultation occurred
 - Records of adverse events
 - Records of amendments
 - Reports of adverse and serious adverse events and action taken
 - Other relevant information such as complaints from participants
- iv. RECs should correspond primarily with the principal investigator or a delegated signatory, and not with the sponsor unless dictated by particular circumstances.

4.5.1.7 Conflict of interest

- i. REC members should disclose information that may lead to perceptions of conflict of interest.
- ii. REC members should not review or make decisions about research proposals in which they are involved personally or financially. When such a proposal is to be discussed, the member concerned should declare the potential conflict and offer to recuse herself from the meeting for that time. Should the member be permitted to remain for the discussion at the discretion of the Chairperson, the member may not participate in the final decision-making on the application in question.

4.5.1.8 Advocacy

The REC should be alert to whether an advocate for special interest groups of participants proposed for particular research would add value to the review process for informed responsible decision making in the context.

4.5.1.9 Translators

- i. Where research participants do not adequately comprehend or speak the language used in the protocol, translation of information and consent documentation is important. Similarly, it is often desirable to have people who are fluent in the language of the intended participants to assist with the consent process.
- ii. The REC should be alert to the potential for poor consent processes in the absence of appropriately translated materials and the availability of translators.
- iii. If a translator will be used in the consent process and be present for the discussions, the information materials should state that privacy will be compromised to that extent.
- iv. A translator should not influence potential participants unduly during the interpretation process.

4.5.1.10 Monitoring

- i. RECs have the right to monitor the research it approves (Declaration of Helsinki 2013 par 23). Researchers should provide appropriate information to the REC to facilitate monitoring, including alerts and investigator brochures. The frequency and type of monitoring should reflect the degree and extent of risk of harm to participants or animals.
- ii. RECs may recommend and adopt any additional appropriate mechanism for monitoring, including random inspection of research sites, welfare monitoring sheets, data and signed consent forms, and records of interviews. Information and consent materials should indicate that such monitoring may take place.
- iii. RECs should request regular, at least annual, reports from principal investigators on matters including but not limited to
 - progress to date, or outcome in the case of completed research
 - current enrolment status (numbers, active or closed)

⁵⁸In some provinces, the legislation calls them Provincial Research and Ethics Committees, which may blur the different roles.

- whether participant follow-up is still active or completed
 - information concerning maintenance and security of records
 - evidence of compliance with the approved protocol
 - evidence of compliance with any conditions of approval
 - negative reports from monitors or GCP inspectors
 - list all adverse events in the past 12 months
 - list all amendments made in the past 12 months.
- iv. RECs should inform principal investigators in writing of concerns arising from such monitoring activities.

4.5.1.11 Suspension or discontinuation of projects

- i. Where circumstances indicate that a project is non-compliant with the approved protocol and the interests of participants are at risk of harm, the REC may withdraw approval, after due process has been followed.
- ii. A clear process should be followed that permits swift but proper investigation and decision-making to ensure protection of participants. The investigation should include interaction with the researchers and other interested parties to ensure a fair and transparent process.
- iii. If the decision is to withdraw approval, the REC should inform the principal investigator and other interested parties, including the institutional authorities, and recommend suspension (temporary stoppage) or termination (permanent stoppage) of the project. It should also recommend remedial action where appropriate.
- iv. In the case of suspension, the principal investigator should comply with the recommendations and any special conditions imposed by the REC.

4.5.1.12 Complaints

- i. Each REC should have a complaints process that is accessible to researchers and other interested persons. In principle, but subject to institutional requirements, complaints about REC-related business should be directed to the REC in the first instance. If the matter remains unresolved, it may be escalated to other specified institutional officials and then to the NHREC.
- ii. A standard operating procedure should detail the procedures to be followed.
- iii. The NHREC is empowered to adjudicate complaints about RECs and to hear a complaint from any researcher who believes that he has been discriminated against unfairly by an REC.
- iv. A framework for the management of complaints and ethics related health research misconduct has been developed by the Complaints and Advisory Disciplinary Committee (CADC) of the NHREC (<http://nhrec.org.za>).
- v. The NHREC, through its CADC, adheres to the following principles when investigating a complaint: fairness, confidentiality, integrity and prevention of detriment.
- vi. All information and consent documentation should include contact details for making complaints about being a research participant. Similarly, a research assistant, researcher or an interested community member should be able to lodge a complaint or grievance related to the research process.

4.6 Compliance Reporting to the NHREC

- i. The NHREC is responsible for registering and auditing RECs.
- ii. RECs should make relevant records available for inspection and audit by the NHREC (or its delegate) upon request.
- iii. RECs must report annually on their activities, 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 matters
 - complaints received and action taken.
- iv. Reports are due by 28 February annually on the REC Reporting Template (<http://nhrec.org.za>).

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Chapter 5

‘HEALTH RESEARCH’ ETHICS INFRASTRUCTURE

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Note REC includes AREC unless otherwise indicated

5.1 Introduction

This chapter presents an overview of the statutory infrastructure and systems designed to regulate and oversee health research. The framework includes the National Health Act 61 of 2003, the Health Research Policy,⁵² and the National Department of Health Strategic Plan 2014/15 – 2018/19.⁵³ The care and use of animals for scientific purposes SANS 10386:2008,⁵⁴ and MRC Guidelines on Ethics for Medical Research Book 3: Use of animals in research and training (2004). International instruments also inform the governance of the conduct of health research.⁵⁵

The National Health Act 61 of 2003 authorizes the appointment of the National Health Research Ethics Council (s 72(1)) and mandates the Minister of Health to appoint members of the Council (s 72(2)(a)). Nominations are called for by notice in the Government Gazette.

Most higher education (tertiary level) and research institutions as well as health institutions have RECs, which are responsible for the ethical review and scrutiny of proposals to do research with human participants. Animal Research Ethics committees (ARECs) exist in institutions where research that uses animals is conducted.

