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South African Ethics in Health Research Guidelines:

Principles, Processes and Structures

2024

Third Edition, version 3.2

NDoH 2024 (v3.2)

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30 YEARS OF FREEDOM

National Health Research Ethics Council
NHREC

A long and healthy life for all South Africans

Minister of Health

Dr MJ Phaahla

Foreword

The health care infrastructure in South Africa, including the excellent professional competence of practitioners and researchers, provides a context for quality health and health-related research. In a world of rapid technological advancements, environmental changes, and the impact of public health emergencies on a scale not previously experienced, health research is vital for the advancement of relevant health care services globally and for the people of South Africa more specifically. The country remains characterised by a high burden of communicable and non-communicable diseases, including those associated with the social determinants of health related to inequalities and inequities found in diverse regions and communities. The evolution of this landscape has created the need for a continued focus on disciplinary health and health-related research as well as an increase in multi- and transdisciplinary research that seeks solutions to the complex problems associated with health and wellbeing. This means that to ensure 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 must continuously be reviewed and strengthened.

The core ethical principles – respect, scientific merit and integrity, justice, care, and beneficence – apply to all forms of research that involve living persons and use of animals for scientific purposes, thereby placing their safety, welfare, and other interests as paramount considerations. These principles apply also to research with human biological materials, data collected from living or deceased persons, protection of personal information and research in the era of Data Science and Generative Artificial Intelligence.

These Guidelines, entitled '*South African Ethics in Health Research: Principles, Processes and Structures*', 3rd edition (NDOH 2024), replace the second (2015) edition. They are the national guide to ensure that research is conducted in accordance with the highest ethical norms and standards for conducting research responsibly and ethically, as measured against these revised, updated, and tailored guidelines appropriate to the needs of South Africa.

- 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) for research involving human participants (HRECs) and the use of animals (ARECs), and give guidance about standard operating procedures
- They describe the research ethics infrastructure and regulatory framework in South Africa

These Guidelines are written for use by researchers from all disciplines who involve human participants in their research or who use animals for scientific purposes, RECs, health care practitioners, health facility administrators, policy makers in government departments, community representatives and more.

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.

Dr MJ Phaahla, MP
Minister of Health
Date: 21/05/2024

Director-General: Dept of Health

Dr SSS Buthelezi

Acknowledgements

Mandated by section 72 of the National Health Act 61 of 2003, the National Health Research Ethics Council (NHREC) is tasked to revise and update the national guidelines for health research ethics. These guidelines entitled '*South African Ethics in Health Research: Principles, Processes and Structures*' 3rd edition (NDoH 2024), provide a strengthened guide to ensure that, in South Africa, health research is conducted responsibly and ethically.

Drawing on relevant publications and international and foreign national ethics codes and research ethics guidelines, the NHREC has produced a document that is relevant to South Africa, while positioned within the matrix of research ethics guidelines available globally.

The key expectations of the Guidelines include that:

- Protocols to conduct research involving humans undergo independent ethics review before research activities start
- Proposed health or health-related research broadly addresses human health and wellbeing and is in the domain of curiosity-driven basic sciences or applied and immediately relevant research
- Protocols to conduct health research stand up to scientific and ethical scrutiny appropriate to the context and disciplines concerned
- Harm to research participants is prevented or mitigated and balanced against the likelihood of benefit to the individual and/or society
- The safety and welfare interests of animals used for scientific purposes are promoted, and there is transparent justification for the use of animals
- Researchers are held accountable for their research activities
- Social and ethical values are promoted

The National Department of Health is grateful to the NHREC as well as Ms T Zondi, Dr T Muthivhi, Dr L Malinga, Mr J van der Westhuizen and Mr R Maluleke from the Secretariat. Work on the revision of DoH 2015 Guidelines involved councillors of three consecutive NHRECs.

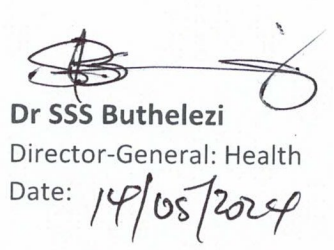
The NHREC (2016 - 2019) included Prof A Pope (Chairperson), Prof MP Sekhoacha (Deputy Chairperson), Prof C Brink, Dr T Burgess, Prof P Engel-Hills, Dr J Gardener, Prof M Greeff, Dr B Mohr, Mrs P Nkambule, Prof S Singh, Ms T Sebata, Dr N Tsotsi.

The NHREC (2020 - 2023) included Prof MP Sekhoacha (Chairperson), Prof P Engel-Hills (Deputy Chairperson), Prof C Brink, Dr C Chauke, Dr D Diale, Dr J Gardener, Dr M Kwinda, Prof M Labuschaigne, Prof L Makhubela (2021-2022), Mrs P Nkambule, Prof E Seekoe, Prof S Singh, Dr E van Vollenhoven and Prof A van der Merwe.

The current NHREC (2023 - 2026) comprises of Prof P Engel-Hills (Chairperson), Prof S Singh (Deputy Chairperson), Prof C Brink, Dr C Chauke, Dr D Diale, Ms Z Jafta, Prof M Labuschaigne, Prof S Matlala, Prof AJ Mbokazi, Prof Z Mkhize-Kwitshana, Prof NM Mooi, Prof L Qalinge, Prof E Seekoe, Mr T Sehloho and Ms T Zondi.

All HRECs and ARECs registered with the NHREC are acknowledged for their diligent and valuable inputs over the full period of the revision. Those REC members who went above and beyond in their contributions and the valuable input of a number of consultation groups are sincerely appreciated for their relevant and helpful guidance. In addition, all other interested parties are acknowledged for their role in the revision of these Guidelines through meaningful engagement as well as expert and technical input.