5.2 National Health Research Ethics Council

5.2.1 Establishment

The National Health Research Ethics Council (NHREC) was established in terms of the National Health Act (NHA). The Council's core responsibilities are to advise the Minister of Health, to set ethical norms and standards for health research and to advance research ethics in South Africa, by promoting compliance by researchers and RECs using existing and new regulations and guidelines. The Council is mandated to register and audit RECs. In addition, the Council has responsibility for adjudicating complaints, for advising institutional committees, researchers and members of the public, as appropriate.⁵⁶

5.2.2 Appointment of Members

The NHA requires the Minister of Health to appoint 15 NHREC members who have knowledge and experience in research ethics or the law and are interested in promoting research ethics. The members' occupational diversity is prescribed. A Code of Conduct guides activities and expectations of members.

5.2.3 Operation

The Council meets at least four times annually, submits an annual report and advises the Minister of Health through the National Department of Health (DoH) about research ethics matters. The NHREC has established committees and working groups in order to perform its functions. The NHREC is supported by a secretariat in the DoH, which maintains a database of health research activities in South Africa. The NHREC maintains active, bilateral relations with the research community, mainly through interactions with REC Chairpersons.

5.2.4 Working Groups and Committees

Various Working Groups and Committees have been established to deal with the Council's responsibilities in a systematic manner. They include

⁵⁶See <http://www.nhrec.org.za> for documentation.

- i. The EXCO
- ii. Complaints, Advisory and Disciplinary Committee
- iii. Quality Promotion and Enhancement Working Group
- iv. Norms and Standards Working Group
- v. Legal and Regulatory Working Group.

5.2.5 Terms of Reference

The statutory functions of the NHREC include

- i. Registration and auditing of RECs
- ii. Adjudication of complaints about RECs
- iii. Referral of matters concerning violations of ethical or professional rules to the relevant health professional council as appropriate
- iv. Recommendation, where applicable, of disciplinary action against persons found to have violated the norms and standards for responsible and ethical conduct of health research
- v. Advising the national and provincial departments of health on matters concerning research ethics and health research.

5.3 Research Ethics Committees

Every institution, health agency and health establishment at which health research is conducted must establish or have access to an REC (NHA s 73). The main responsibility of each REC is to conduct rigorous ethics review of research proposals to ensure that the welfare and other interests of participants, researchers and animals used in research are properly protected and that the research will be conducted in accordance with the required ethical norms and standards. Section 73 states that RECs must 'grant approval...where research proposals and protocol meet the ethical standards of that health research ethics committee'.

5.4 Registration and audit of committees

Section 72(6)(b) of the NHA requires the NHREC to register and audit health RECs. The principle of empowerment is central to the registration and audit process.

5.4.1 Introduction

Health research is intended to improve health practice and, consequently, the health and well being of South Africa's people. Part of the framework that facilitates this process includes standardization of infrastructure and standard operating procedures for RECs, with a strong emphasis on guidance, training, support and feedback. To this end, the NHREC conducted a comprehensive administrative audit of RECs in South Africa, requiring each to register and to comply with various administrative and record keeping standards. Follow-up contact is designed to facilitate improvement and compliance with expected standards. When an REC or AREC persistently fails to comply with expected standards, the NHREC is required to enforce the standards, e.g. by suspending operations until compliance is achieved. Capacity evaluation and enhancement for committees are important functions of the NHREC.

5.4.2 Registration

All RECs must follow the registration process as outlined on the website.⁵⁷ Once the administrative registration and audit process is completed, the register is publicly listed on the website.

5.4.3 Audit

The criteria for auditing are based on this and other internationally recognized guidelines. Independent auditors are appointed to ensure that committees comply with essential requirements.

After the first audit, appropriate guidance and recommendations for improvement are provided as appropriate. A follow-up audit is carried out to ensure that required revisions are completed. An annual review by questionnaire is administered to all registered committees.

When registration is revoked, the committee concerned may not review health research. NHREC informs the committee of the revoked registration status and outlines the steps that should be taken to rectify matters so that registered status may be reinstated.

Every three to five years, a complete audit is done to review the capacity status quo of each REC. Criteria for registration and auditing of committees may be changed as determined by the NHREC to reflect new ethical concerns or standards arising from the national or international ethics dialogue. RECs will be informed of additional requirements.

⁵⁷ <http://www.nhrec.org.za>.

5.4.4 Capacity building for ethics committees

As indicated above, the audit process strongly emphasizes facilitation of guidance, training, support, and feedback as capacity building interventions. The aim is to foster a collaborative and mutually supportive environment in the research ethics context. The overall goal is to achieve a system that adheres to high standards across the board so that South Africans can rightfully be confident that the health research ethics infrastructure conducts itself with integrity, according to the highest ethical standards.

Identified resources, including Standard Operating Procedures, training materials, courses, web-based information, as well as query and appeal processes, are available to enable unregistered RECs to register and become compliant.

5.5 Statutory entities relevant to research

Certain statutory entities and professional bodies are relevant to research insofar as gatekeeping and professional standards for researchers are concerned. Some of the more significant entities and bodies are explained below.

5.5.1 The Medicines Control Council

The Medicines Control Council (MCC) is the statutory body tasked with ensuring that the pharmaceutical drugs available for use in South Africa are safe, are of the requisite quality, and have the required efficacy (effect). In order to carry out this mandate, the MCC must decide, based on sound scientific evidence and other relevant information, whether the decision to permit registration of a particular drug for particular uses is in the interest of public health.

Additionally, the MCC must approve the use of unregistered medicinal substances for research purposes, as well as sanction new applications of registered substances where a dose change, method of administration, etc is to be tested. Consequently, all clinical trials of registered and unregistered substances or interventions are reviewed by the MCC. Clinical trials are conducted in accordance with these guidelines and the Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa. Breaches of the guidelines may lead to termination of the trial by the MCC. This means that the MCC and the NHREC have concurrent jurisdiction over clinical trial research: the MCC focuses specifically but not exclusively on the scientific aspects, while the NHREC focuses specifically but not exclusively on the ethical aspects.