The National Department of Health and the NHREC are very grateful to Prof A Pope who donated her time and expertise to lead the editing of these guidelines.



About these Guidelines

Context

These Guidelines are issued by the South African National Health Research Council (NHREC), under the auspices of the National Department of Health of the Republic of South Africa (NDoH), as mandated by Section 72 of the National Health Act 61 of 2003 (NHA). These Guidelines draw their authority from the NHA and associated regulations, and bind all health and health-related research involving human participants, and the use of animals in research for human health purposes, within South Africa (see also 1.7). The minimum norms and standards for South Africa, as contained in these Guidelines, are established by the NHREC, its application overseen by institutional research ethics committees (RECs) registered with the NHREC, and implemented by the researcher(s) in studies approved by the relevant REC(s). Importantly, the Guidelines are not intended to be a detailed instruction manual, but rather to explain principles and to provide binding normative[1] and illustrative informative[2] guidance on how to think about the principles in practical contexts.

Citation

How to reference *(suggested)*

National Health Research Ethics Council (2024) ***South African Ethics in Health Research Guidelines: Principles, Processes and Structures***, 3rd ed. National Department of Health of the Republic of South Africa. Pretoria: NDoH. 137p. ISBN 978-0-621-52027-9.

Note! The referencing may be adjusted as per citation style.

Short name

NDoH 2024

URL *(to download the NDoH 2024 Guidelines in PDF format)*:

https://www.health.gov.za/nhrec-documentation/

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Previous editions

- **DoH 2004**
  National Health Research Ethics Council (2004) ***Ethics in Health Research Principles, Structures and Processes***. National Department of Health of the Republic of South Africa. Pretoria: NDoH. 67p. ISBN: 1-920031-0409
- **DoH 2015**
  National Health Research Ethics Council (2015) ***Ethics in Health Research Principles, Processes and Structures***, 2nd ed. National Department of Health of the Republic of South Africa. Pretoria: NDoH. 94p. ISBN: 978-1-7764880-0-1

[1] Normative here refers to provisions of the Guidelines that must be complied with.

[2] Informative here refers to recommended best practices or illustrative examples, that may be adapted by RECs and other stakeholders to accommodate own needs within unique or particular contexts and serving to guide informed decisions and choices for implementation.

Document history

Below is a summary of minor amendments to the current edition of the NDoH 2024.

Version	Reason for Amendment	Effective Date
3.0	**Implementation**	August 2024
3.1	**Section 4.3.2** Heritable Human Genome Editing: - Section removed pending further national stakeholder engagement	March 2025
3.2	**Version 3.2 is based on minor editorials:** Sec 1.1 Introduction: – minor editorial Sec 3.1.1 Scientific basis for decision-making in the review process: – Expanded on the scientific review recommendation and removed the SA GCP requirements with respect to SAHPRA scientific approval Sec 5.2.2 Terms of Reference and Standard Operating Procedures: – Expanded on the definition of Terms of Reference and Standard Operating Procedures Sec 5.2.3.2 Administrative Support and resources: – Minor editorials Sec 5.3 Role of the Research Ethics Committee: – Content restructure Sec 5.3.1 REC Membership Composition: – Expanded text to include clinical trials content Sec 5.3.2 Appointment of Chairperson: – Clarity on the term of office of the Chairperson Sec 5.3.2.1 Additional considerations for ARECs: – Amendment of the requirement for AREC chairperson Sec 5.3.2.2 Appointment of REC members : – Clarity provided on the term of office of members Sec 5.4 Education and Training in Research Ethics: – Further clarity provided on training requirements Sec 5.4.2 Expectations of training outcomes: – Further clarity provided on training outcomes Sec 5.4.2.1 International collaborators with existing training in research ethics: – Expanded and clarity provided to this section Sec 5.5.1.2 Application for ethics review: – Further clarity provided Sec 5.5.1.3 REC decision making and feedback to applicants: – Content restructure Sec 5.5.1.6 Rapid Review: – Minor editorials Sec 5.5.1.8 Archiving: – Further clarity provided Sec 5.5.1.14 Complaints and queries: – Further clarity provided Sec 5.6 Compliance reporting to the NHREC: – Further clarity provided Sec 6.5.2 South African National Clinical Trial Register: – Removal of HREC responsibility	May 2026

Contents

Acronyms

The following represent commonly used terminology and abbreviations/acronyms:

Term/Abbreviation	Definition
AIO	Authorised institutional official
AREC	Animal Research Ethics Committee
BESEC	Biological and Environmental Safety Ethics Committee
CAB	Community advisory board
CAMS	Complementary and alternative medicines
DALRRD	Department of Agriculture, Land Reform and Rural Development
DTA	Data Transfer Agreement
NDoH 2024	South African Guidelines on Ethics in Health Research Principles, Processes and Structures, 3rd ed., 2024
GCP	Good Clinical Practice
HBM	Human biological material
HREC	Human Research Ethics Committee. There should be a clear distinction between "health" and "human".
IACUP	Institutional animal care and use programme
IHHRP	Institutional human health research programme
MHCA	Mental Health Care Act 17 of 2002
MoA	Memorandum of Agreement *(i.e., broad outline of planned collaboration)*
MoU	Memorandum of Understanding *(i.e., intent to collaborate)*
MTA	Material Transfer Agreement *(i.e., regarding human biological material)*
NDoH	National Department of Health *(of the Republic of South Africa)*
NHA	National Health Act, Act No 61 of 2003
NHRC	National Health Research Committee
NHRD	National Health Research Database
NHREC	National Health Research Ethics Council *(under the auspices of the NDoH)*
NSPCA	National Society for the Prevention of Cruelty to Animals
Organisation/institution	The organisation/institution with responsibility for the REC
PHRCs	Provincial Health Research Committee
REC	Research Ethics Committee, referring to both ARECs and HRECs
SA GCP 2020	South African Good Clinical Practice: Clinical Trial Guidelines, 3rd ed. 2020.
SAE	Serious adverse event
SAHPRA	South African Health Products Regulatory Authority

Term/Abbreviation	Definition
SANCTR	The South African National Clinical Trials Register
SANS 10386:2021	South African National Standard: Care and Use of Animals for Scientific Purposes, 2nd ed., 2021
SAPS	South African Police Service
SAVC	South African Veterinary Council
SI	Serious incident
SOP	Standard Operating Procedure
ToR	Terms of Reference

Chapter

1 Ethics in Research

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

1.1 Introduction

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). Section 27(1) of the Bill of Rights guarantees the right of access to health care services, while section 12(2) 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[3] without their informed consent'.*

The National Health Act 61 of 2003 (NHA) provides statutory authority for governance of 'health research' and the necessary research ethics regulatory infrastructure, as determined by the National Health Research Ethics Council (NHREC).

The NHA defines 'health research' to include any research which contributes to knowledge of-

a) the biological, clinical, psychological or social processes in human beings,
b) improved methods for the provision of health services,
c) human pathology,
d) the causes of disease,
e) the effects of the environment on the human body
f) the development or new application of pharmaceuticals, medicines, and related substances, and
g) the development of new applications of health technology

In line with its statutory obligation to develop and promote norms and standards for research, the NHREC intends these guidelines to provide the minimum national benchmark of norms and standards for conducting responsible and ethical research in South Africa. The guidelines are intended to be as inclusive as possible, so that researchers in all disciplines who involve human participants or use animals in research will find assistance in these guidelines (see also 1.7).

The core ethical principles outlined in these guidelines apply to all forms of research and methodologies that involve living human participants and use of living animals, ranking the safety, welfare and health interests of both humans and animals as paramount. Health and safety issues include those that may arise in the environment of research, e.g., viruses, parasites, bacteria, as well as quality of the air, water, and land in the environmental context.

The ethical principles apply also to research involving use of human biological materials and data collected from living or deceased persons, including human embryos, fetuses, fetal tissue, reproductive materials, and stem cells.

Research that relies exclusively on information that is publicly available and does not require gate keeping, site or platform permission, or that is accessible in terms of legislation or regulation may need to undergo formal ethics review, depending on ethical considerations relevant to the research.

Research involving observation of people in public spaces (including virtual 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

[3] The 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'.

- dissemination of research findings does not identify individuals or groups
- the researcher does not make audio, or visual recordings

Quality assurance and quality improvement studies (audits), programme evaluation activities, performance reviews and consumer surveys 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.

For conducting clinical trials with human participants, this document must be used in conjunction with the South African Health Products Authority's Good Clinical Practice: Clinical Trial Guidelines (2020) 3rd edition or its successor.

For clinical and pre-clinical trials in animals, including both target and model species, this document must be used in conjunction with any requirements of the South African Health Products Authority (SAHPRA) [veterinary-portal].
Complementary use of applicable Veterinary Good Clinical Practice guidelines, such as the VICH GL9 (GCP) 2000 of the European Medicines Agency [pdf] or later version available online is advised.

1.2 NHREC as regulatory authority

The National Health Research Ethics Council (NHREC) takes its authority from section 72 of the National Health Act (NHA). The NHREC was established in 2006.

In terms of its statutory authority, 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 human 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.

The NHREC firmly supports ethical practice of health and health-related research and asserts that research should reflect the attributes of the philosophy of ubuntu, such as but not limited to respect for human dignity, compassion, and harmony. These attributes should be pursued together with the research integrity core values of scientific merit, openness, distributive and social justice, care, beneficence and nonmaleficence. Of highest priority for the NHREC are continuous refinement of ethics guidelines, ongoing support of RECs, and strengthening of review and oversight processes to protect the rights, safety and welfare interests of humans involved in research, particularly vulnerable participants; and to protect the welfare and safety interests of animals used for scientific purposes; as well as to protect safety and other interests of researchers.

Researchers should be familiar with legislation, regulations, and other binding instruments relevant to research. See Appendix A1.2 *List of statutes, regulations, and other instruments*.

1.3 The research context

South Africa provides a rich context for health and health-related research because of its diverse and advanced health care and research infrastructure, skills, and expertise. The country is also characterised by a high burden of communicable and non-communicable diseases, including those associated with poverty and underdevelopment, creating the need for a broad spectrum of health and health-related research. See the National Department of Health's Strategic Health Plan 2020/21-2024/25 or its successor[4].

[4] https://health.gov.za/strategic-plans/.

South Africa is often viewed as 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.

To ensure that South Africa's people and animals 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 reviewed and strengthened to ensure that the appropriate ethical standards are upheld.

It is expected that all researchers who conduct research in South Africa comply with these guidelines.

South Africa recognises and protects freedom of expression (section 16 of the Bill of Rights), which includes academic freedom and freedom of scientific enquiry (section 16(1)(d)). High quality scientifically sound ethical research relies on the ability to exercise the freedom to research, write and speak robustly and professionally, without fear or favour on any topic including the impact of science on society. Exercise of these freedoms is conditional on the responsibility to conduct and communicate scientific work with integrity, respect, fairness, trustworthiness, and transparency, and to consider the consequences of new knowledge and its application.[5]

The research context received an additional layer of regulation due to the enactment of the Protection of Personal Information Act 4 of 2013 (POPIA), which regulates processing of personal information in response to development of measures to protect privacy. POPIA provides guidance on how personal information may be processed.