5.5.2 South African National Clinical Trial Register

Sponsors of clinical trials must register all South African-based trials on the South African National Clinical Trial Register (SANCTR) which is managed by the Department of Health. If the trial has no commercial sponsor, the Principal Investigator (PI) must register the trial. See the Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa (SAGCP) for more information. Note that it is not the responsibility of RECs to oversee compliance with this requirement.

5.5.3 South African Nursing Council

Section 36(2) of the Nursing Act 33 of 2005 provides that 'A certificate of registration is proof of registration for a period of one year after its date and thereafter an annual practising certificate, issued upon payment of the prescribed annual fee and the submission of such information as may be required by the Council to keep accurate statistics on human resources in nursing, is proof of registration in the absence of any credible evidence to the contrary'.

Research institutions or researchers may employ retired nurses and other categories of enrolled nurses who may not have paid their annual fees necessary to maintain registration with the SA Nursing Council. To practise without being registered or being in possession of an annual practising certificate is to commit an offence in terms of the Nursing Act (s 55). It is important for nurse members of a research team to evidence registration as part of professional competency requirements.

5.5.4 Provincial Research Committees

The White Paper on the Transformation of the Health System in South Africa outlines the importance of knowledge, information and empirical evidence as the backbone of health policy. The Health Research Policy in South Africa (2001) identified Provincial Health Research Committees as important mechanisms for coordinating health research and facilitating efficient use of limited research resources. Provincial Health Research Committees are not mentioned in the National Health Act (Act No. 61 of 2003), which establishes the National Research Coordination Committee, but they are clearly integral to the system. Research, especially that using state or provincial facilities and resources, should link to health care system priorities and findings should be integrated into policy planning and management of health programmes.

Provincial Research Committees⁵⁸ were established to liaise with researchers to ensure that the greatest health needs of each province are being addressed. Their focus is also on the effect of research activities on services. To that end, they perform a gate-keeping role by managing access to health facilities. They accept ethics approval granted by a registered REC. Some provinces have also established separate provincial research ethics committees. These committees are important in areas of the country where other RECs are not active. They are in the process of registering with the NHREC.

⁵⁸ In some provinces, the legislation calls them Provincial Research and Ethics Committees, which may blur the different roles.



Chapter 6

QUALITATIVE RESEARCH⁵⁹

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6.1 Introduction

This chapter is offered to assist RECs and researchers to ensure that qualitative research is reviewed appropriately. As indicated in chapter 1, perceptions exist that the 'medical model' of ethics review prevails and that it is inappropriately applied to research that may use qualitative research methodologies. As research becomes more trans disciplinary, proposals increasingly include mixed methodologies, including qualitative methodologies.

This section assists RECs and researchers by providing an approach to reviewing qualitative research proposals, but it does not provide detailed guidance on specific details that may arise in such proposals that will require consideration of specialised published guidance and authorities.

It is important that RECs review different methodologies appropriately and in accordance with accepted methodological standards of different research and academic disciplines.

It is important to recognize that, although research methodologies and analytic paradigms may differ, all research must be judged against the same ethical principles. No philosophical justification exists for judging different methodologies against different ethical standards. However, RECs must be familiar with qualitative research paradigms so that methodological issues are competently reviewed.

6.2 Nature of qualitative research

Researchers use qualitative research methods to find out and understand 'how people think about the world and how they act and behave in it...[Understanding is] based on discourse, actions and documents'.⁵⁹ Individuals, organisations and communities and interactions between and among them may be seen as socially constructed⁶⁰ and hence dependent on the social context in which they are found. The perspective of the researcher thus adds to the knowledge construction as observer, participant (for some methodologies) and analyst. Consequently, qualitative researchers have specific criteria that are applied to determining the credibility and trustworthiness of their data (analogous to reliability and validity of quantitative data).

6.3 Methodological approaches and requirements⁶¹

6.3.1 Diversity of approaches

Methodological approaches to qualitative research include but are not limited to ethnography, participatory action research, oral history, phenomenology, narrative inquiry, grounded theory and discourse analysis.

6.3.2 Inductive understanding

Usually, an inductive understanding of participants' worlds precedes attempts to gain an analytic understanding of their experiences.

6.3.3 Dynamic, reflective and continuous research process

During the course of the research, questions, concepts, theories, strategies and ways to engage with and gather data may emerge which may require that the researcher practise ongoing reflective, flexible and responsive approaches to ensure that the rigour, credibility and trustworthiness of data collection and analysis are maintained.

6.3.4 Data collection and sample size

⁵⁹ Tri-Council Policy Statement (Canada) 2010, 135.

⁶⁰ Tri-Council Policy Statement (Canada) 2010, 136.

⁶¹ Sections 6.3 & 6.4 are very closed based on the Tri-Council Policy Statement (Canada) 2010 Chapter 10, 136-145.

In general terms, depth of research is emphasised over breadth of research. Consequently, samples and sites are selected for their usefulness as rich sources of information. Selection of participants may be guided by emerging patterns over the course of data collection. Sample sizes are usually small.

Multiple methods of data gathering may be used to elicit data from multiple sources. For example, interviews, participant observation, and focus groups may be used. Increasingly popular but ethically challenging are research methods that involve capture of photographic and video data of participants or contexts. The risk/benefit ratio and confidentiality considerations are especially but not exclusively pertinent.

6.4 Approach to ethics review of qualitative research

As outlined above, qualitative research is inherently dynamic and may be based on assumptions that are different from those that inform quantitative research.

Best practices, standards and expectations that may exist in the different disciplines must be considered. However, as stated previously, the moral standards by which we judge the ethical acceptability of planned research do not differ just because a different methodology is to be used. Consequently, the principles outlined and discussed in chapter 2 are relevant also to qualitative research.

While researchers may refer to discipline- or paradigm-specific ethical norms and frameworks, adherence to national research ethics guidance is also required. As in quantitative research, RECs must consider any ethical tensions arising from specific methodologies and analytic approaches competently, fairly and without prejudice.

As in quantitative proposals, researchers should explain the intended process of the research, including its predictability or lack thereof, and how foreseeable ethical issues will be managed. This information must also appear in the information for potential participants.

6.5 Criteria for review process

In chapter 3 (3.1) the key criteria for the review process are outlined and discussed. These same criteria are relevant to review of qualitative research, with adjustments to emphasise aspects peculiar to qualitative research. However, the general requirements for role player engagement, social value, scientific validity and integrity, informed consent, risk/benefit ratio, protection of privacy and confidentiality are the same for all research. The discussion that follows should be read together with chapter 3.

Specific ethical issues may arise with gaining access, building rapport, conducting ethnographic observations, in-depth interviews and focus groups, using data and reporting results. Attention should be given to issues of consent, confidentiality, social and psychological harms, privacy as well as the anticipated relationships between researchers and participants when assessing the design, review, conduct and reporting of the research. Some may be evident in the design phase, while others will only arise during the research, in which case the researcher must exercise discretion, sound judgement, consultation and flexibility in accordance with the level of risk of harm and possible benefits of the research. The basis for the exercise of discretion and the degree of flexibility should be considered at the design phase. The REC Chairperson should be consulted when doubt arises.

APPENDIX 1

Glossary

Academic freedom – the collective freedom of researchers, including students, to conduct research and to disseminate ideas or findings without religious, political or institutional restrictions; it includes freedom of inquiry and freedom to challenge conventional thought. Academic freedom does not mean freedom to ignore ethical issues

Accountability – the measure by which it can be demonstrated that responsibilities have been or are being fulfilled; it may involve reporting upwards in a hierarchical structure

Adolescent – a child between 12 and 17 years of age

Anonymous data or specimen – data or biological materials without any overt identifying information or link to a specific donor

Audit – subset of research; not clinical practice but a review of clinical practice

Autonomy – the capacity to understand information; to act on it voluntarily; to use own judgement to make decisions about own actions, including whether to participate in research

Biobank – see **Repository**

Human biological materials – materials including blood and blood products, DNA, RNA, blastomeres, polar bodies, cultured cells, embryos, gametes, progenitor stem cells, small tissue biopsies and growth factors

Broad consent – donor permits use of biological materials for future studies, subject only to further prior ethics review and approval

Capacity – the ability to understand relevant information; to appreciate the consequences of decisions based on the information

Caregiver – a person who in fact cares for a child (s 1 Children's Act, 38 of 2005); a caregiver must safeguard the child's health, well-being and development; and protect the child from abuse and other harms; a caregiver exercises the parental right to consent to medical examination or treatment of the child

Child – a person under 18 years (s 28 Constitution; s 1 Children's Act)

Child-headed household – a household per s 137 Children's Act

Clinical equipoise – literally means a state of balance or equilibrium; in the research context it means that, amongst health care experts, uncertainty prevails about whether a particular treatment or intervention is better than another. This principle forms the basis for conducting clinical research

Clinical research – research intended to test safety (not harmful or dangerous to human health), quality (ingredients are of good quality), effectiveness (working to diagnose, treat, prevent or cure a disease condition) and efficacy (better/best when compared with other treatment or medicine for a similar condition) of new and/or existing or old medicines, medical devices and/or treatment options, using human participants. (South African Clinical Trials Registration <http://www.sanctr.gov.za/Resources/Whatisaclinicaltrial/tabid/175/Default.aspx>);

the Ottawa Statement defines 'trial' as a prospective controlled or uncontrolled research study evaluating the effects of one or more health-related interventions related to prevention, health promotion, screening, diagnosis, treatment, rehabilitation, or organization and financing of care.

'Intervention' refers to a deliberate act applied to an individual or group of individuals. Health-related **interventions** include but are not limited to the use of pharmaceuticals, biological products, surgery, procedures, radiation, devices, education, counseling, behaviour change, complementary health modalities, and management or economic policies. The word '**medicine**' includes medicines used to treat diseases (therapeutic medicines), to prevent diseases (prophylactic medicines, e.g. vaccines), and those used in special investigations (diagnostic medicines, e.g. medicines used during special X-ray examinations to map out kidneys).

Coded data or materials – identifiers are substituted by a number, symbol or other method to provide a code; a key to the code exists so that the specimen can be linked to its original source

Coercion – extreme form of undue influence, involving a threat of harm or punishment for failure to participate in research; see Undue influence

Collaborative research – involves co-operation of researchers, institutions, organizations or communities, each contributing distinct expertise, characterized by respectful relationships

Community – a group of people with a shared identity or interest that has the capacity to act or express itself as a collective; it may be territorial, organizational or a community of interest

Community engagement – a process that establishes an interaction between researchers and a community regarding a research project; it signifies the intention of forming a collaborative relationship; the degree of collaboration may vary depending on the circumstances

Confidentiality – the responsibility to protect information entrusted to researchers for research purposes from unauthorized access, use, disclosure, modification, loss or theft

Conflict of interest – incompatibility of duties, responsibilities or interests (personal or professional) of a person or an institution as regards ethical conduct of research so that one cannot be fulfilled without compromising another

Consent – indication of agreement to participate in research, based on adequate knowledge and understanding of relevant information, and freely given

Database – a collection of information including images (data) arranged to facilitate swift search and retrieval

Decisional analysis – use of a systematic approach to ethical evaluation especially the ratio of risk of harm to likelihood of benefit

Discomfort – a negative effect experienced in research less serious than harm

Donor – the person (living or deceased) from whose body biological materials have been removed or withdrawn

Ethics review – review of research proposals or protocols by RECs prior to commencement of the research

Guardian – a person appointed by a court to look after the financial and welfare interests of a minor, or a person appointed by a parent with sole responsibility for the minor in terms of that parent's Will

Harm – anything that has a negative effect on participants' welfare, broadly construed; its nature may be physical, emotional, psychological, social or legal

Health research – contributes to knowledge of biological, clinical, psychological, or social welfare matters including processes; causes and effects of and responses to diseases; effects of environment on humans; methods to improve health care delivery; new pharmaceuticals, medicines, interventions and devices; new technologies to improve health and health care

Identifiable information – reasonably expected to identify an individual alone or in combination with other information

Directly identifying – direct identifiers e.g. name, identity number

Indirectly identifying – combination of indirect identifiers e.g. date of birth, address, unique personal characteristic

Coded information – direct identifiers removed; replaced by code

Anonymised information – irrevocably stripped of direct identifiers; no code

Anonymous information – never had identifiers

Identifier – information such as a name, initials, address, folder number, or biometric identifier (e.g. finger print) that can identify a particular donor

Incentive – anything offered to encourage participation in research

Incidental findings – unanticipated discoveries made in the course of research that are outside the scope of the research

Inconvenience – a minor negative effect experienced in research less serious than discomfort

Low risk research – where the only foreseeable risk is one of discomfort

Minimal risk research – where probability and magnitude of possible harms implied by participation are no greater than those posed by daily life in a stable society or routine medical, dental, educational or psychological tests or examinations

Minor – a person under 18 years (s 17 Children's Act)

Narrow consent – donor permits single use only of biological materials; no storage; no sharing of data or specimen; new consent if further use wanted.