Research activities are classed as a 'legitimate interest' in terms of the Act, which means that some flexibility is built in, provided the protective measures are adhered to. Researchers and RECs must pay careful attention to protocol measures to protect privacy and confidentiality interests.

POPIA stipulates that the right to privacy includes 'protection against unlawful collection, retention, dissemination and use of personal information' (Preamble to the Act). Consent to processing of personal information in terms of POPIA requires a 'voluntary, specific, and informed expression of will', separated from the consent to participate in research.

In general terms, a participant 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 participant, 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.

1.4 Research involving human participants

Every organisation/institution, health agency and health establishment at which health research involving human participants, must establish, or have access to a registered Human Research Ethics Committee (HREC) (NHA section 73(1)).

1.5 Care and use of animals for scientific purposes

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 section 73(1)).

1.6 Ethical research review

The NHA (section 72(1)) requires that protocols and protocols to conduct 'health research' must undergo independent ethics review before the research is commenced (see 5.3).

Retrospective review and approval of protocols are not permitted.

[5] Statement on Academic Freedom from the Academies of Science of South Africa (ASSAf) S. Afr. j. sci. vol.106 n.3-4 Pretoria Mar./Apr. 2010.

Ethics review of proposed 'health research' must be conducted by the HREC or AREC that is registered with the NHREC (section 73(2) of the NHA).

RECs must review research protocols prospectively to ensure that they meet the accepted ethical norms and standards before research commences, using these Guidelines as a minimum benchmark (NHA section 73(2)(b)).

RECs must ensure that research protocols stand up to scientific and ethical scrutiny appropriate to the disciplines concerned.

The review process entails an independent and objective assessment of the potential effect of the proposed research on potential participants, animals, or the environment, e.g., plants used in health research, and on the general day-to-day functioning of the infrastructure that provides the site or context for the research.

The review must ensure that the ethical and appropriate scientific standards are maintained to

- protect participants from harm by minimising risks of harm to the extent possible and then balancing the risk of harm against 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 and, where appropriate, expect them to provide adequate and suitable support, including referral to appropriate free support services when potential harm might result from participation in the research activity
- promote important social and ethical values.

Ethics review is not about obstructing scientific progress or innovative research. Rather, the review process should promote ethical conduct of research by encouraging co-operation between RECs and researchers to ensure a comprehensive and frank assessment of the ethical implications of protocols so that the environment, human participants, animals, and researchers can be protected appropriately.

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.

1.7 Purpose and status of these Guidelines

These Guidelines are intended to provide the minimum national benchmark of norms and standards for conducting responsible and ethical research in South Africa.

The Guidelines address health and health-related research broadly to achieve the specific goal of providing guidance for all research involving human participants or the use of animals (mostly vertebrates and higher invertebrates) to be conducted in accordance with the ethical norms and highest standards. This is consistent with the understanding that research means a systematic collection, synthesis and analysis of information undertaken with the goal of producing new knowledge or improved understanding of being human in its environment or context.

These Guidelines speak broadly to health research, i.e., research that relates to health or will have an impact on health. The effect of health research on the environment is also considered. The scope includes research carried out in a health care facility, as well as research conducted in any other environment where the wellbeing of humans is investigated, including research conducted in terms of disciplines such as anthropology, history, linguistics, i.e., research ethics is applicable to every discipline. The Guidelines do not advocate the so-called 'medical model' of ethics review for general use. Where 'medical' sounding guidance is provided, this is aimed specifically at clinical research, rather than generally.

In general terms, research involving humans 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, seeking new knowledge. However, researchers are increasingly also using qualitative methodologies for health-related research, as is the case with the humanities, social and behavioural sciences, which use both qualitative and quantitative methods as well as analytical frameworks, all of which may be aimed at contributing to knowledge about being human in the environment and other contexts.

Research that uses animals for scientific purposes (e.g., pre-clinical research), including testing (e.g., vaccines, drugs, medical devices, etc) and health-related education and training (e.g., surgery, anatomy, physiology, clinical skills, etc.), and research that uses animals aimed at improving human health is included in the scope of 'health research'. These Guidelines exclude use of animals for cosmetic testing.

The minimum benchmark for research that uses animals is found in the South African Bureau of Standards SANS 10386:2021 2nd ed. Whilst these Guidelines endorse the ethical principles laid down in SANS 10386:2021 2nd ed., they sometimes increase required levels of scrutiny or additional considerations.

These Guidelines are legally binding: their authoritative status originates in section 72 of the NHA, which requires the NHREC to develop norms and standards for research with human participants, research involving use of animals, and clinical trials. The statutory authority that underpins the Guidelines is further elucidated in the associated regulations, especially R.719 Regulations relating to research with human participants; GG No 38000 19 September 2014; Clause 2 which reads:

> *'Health research that involves human participants must…*
> *(a) comply with the Department of Health national ethical guidelines for research with human participants at a minimum...'*

and

R.839 Regulations relating to the National Health Research Ethics Council; GG No 33574 23 September 2010; Clause 1 which reads:

> *'Animal research means the conducting of research on animals for human health research benefit...'*

1.8 Structure of these Guidelines

Chapter & title	Description
Chapter 1: **Ethics in research**	Introduces the broad context of health research ethics in South Africa.
Chapter 2: **Guiding principles for ethical research**	Discusses the broad principles underpinning research that inform the norms and standards, as well as the procedures and decision-making processes for ethical review of research proposals.
Chapter 3: **Norms and operational processes for ethics review**	Provides detailed explanation of the applied norms and standards, as well as operational processes and procedures for ethics review and decision-making to promote responsible, ethical and safe research.
Chapter 4: **Human and animal biological material and data for research**	Discusses use of human and animal biological material and data for research, then databases, storage and access, followed by genetic and genomic research.
Chapter 5: **Research Ethics Committees**	Discusses the governance frameworks for, role of, education and training, SOPs and compliance matters related to RECs.
Chapter 6: **Health Research Ethics Infrastructure**	Describes the NHREC, institutional RECs, registration & audits, as well as statutory entities related to the 'health research' ethics infrastructure for South Africa.
Appendices	Glossary and references, HREC samples and examples, and AREC examples.