Negligible risk research – where the only foreseeable risk is one of inconvenience

Neonate – a newborn child

Non-therapeutic interventions – interventions not directed towards health-related benefit for a participant but towards improving generalisable knowledge (NHA Reg 135)

Observational research – study of behaviour in a natural environment where people involved in their usual activities are observed with or without their knowledge; observational research also occurs in clinical research e.g. when a researcher observes individuals or measures particular outcomes, without intervention e.g. no treatment is given); an observational study describes a wide range of study designs including prospective and retrospective cohort studies, case-control studies, and cross-sectional studies, a defining feature of which is that any intervention studied is determined by clinical practice and not the protocol.

Orphan – a child without a surviving parent to care for him (s 1 Children's Act)

Privacy risks – potential harms to participants from collection, use and disclosure of personal information for research purposes

Protocol – document that provides background, rationale and objectives of research; describes its design, methodology, organization and conditions under which it is to be conducted and managed

Qualitative research – involves studied use of empirical materials such as case studies, personal experience, life stories, interviews, observations, and cultural texts

Registry– a collection of information (data) from multiple sources, maintained over time with controlled access through a gatekeeper organizer

Reimbursement – payment to participants to ensure they are not disadvantaged financially directly or indirectly by participation in research; directly means actual costs incurred and indirectly means losses that arise because of participation

Repository– a collection, storage and distribution system for human biological materials for research purposes including blood, urine, faeces, bone marrow, cell aspirates, diagnostic specimens, pathology specimens and so on. Usually demographic and medical information about the donors is included in the repository as are codes that link the material to the donors

Research – includes a range of activities conducted by many different disciplines that may use different methodologies and explanatory frameworks to extend knowledge through disciplined inquiry or systematic investigation

Risk – function of the magnitude of harm and the probability that it will occur

Risk of harm to likelihood of benefit ratio – analysis of whether the risk of harm implied is justifiable in light of the likelihood of benefit

Therapeutic intervention –interventions directed towards direct health-related benefit for a participant (NHA Reg 135)

Tiered consent – donor permits use of biological materials for current study; and chooses whether to permit storage for future use, sample and data sharing.

Undue influence – effect of an unequal power relationship on voluntariness; may occur when recruitment of participants is done by authority figure

Virtual Repository– a digitised system that manages distributed bar-coded electronic versions of material, data or images through shared data systems

Vulnerability – diminished ability to fully safeguard one's own interests in the context of a specific research project; may be caused by limited capacity or limited access to social goods like rights, opportunities and power

APPENDIX 2

Resources

Online training opportunities

These links are to FREE online training in research ethics and some also do Responsible Conduct of Research

1. The AMANET (African Malaria Network Trust)

<http://webcourses.amanet-trust.org/mod/resource/view.php?inpopup=true&id=116>

The AMANET (African Malaria Network Trust) web-based health research ethics training programme aims at providing the basic understanding in biomedical research ethics. On the premise of scarcity of resources and opportunities for such training for Africans, this effort hopes to provide this service to the many African members of IRB's and investigators who may wish to undertake the course at home or in their office and at their own time up to a maximum period of four months for each student number issued.

2. Cameroon Bioethics Initiative (CAMBIN)

www.cambin.org/cambin-training

3. <https://camtools.cam.ac.uk/wiki/site/e30faf26-bc0c-4533-acbc-cff4f9234e1b/ethnographic%20and%20field%20study.html>

4. <http://www.fhi360.org/training/en/RETC2/index.html>

5. <http://www.responsiblesearch.org/>

6. NIH Office of Extramural Research

<http://phrp.nihtraining.com/users/login.php>

7. Macquarie University Australia: Human Research Ethics for the Social Sciences and Humanities

http://www.mq.edu.au/ethics_training/index.php

8. PEERRS, the University of Michigan's Program for Education and Evaluation in Responsible Research and Scholarship

<http://my.research.umich.edu/peerrs/>

9. PRIM&R Public Responsibility in Medicine and Research

<http://www.primr.org/ResourceCenter.aspx?id=262>

'For more than 38 years, PRIM&R has offered learning opportunities in the fields of biomedical and social/behavioral/educational research. Our goal is to provide current information on the ethics and legal issues related to human and animal research, as well as to offer best practices and strategies for implementing successful programs for human subjects' protection and animal care and use. PRIM&R's conferences, educational programs, web-based seminars ("webinars"), and reference materials have become standard resources in the fields of research ethics and subjects protections.'

10. TRREE (for Training and Resources in Research Ethics Evaluation)

<http://elearning.trree.org/mod/resource/view.php?id=70>

TRREE is headed by a consortium of interested persons from Northern and Southern countries. It aims to provide basic training, while building capacities, on the ethics of health research involving humans so that research meets highest standards of ethics and promotes the welfare of participants. TRREE achieves this goal primarily by developing a training programme with local collaborators. In its initial stages TRREE focused primarily, but not exclusively, on the needs of African countries.

TRREE provides free-of-charge access to:

- e-Learning: a distance learning program and certification on research ethics evaluation
- e-Resources : a participatory web-site with international, regional and national regulatory and policy resources

There are other opportunities available but not all are free.

Guidelines

Australian code for the care and use of animals for scientific purposes (8th Edition) 2013
Australian National Statement on Ethical Conduct in Human Research (2007)

AVMA Guidelines for the Euthanasia of Animals: 2013 Edition

Canadian Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (2010)

Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO) International Ethical Guidelines for Biomedical Research Involving Human Subjects Geneva 2002

Council for International Organizations of Medical Sciences (CIOMS) (2002)

Council of Europe Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine Oviedo 1997

Council of Europe Steering Committee on Bioethics: Guide for Research Ethics Committee Members (2011)

Department of Health RSA Ethics in Health Research: Principles, Structures and Processes Pretoria 2004

Department of Health RSA Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa Pretoria 2006

DIRECTIVE 2010/63/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 22 September 2010 on the protection of animals used for scientific purposes

<http://osp.od.nih.gov/office-clinical-research-and-bioethics-policy/clinical-research-policy/ethical-issues-international-research>

ICH Guidelines

International Compilation of Human Research Standards compiled by the Office for Human Research Protections US Department of Health and Human Services <http://www.hhs.gov/ohrp/international/index.html>.

Medical Research Council of South Africa Guidelines on Ethics for Medical Research: General Principles Pretoria 2002

Medical Research Council of South Africa Guidelines on Ethics for Medical Research: Use of Animals in Research and Training (2004)

Montreal Statement (2013)

NIH ARENA/OLAW IACUC Guidebook, 2002, Institutional Animal Care and Use Committee Guidebook

Nuffield Council on Bioethics: the Ethics of Research Related to Healthcare in Developing Countries (1999)

Nuremberg Code (From 'Trials of War Criminals Before the Nuremberg Military Tribunals Under Control Council Law No 10' Vol 2, Nuremberg, October 1946 – April 1949)

Singapore Statement (2010)

South African Bureau of Standards' South African National Standard (SANS 10386:2008 or latest version) for the Care and Use of Animals for Scientific Purposes

The IACUC Handbook, Third Edition, Published: May 20, 2014 by CRC Press Content:827 Pages Editor(s):Jerald Silverman, Mark A. Suckow, Sreekant Murthy

US Federal Policy for the Protection of Human Subjects Code of Federal Regulations (CFR also know as the Common Rule)<http://osp.od.nih.gov/office-clinical-research-and-bioethics-policy/clinical-research-policy/research-involving-human-subjects>

World Health Organization (2000) Operational Guidelines for Ethics Committees that Review Biomedical Research TDR/PRD/ETHICS/2000.1

World Health Organization Operational Guidelines for Ethics Committees that review Biomedical Research TDR/PRD/ETHICS/2000

World Health Organization Standards and Operational Guidance for Ethics Review of Health-Related Research with Human Participants (2011)

World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects 1964, most recently amended in 2013

World Medical Association: Declaration of Helsinki (2013)

APPENDIX 3

Templates

1. Mandatory reporting of abuse

How to respond adequately to the reporting requirement within a research context:

Note that arrangements and negotiations e.g. with Childline South Africa or other agencies, should be made in advance of the application for ethics review. The applicant should be able to assure the REC about the referral arrangements.

1. Disclosure by any adolescent under 16 years of sexual or other abuse, or on whose behalf abuse is reported by a peer, caregiver, guardian or family member or other relevant person, should trigger an immediate termination of further interviews with the respondent and members of the household.
2. If there is a clear statement that the parties involved in the abuse include an adult (anyone 18 years or older) or anyone who is more than two years older than the adolescent (s 56(2)(b)), the interviewer should report the matter to Childline South Africa at toll free: 0800 055 555 [or another child protection agency]. Childline should contact a registered social worker in the area who should investigate and inform the South African Police Service (SAPS) accordingly. The interviewer should record details of the child's name, physical address and the name of the school the child attends. As proof of complying with the statutory reporting obligation, the interviewer should insist on a Childline reference number.
3. Any secondary reporting of abuse, e.g. where a child indicates that she has reported the abuse to a teacher or another adult but that no action has been taken, the matter should be brought to the attention of Childline, who should deal with the matter. Again, the interviewer should insist on a Childline reference number, as proof of reporting.

If there is uncertainty about whether to report, the interviewer should consult with the Principal Investigator. [Insert conditions appropriate to the circumstances]

Examples in practice	Action by researcher
A 14 year old tells of having sex with her 17 year old boyfriend	Childline → Police
A 12 year old reports 'having sex' with 19 year old neighbour	Childline → Police
An 11 year old tells of a previously reported incident of 'bad touching' by adult aunt that went to court	No action; ask whether the child wants to talk to someone
A 15 year old relates rape by father	Childline → Police
A 13 year old boy relates anecdote of sex with 15 year old girlfriend	Not over two years, so no action
A 13 year old says she is 'having sex' but does not disclose who the partner is	No action
A 17 year old brags that he has 'forced' many girls into having sex with him	No action
A 17 year old learner speaks of having become pregnant by a school teacher who she does not identify	Ask whether she wants to speak to someone
A 18 year old learner points out a female school teacher with whom he says he is 'sleeping'	Ask whether he wants to speak to someone

2. Insurance information for consent documentation

This template is based on DoH 2006, MCC Clinical Trials Compensation Guidelines and Venter v Roche Products (Pty) Ltd et al (12285/08) [2013] WCHC 7 May 2013 and on appeal (A11/2014) 22 October 2014.

Notes for researchers:

- i. Research study insurance does not substitute malpractice insurance
- ii. ABPI guidelines on compensation apply only to unlicensed substances used in Phase II and III clinical trials; reference to ABPI compensation should not be a standard paragraph in all consent documents
- iii. Participants may not recognize symptoms of side effects or have ready means to take action

‘What happens if I get hurt taking part in this study?’ (or equivalent heading)

This research study is covered by an insurance policy taken out by [name of institution] in the event that you suffer a bodily injury as a result of taking part in the study.

The insurer will pay for all reasonable medical costs required to treat your bodily injury, in accordance with the SA Good Clinical Practice Guidelines (2006 or latest version), which are based on the Association of the British Pharmaceutical Industry Guidelines. You may request a copy of these guidelines from the study doctor.