Chapter

2 Guiding Principles for Ethical Research

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 protocols that involve human participants and use of animals for scientific purposes.

2.1 Ethical principles

2.1.1 Broad ethical principles applicable to participation of humans in research

2.1.1.1 Beneficence[6] and non-maleficence

These terms refer to the ethical obligation to maximise benefit and to minimise harm and require that the anticipated risks of harm posed by the research must be reasonable, considering anticipated benefits; that the research design must be scientifically sound and ethical; and that the 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 or at least understand what it means to be human, even if only as a medium to long term goal. If the research is not directed towards this goal, then it is unlikely to be ethical. The intention is not to discourage 'blue sky' research,[7] but rather to prevent research which is futile.

2.1.1.2 Distributive justice (equity)

This phrase signifies 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 equity is expressed in the research context. 'The principle of justice holds that particular individuals, groups or communities should neither bear an unfair share of the direct burdens of research participation, nor should they be unfairly excluded from the potential benefits of research participation.'[8] 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.

2.1.1.3 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 (autonomy). 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, privacy and confidentiality, wellbeing, and safety interests of all research participants are primary concerns in research that involves human participants. Autonomy includes the ability to deliberate about a decision and to act on that decision.

Usually, recruitment of participants focuses on the individual who chooses autonomously whether to participate. The SAN Code of Research Ethics (2017) explains the importance for the research context of the moral values of respect, honesty, justice and fairness, care, and due process for the research context. The African philosophical concept of Ubuntu incorporates these values. as well as social and health equity, distributive and social justice, and reciprocity, which feature strongly in public health approaches. Social science principles, e.g., respect for cultural diversity, stakeholder engagement, and local traditions and schools of thought are also relevant. Social context is also emphasised insofar as research participants choose whether to participate from within their community context, including consultation with others.

Interests of participants should usually outweigh the interests of science and society (see 3.1.7). This view is expressed by the requirement that the

[6] The principle of beneficence includes beneficence (do good), non-maleficence (do no harm), autonomy (the freedom to choose freely, where they are able), justice (ensuring fairness).

[7] Blue sky (or blue skies) research refers to self-initiated, curiosity driven basic research to expand knowledge and further understanding, without a clear idea of its practical implementation.

[8] TCPS 2 (2022), 66.

balance of risk of harm and likelihood of benefit should favour participants. Sometimes public health approaches may require more attention to societal interests, e.g., when clinical research is conducted during a public health emergency, it is done for the greater good (see 3.3.2.2 for details).

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.

2.1.2 Broad ethical principles applicable to use of animals for scientific purposes

Equivalents of the principles of beneficence and non-maleficence, distributive justice, and respect (described above regarding human participants), can be described for animals used for scientific purposes. The principles of 'Replace', 'Reduce', 'Refine', 'Respect' and 'Responsibility' serve the welfare and safety interests of animals (see 3.2).

These Guidelines recognise the inherent ethical dilemma that, on one hand, use of animals for scientific purposes[9] is regarded as indispensable to support science that could lead to reduction of human and animal suffering. On the other hand, these animals are sentient beings capable of experiencing emotional and physical pain and suffering associated with their use for scientific purposes.

2.2 Role of ethical principles

Ethical principles assist RECs to identify and protect the interests of research participants and animals in a variety of research contexts and to promote development of high-quality knowledge that may benefit future generations. Persons who conduct research in South Africa are expected to be guided by these principles which underscore responsible and ethical research conduct.

[9] SANS 10386:2021 2nd ed. refers to 'the use of animals for scientific purposes', and includes ALL use of animals in science, not just research. It includes research, teaching & training, field trials, product testing, diagnosis, production of biological substances or responses, environmental studies.

Note: Detailed discussion about how to apply these principles is in 'Chapter 3: *Norms and operational processes for ethicsreview*'.

2.3 Key norms for ethical research with human participants

2.3.1 Relevance and value

Research should be relevant and responsive to the needs of the people of South Africa. The protocol 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 wellbeing 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. The expectation is that the discipline's body of knowledge will be enhanced.

It should be noted at this point that an additional body of knowledge is implicated by and relevant to ethics review of the protocol, viz., research scholarship, which currently seldom receives much attention during the review process. The scientific contribution of any research project should be explained in terms of the anticipated contribution to expansion of the knowledge base concerned, as well as to enhancement of distinct research designs and complementary approaches. In light of the increasing use of interdisciplinary thinking, contributions to bodies of knowledge should be recognised as multi-tiered endeavours.

2.3.3 Stakeholder engagement

Researchers should involve and collaborate with stakeholders at an early stage and in a sustained manner, for the duration of the study, to enhance the scientific and ethical quality of a study. For example, co-researchers, academics and non-

academics such as community representatives, governmental departments. This approach fosters transparency and likely increases the acceptability of the research for the stakeholders. It also facilitates the possibility of harnessing stakeholder expertise where appropriate and serves to offset power differentials where these exist.