The insurer will pay without you having to prove that the research was responsible for your bodily injury.

The insurer will not pay for harm if, during the study, you

- Use medicines or other substances that are not allowed
- Do not follow the study doctor's instructions
- Do not tell the study doctor that you have a bad side effect from the study medicine
- Do not take reasonable care of yourself and your study medicine

If you are harmed and the insurer pays for the necessary medical costs, usually you will be asked to accept that insurance payment as full settlement of the claim for medical costs. However, accepting this offer of insurance cover does not mean you give up your right to make a separate claim for other losses based on negligence, in a South African court.

It is important to follow the study doctor's instructions and to report straight away if you have a side effect from the study medicine.

See also Medicines Control Council Clinical Trial Compensation Guidelines available at <http://www.sahealthinfo.org.ethics/book1.htm>

3. Novel, Innovative or Unproven Treatment

<Insert hospital name>

NOVEL, INNOVATIVE OR UNPROVEN TREATMENT CONSENT FORM

How to use this Consent Form

Read carefully through the whole document
Fill in the RED areas ELECTRONICALLY (for future data collection)
Make sure that all the necessary information is included
The information written in BLUE is for guidance and should be removed before finalizing the document
Print three (3) copies: one for patient's folder, one for PTC, and one for the patient or her family

This document is for a single patient use and a single treatment course only.

This document tells you about a treatment for your (your child's) condition that is still experimental but which your doctors would like to try. You are not being asked to join a research project. Important differences exist between experimental treatment and a research project.

This treatment is experimental because

<delete options that do not apply>

It has been tested for conditions other than yours (your child's).

It has been tested for use with adults but not for use with children (<18 years; <12 years)

It has not been registered in South Africa for use for your condition.

Name of Drug Or Intervention	Single Patient Use of <Insert Investigational Drug or Intervention Name>
Treating Health care worker(s):	<Insert Name > <Insert Address/Medical ward details> <Insert Phone Numbers/ Medical ward extension>
Emergency Contact	<Insert Emergency Contact Information> <Insert Phone Number/Pager, etc>

<Insert name of investigational drug or other intervention> is a treatment that <insert either current approval status by the Medicines Control Council for another condition or provide a patient appropriate explanation of what the investigational drug or intervention is intended to do>.

This treatment is not approved for <indicate what condition the patient has>, which means its use is experimental. We are not sure that this experimental treatment will cure or improve your condition. But in your circumstances, we offer you the opportunity to try it.

We must get permission from the hospital authorities before we may use this experimental treatment for you. The hospital authorities keep a careful watch over your welfare interests, especially that you should choose voluntarily. This is why you are asked to choose whether you would like to try the experimental treatment before we request permission to use the drug for you.

You do not have to use the experimental treatment.

Why is this experimental treatment being offered?

Your doctors think this experimental treatment may offer an option for your clinical care, as <insert in plain language a description that describes why this treatment is the best option for the patient in the circumstances >

How long will I take this experimental treatment?

The total length of time you would receive this treatment will depend on many factors including: (i) how your medical condition responds to the experimental treatment, and (ii) further information about this use of the drug in your medical condition

[Incorporate a specific schedule for the receipt of the investigational drug, if one is known]

What does the experimental treatment involve?

You will receive this experimental treatment in <location where the treatment (i.e. hospital (clinic/medical ward/OPD), home, private care, etc) will be given>. You will be asked to take a <insert appropriate dose (mg/mcg/ml)> dose <insert dosing schedule, i.e. once-off, once per day, 12 hourly, etc>

[Be sure to include any other drugs that are taken in combination with the experimental treatment drug if appropriate

Provide information pertaining to any safety or other assessments needed during the time that the patient receives the experimental treatment drug]

What are the possible side effects or risks of harm?

- Likely: <Provide appropriate risk listing>
- Less Likely: <Provide appropriate risk listing>
- Rare: <Provide appropriate risk listing>
- Unknown Side Effects:

There may also be other side effects, unknown at present, that could harm you while you are using this experimental treatment or after you have finished using it. We cannot predict what these currently unknown side effects may be. This is why it is very important that you must report any side effects you experience to your doctors immediately. We want to be able to treat any reaction quickly and appropriately.

The possibility exists that you could have a reaction that, if not treated properly, could be life threatening

What are the possible benefits of using this experimental treatment?

You may or may not receive any benefit from using this treatment; in other words, your condition may not respond to the treatment.

What if new information about the experimental treatment becomes available?

While you are using this treatment, we may find out more information that could be important to your treatment. This includes information that might cause you to change your mind about taking the drug. We will tell you as soon as possible if such information becomes available so that you are informed at all times.

What other choices do I have if I do not use this experimental treatment?

Your doctors think that, at the moment, there are no other satisfactory alternatives available to you. You do have the option of deciding to refuse further treatment and only accept care for comfort. You can discuss these options with your doctors.

What happens if I am harmed because of using the experimental treatment?

We will give you the necessary medical care to treat the harms or injuries that result directly from using the experimental treatment.

When will my participation be over?

Your participation will last until <insert endpoint in appropriate language based on investigational drug being used>.

If you decide to use this experimental treatment, you are free to stop taking it any time. Please inform your treating physician(S) if you choose to do this, so appropriate follow-up can occur.

[Ensure that whether withdrawal is possible is clear to patient or family member]

Who can see or use my information? How will my personal information be protected?

The personal information in your medical record will be kept confidential as is usual with health information. However, we cannot guarantee total privacy. Your personal information may be shared with other health care professionals where it is in your best interest to do so and if required by law.

Who can I call if I have questions, concerns or complaints?

If you have questions, concerns or complaints, you should speak to your doctor listed on page one of this form.

Who will know that I am receiving an experimental treatment?

Your doctors and the rest of the medical team will know that you are using an experimental treatment. As explained above, your doctor will have obtained permission from the hospital authorities to use it. As is usual, your privacy interests will be respected and information about your treatment and condition will be confidential to the extent possible.