Engagement involves implementing actions to meet the needs and expectations of the different stakeholders and aims to achieve accepted outcomes for all parties, with levels of collaboration dependent on the prevailing circumstances. Engagement efforts may comprise of various activities, including awareness-raising initiatives for stakeholders, including 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. However, this does not mean that participants should be exposed to unacceptable risks of harm on the basis that 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.

When assessing considerations of risk of harm, and likelihood of benefit in social science research, RECs must be mindful that the nature and degree of such harms and benefits will vary, sometimes considerably, from those found in biomedical and health research studies. Instead of primarily involving potential 'biophysical harm, social science research often poses psychological harm, (e.g., emotional distress), moral harm, (e.g., deception), social harm, (e.g., stigmatisation), legal harm (e.g., loss of income)'.[10]

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 based on 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 (section 8 of the Constitution). Similarly, persons should not be targeted for research based unfairly on 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 study, as part of the commitment to an ongoing consent process. In some circumstances, research may not require prior consent (See also 3.1.10 and 3.2.2).

2.3.7 Ongoing respect for enrolled participants

Ongoing respect means that, once enrolled, researchers should continue to respect the autonomy of participants by ensuring that they continue to be willing to participate, and they know and understand their right to withdraw from the study. Researchers are also expected to demonstrate respect for the participants by continuing to monitor their welfare during the research period and, when appropriate, to inform them of results or findings of the research. The

[10] Hoffmann WA & Nortjé N (2019). Chapter 16: Ethics review framework and guidelines for social science research. (*In* Nortjé N, Visagie R & Wessels JS (*eds*.), 2019. *Social Science Research Ethics in Africa*. Springer Verlag. pp. 229-248. DOI: 10.1007/978-3-030-15402-8.)

ethical duty of confidentiality must be exercised rigorously throughout the life of the study.

2.3.8 Researcher competence and expertise

Researchers must be suitably qualified and technically competent (suitably trained and supervised, in the case of student researchers - see also 5.4.2.2) to carry out the proposed research. The principal investigator (PI) or research leader has primary responsibility to ensure the safety and wellbeing of participants, the scientific integrity of the protocol, research data management, and responsible implementation of that protocol. For international multi-site research, at least one (co-)PI must be physically in South Africa.

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.[11] In addition, researchers must 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.

2.4 Key norms for ethical research that uses animals

2.4.1 Animal welfare

In a study that uses animals

a) **'Replace'** refers to replacement of animals as sentient beings with non-sentient alternatives (absolute replacement), with less sentient animals (relative replacement), with animals euthanised for purpose of *ex vivo* research (partial replacement).
b) **'Reduce'** refers to use of the minimum number of animals that will provide statistically viable results to achieve the objectives of the study (i.e., the optimal number of animals), which has been determined in a scientifically justifiable manner, and which will not lead to greater suffering of an individual animal. 'Reduce' refers also to proper management of breeding programmes to minimise overbreeding of animals in captivity.
c) **'Refine'** refers to all considerations and efforts to optimise animal wellbeing during their use in a study and their exposure to associated activities, including proactive consideration and responsive implementation of mitigation strategies to minimise the likelihood, degree and duration of negative impact, as well as positive welfare promotion. Associated measures include, but are not limited to, assurance of competence, justified choice of animals and animal models, implementation of best available techniques and practices, an understanding of any and all potential or real study-related psychosocial harm (e.g., stress) and/or physical harm (e.g., pain) to the animal.

2.4.2 Social value

a) **'Respect'** includes respect for:
   i. the inherent or intrinsic value of animals as sentient beings, and accordingly the regard for and preservation of their dignity[12]
   ii. fellow research team member
   iii. animal owners and the broader community
   iv. the environment.
b) **'Responsibility'** refers to a culture of care amongst staff and students of institutions doing research that involves use of animals as an integral part of the broader institutional Animal Care and Use Programme. This involves sensitisation, training,

[11] Academic and research institutions usually have standardised methods of ascertaining and monitoring competence and integrity amongst their researchers. This guidance (above) is general rather than aimed at any specific discipline.

[12] Compare SANS 10386:2021 2nd ed., clause 4.2.4, where this is indicated as an obligation.

accountability, and institutional commitment to support ethical conduct of research. In this context, *'Accountability'* extends to public transparency in the tracking of institutional 3 Rs implementation, i.e. monitoring of animal numbers (i.e. *Replacement* and *Reduction*) and severity of harm resulting from procedures (i.e., *Refinement*) over time, including the consideration to make such information publicly available.

c) **'Regulation'** includes legal and ethical compliance as well as professional regulations, permissions, conventions, etc.

2.4.3 Scientific integrity

a) Data obtained during research must be **'Reproducible'** and reporting of data must be transparent, hence the importance of providing a scientifically sound design and methodology for review and approval.
b) The experimental setting must be **'tRanslatable'** to ensure generalisability and practical application of findings.
c) Motivation for a study should be **'Relevant'** and add value to the body of knowledge.

2.4.4 Interdependence of norms

The application and impact of the various principles on overall ethical conduct overlap. This can be seen in the following:

a) **'Reliability'** describes the overlap between animal welfare and scientific integrity, for example unwell animals do not yield scientifically reliable results.
b) **'Reckoning'** describes the overlap between scientific integrity and social values, which refers to accountability of the researcher towards the science and society.
c) **'Righteous'** describes the overlap between animal welfare and social values, implying that the right thing to do is to care for animal wellbeing and social norms.