Because of its experimental nature, we will want to write a report about what we learn from using this therapy for your treatment. This is to make the information available so that other doctors can learn more about it too. However, your identity will not be revealed when we write up our notes for publication or discuss the treatment at meetings or conferences.

When you sign this form, you are agreeing to use the experimental treatment for your <insert patient's condition>. Your signature indicates that you have read this form, your questions have been answered, and you have decided to use the experimental treatment. You understand also that we will want to write a report for publication.

You will have a copy of this form to keep.

_____ Name of Patient	_____ Signature of Patient	_____ Date
_____ Name of Parent/Guardian/ Treatment proxy	_____ Signature	_____ Date
_____ Name of Health care worker	_____ Signature of Health care worker	_____ Date

4. Consent for storage and future use of unused samples of biological materials



Research Ethics Review Committee (WHO ERC)

20, AVENUE APPIA – CH-1211 GENEVA 27 –SWITZERLAND – [HTTP://INTRANET.WHO.INT/HOMES/RPC/ERC](http://intranet.who.int/homes/rpc/erc) –
[HTTP://WWW.WHO.INT/RPC/RESEARCH_ETHICS](http://www.who.int/rpc/research_ethics)

***Informed Consent Form Template for
Consent for Storage and Future Use of
Unused Samples***

Notes to Researchers:

1. Please note that this is a template developed by the WHO ERC to assist the Principal Investigator in the design of their informed consent forms (ICF). It is important that Principal Investigators adapt their own ICFs to the outline and requirements of their particular study.

The logo of the Institution must be used on the ICF and not the WHO logo.

2. The informed consent form consists of two parts: the information sheet and the consent certificate.

3. Do not be concerned by the length of this template. It is long only because it contains guidance and explanations for you which you will not include in the informed consent forms that you develop and provide to participants in your research.

4. In this template:

- square brackets indicate where specific information is to be inserted
- bold lettering indicates sections or wording which should be included
- standard lettering is used for explanations to researchers only and must not be included in your consent forms. The explanation is provided in black, and examples are provided in red in italics. Suggested questions to elucidate understanding are given in black in italics.

TEMPLATE ON FOLLOWING PAGE

Additional Consent to [Name of Project]

Include the following section if the research protocol calls for storage and future use of samples

This Statement of Consent consists of two parts:

- Information Sheet (to share information about unused samples with you)
- Certificate of Consent (to record your agreement)

You will be given a copy of the full Statement of Consent

Part 1. Information Sheet

Explain that you are seeking permission to store their unused samples for possible future use in either your own research or someone else's research. State that they need to make some decisions about their blood/tissue/sperm/sputum sample because they gave you permission only to use it for the current research.

Explain that sometimes people don't want their samples used for research into areas they might not agree with, for example, research into birth control or reproductive technology. Use lay terms to explain research possibilities. If genetic research is a possibility, explain what this is and any implications for them. State that they can tell you if there is something they don't want their sample used for, or if they don't want their sample used at all.

Inform the participant that, at present, the researchers can trace which blood/tissue/sperm/sputum sample belongs to the participant. In most cases, the participant must decide whether they want to let the researchers keep the sample but get rid of all identifying information, or whether they are comfortable with the researchers knowing whose sample it is. Explain the risks and benefits of each of these options. Inform the participant of researcher obligations in cases where the sample remains linked. These obligations include informing the participant of results that have immediate clinical relevance.

Inform participants that their sample will not be sold for profit and that any research which uses their sample will have been approved.

Right to Refuse and Withdraw

Explain that the participant may refuse to allow samples to be kept or put restrictions on those samples with no loss of benefits and that the current research study will not be affected in any way. Inform the participant that they may withdraw permission at anytime and provide them with the name, address, and number of the person and sponsoring institution to contact.

Confidentiality

Briefly explain how confidentiality will be maintained including any limitations.

You can ask me any more questions about any part of the information provided above, if you wish to. Do you have any questions?

Part II. Certificate of Consent

If any of the (TYPE OF SAMPLE i.e. blood, tissue) I have provided for this research project is unused or leftover when the project is completed (Tick **one** choice from each of the following boxes)

- ☐ I wish my [TYPE OF SAMPLE] sample to be destroyed immediately.

☐ I want my [TYPE OF SAMPLE] sample to be destroyed after ____ years.

☐ I give permission for my [TYPE OF SAMPLE] sample to be stored indefinitely

AND (if the sample is to be stored)

- ☐ I give permission for my (TYPE OF SAMPLE) sample to be stored and used in future research but only on the same subject as the current research project : [give name of current research]

☐ I give my permission for my [TYPE OF SAMPLE] sample to be stored and used in future research of any type which has been properly approved

☐ I give permission for my [TYPE OF SAMPLE] sample to be stored and used in future research except for research about [NAME TYPE OF RESEARCH]

AND

- ☐ I want my identity to be removed from my (TYPE OF SAMPLE) sample.

☐ I want my identity to be kept with my (TYPE OF SAMPLE) sample.

I have read the information, or it has been read to me. I have had the opportunity to ask questions about it and my questions have been answered to my satisfaction. I consent voluntarily to have my samples stored in the manner and for the purpose indicated above.

Print Name of Participant _____

Signature of Participant _____

Date _____

Day/month/year

If illiterate, a literate witness must sign (if possible, this person should be selected by the participant and should have no connection to the research team). Participants who are illiterate should make their mark.

I have witnessed the accurate reading of the consent form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Print name of witness _____

Signature of witness _____

Date _____

Day/month/year

AND mark of participant

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Statement by the researcher/person taking consent

I have read out the information sheet to the potential participant accurately and, to the best of my ability, I have ensured that the participant understands that the following will be done:

- 1.
- 2.
- 3.

I confirm that the participant had the opportunity to ask questions about the nature and manner of storage of the samples, and that all the questions asked by the participant were answered to the best of my ability. I confirm that consent has been given freely and voluntarily.

A copy of this document has been provided to the participant.

Print Name of Researcher/person taking the consent _____

Signature of Researcher /person taking the consent _____

Date _____

Day/month/year

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