Applying the principles discussed above, reveals that proper ethical conduct of research involves and is dependent on ethical considerations and corresponding responses during all phases of a study, from planning to conclusion.[13] It entails continuous feedback loops of observation, monitoring, reporting, consulting and learning, as well as modification. For example, ethical considerations are relevant to

- conceptualising, planning, and designing a study
- education, training and assurance of competence or researchers
- scientific and ethics review and approval
- monitoring and
- considerations during execution of the study
- reporting of unexpected adverse events or incidents, followed by learning and modification as appropriate
- post approval monitoring
- eventual reporting or publication
- record keeping.

Proper ethical conduct of research also involves appropriate communication, interaction, and consultation with relevant stakeholders, including between researcher and students, with experts, professionals, literature, oversight committees, research facility or site staff and management, etc.

[13] See also Brink CB & Lewis DI. (2023) The 12 Rs Framework as a comprehensive, unifying construct for principles guiding animal research ethics. ***Animals***,13(7):1128. doi 10.3390/ani13071128 [article].

Chapter 3

Norms and Operational Processes for Ethics Review

This chapter describes the 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 protocols. The chapter is relevant also for researchers (appropriate planning of protocols), funders (understanding implications of funding requests), potential participants (understanding the context under consideration). In what follows, the minimum benchmark for promoting responsible, ethical, and safe research is described and discussed.

Note: Details regarding norms and operational processes for research using animals may be found in '*The care and use of animals for scientific purposes*' SANS 10386:2021 2nd ed. or its successor. While the norms and procedures discussed below apply also to research with animals, as appropriate, the focus in this chapter is mostly on research with human participants.

3.1 Ethical basis for decision-making in the review process

Note: RECs should use the principles outlined in '*Chapter 2: Guiding principles for ethical research*' and elaborated below as the basis for evaluating research protocols. The guidelines should be readily accessible to researchers and other interested persons.

Key considerations for review and evaluation processes include:

3.1.1 Scientific design, aims and objectives

The ethical implications of the methodology and design of a research protocol must be reviewed objectively and independently (see 5.3). This process is not an opportunity for the REC to substitute its preferred opinion for that of the PI or research leader. If there are queries or disagreements about the ethics of the protocol, all efforts must be made to establish how best to assist the researcher to comply with the ethical standards.

Note: It is strongly recommended that scientific review should precede ethics review by the REC and that the report on the scientific review should accompany the protocol to the REC. Where the scientific review is not available at the time of ethics review, a conditional approval may be granted with final approval once scientific approval becomes available. This practice fosters transparency and avoids unnecessary duplication of work.

Ideally, before submission to the REC, persons with discipline specific expertise and experience should assess whether

- the proposed methodology and study design of the protocol are sound and align with the relevant disciplinary research standards
- the study is feasible for the circumstances, considering the available resources
- the importance and novelty of the scientific question are appropriate
- the stated aims and objectives are achievable and will likely produce valid outcomes
- the evaluation of relevant literature and previous studies are thorough and appropriate
- the researchers are suitably qualified
- the suggested research data management plan seems appropriate
- there is a results dissemination plan
- potential or existing conflicts of interest are addressed.

If separate scientific review capacity is not available, the REC must ensure that the abovementioned elements are satisfactorily explained in the protocol.

Where site permissions are required, e.g., from Provincial Health Research Committees (PHRCs) or appropriate Health Management, to conduct research in health care facilities, RECs must delay granting full approval until these permissions are received. This is to prevent research from beginning before the facility knows it will happen.

For research within the social context, i.e., including quantitative and qualitative research methods or approaches, the chosen theoretical paradigm and methodology must be assessed for suitability in light of the stated aims and objectives (see 3.3.1). The ethical implications of the selected design, methodology and research plan must also be analysed.

Scholarly disciplines and fields of research vary considerably regarding their conventions for scholarly review, including the stage at which the review takes place. These discipline variations must be considered by RECs. Duplication of scholarly peer review should be avoided if possible. However, the scholarly reviews must be rigorous and robust to ensure high standards of research are maintained. To this end, researchers should provide clear evidence of previous scholarly assessments and the outcomes where appropriate. RECs may request full documentation of scholarly reviews.

Note: 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, considering the aims and objectives and proposed methodologies. Underpowered quantitative studies may be futile (but see also 5.4.2.2). 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 (selection criteria) must be clear, explicit, and reasonable. Especially 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, excluding convenience. Inclusion and exclusion criteria have ethical implications (e.g., fairness of selection) and are not just of scientific relevance. For example, to exclude persons who are HIV positive is likely to be unfair if there is no relevant justification.

For research with animals, the protocol must justify the use of the chosen animals and the model for the study.

3.1.3 Selection of study population and sampling

The principle of distributive justice requires that no groups or categories of persons should 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, including differently abled 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.

For research with animals, the concern is to apply the principle of **'Reduction'**, i.e., to use as few animals as possible, without compromising scientific integrity.

3.1.4 Community and stakeholder engagement

Perceptions about respect for research participants depend to some extent on how the planned research is introduced or presented to the people where the research is intended to be carried out. Researchers who engage with members of the community or with selected stakeholders are preparing the way for a more positive reception than would be possible if the research were imposed unilaterally.

Whilst the terms 'stakeholder' and 'community' are sometimes used interchangeably, they are distinguishable in significant ways. 'Stakeholder' is a subset of 'community'; the latter term has different meanings for different contexts. Sometimes a community is identified geographically, other times, it is identified by association or age or other social determinant. Engagement with community members is intended to hear views from as many people as possible, so that the overall community contributes to shaping outcomes that align with their needs and aspirations. Such engagement requires that all reasonable steps are taken to

ensure that the views of those concerned, including those who are vulnerable and marginalised, are solicited. Community engagement always requires a level of humility on the part of the researchers as the community are the experts and holders of local knowledge (see also 3.3.5.2). The community engagement should build community contributors as partners, and the ethical standard of respect should be obvious in all engagement, including the process of community consent as well as individual consent of each participant.

For research conducted in a specific community, researchers should ensure that dialogue about planning and implementing research within the community takes place with a random but representative group of people to prevent perceptions of exclusivity, bias and elitism, depending on the circumstances. Depending on the nature of the study, such engagement may be seen as researching with the community rather than research on the community.

Stakeholder engagement, on the other hand, permits selected individuals or groups who have an interest or stake in the research to be involved for relevant reasons to provide a high level of impact or influence on the planned project. This form of engagement involves implementing actions to meet the needs and expectation of the different role players and stakeholder groups and aims to achieve accepted outcomes for all the parties with the level of collaboration dependent on the circumstances.

In communities where research occurs frequently, one or more Community Advisory Boards (CABs) may be established to serve as a hybrid of the two groupings.

The most inclusive level of engagement is one in which local stakeholders work collaboratively with the researchers and take part in decision-making processes throughout the research endeavour from conceptualisation of research design, planning, implementation, data collection, analysis, to evaluation of the process and even publications emanating from the study. However, not all types of research lend themselves to these aspirations.

Research protocols should demonstrate planning for the engagement of relevant stakeholders, where appropriate. In general, engagement should be inclusive, sustained across the lifecycle of the study, responsive to context and dynamic over time. Engagement should also be planned in writing, and appropriately funded. The intensity of stakeholder engagement should be tailored to key factors, such as the potential vulnerability of participants or community stakeholders, the risks of the study interventions or procedures, the complexity or novelty of the study design, the stigma associated with the condition under investigation where relevant, or other key factors.

The research protocol should show appropriate plans for activities and mechanisms to enhance collaboration and communication and that the researchers are striving to conduct research using a partnership approach. This process should engage community contributors as partners, and the ethical standard of respect should be obvious in all engagement activities, including the process of community engagement as well as individual consent of each participant.

An important consideration for the REC reviewer is to establish whether there is evidence that the local context has been considered. For example, whether researchers have considered the resources needed in that context for engagement. Researchers should be aware that planned use of virtual platforms and social media may exclude community members in the absence of appropriate local infrastructure. The protocol must explain how community engagement will occur despite the challenges.

REC review of engagement should preserve the need for researchers to be able to adapt their engagement strategies post-approval in a manner that is responsive to key contextual developments and stakeholder inputs.

3.1.5 Recruitment and enrolment

Recruitment strategies 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 protocol and

the recruitment materials should be included with the protocol, e.g., posters, flyers, advertisements, and recruitment via social media. 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 protocol 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. In the biomedical context a 'therapeutic misconception prevails when a patient/participant believes that the primary purpose of a trial procedure or intervention is to confer therapeutic benefit on her rather than to generate knowledge, thus confusing the purpose of research and the purpose of treatment.'[14] For social science research, the notion of misconception is better understood as research misconception, i.e., where participants may have misconceptions about the purpose, procedures or outcomes of the research, or the role of the researcher. An example of this would be where a learner is recruited to take part in a study on curriculum design and where the learner or parent may believe that by participating in the study, the learner would achieve better learning outcomes (immediately), or where the purpose of a study is presumed to eradicate a problem rather than to be a mere investigation thereof.

3.1.6 Research procedures

The planned research procedures should be described so that the rationale and details are clear to the REC. Procedures that are considered standard of care should be distinguished from procedures that are required only for research purposes. This distinction helps when evaluating the balance between the potential risk of harm and the likelihood of benefit.

Where researchers use emergent methodologies or plan to conduct their research in phases, they should provide the REC with a clear description or discussion of their research approach and design. Researchers must make it explicit that their research procedures are emergent and must provide the REC with a detailed plan for continuing review submissions to keep the REC up to date on emerging activities and procedures.

The protocol should explain whether specific research-related results, including incidental findings, test results and other findings relevant to the wellbeing of the participant, will be made known to participants.

The appropriate expertise and qualifications of researchers (including PIs, research assistants and others who will do the work of research, including recruitment), study and project leaders to perform the proposed research-related procedures should be assured, e.g., paediatric training is required for paediatric research procedures and educational training for educational research procedures.

Research should not disrupt routine practices at a research site or facility without having made prior arrangements with the parties involved. For example, in health care settings, study procedures should not affect the routine treatment and management of patients, the duties of staff, or the functioning of the facility. Asking nurses to conduct informed consent procedures on behalf of the researcher without prior negotiation with the relevant authorities is not acceptable. In the case of research conducted in other settings, e.g., educational settings, care should be exercised not to disrupt routine practices without the parties involved having made prior arrangements. Asking teachers to administer a questionnaire during class time without authorisation is not acceptable. Furthermore, research procedures should not draw resources from public facilities, i.e., anything that incurs a cost at the facility that is research-related, should be paid for from the research budget.

[14] See SA GCP (2020) 10.10.2.

3.1.7 Risk of harm and likelihood of benefit[15]

The ratio of risk of harm to likelihood of benefit[16] 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. 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 protocol 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, e.g., if emotional distress is a likely side effect of research procedures, arrangements to facilitate access to assistance should be made
- the researcher should provide a distress protocol for studies that could trigger emotional trauma or psychological distress.

Note: Counselling and support services should be free to participants who need them, locally accessible and where necessary, immediately accessible to the participants who need these services. Where the referral pathway is to a public health centre, this must be negotiated carefully with the centre, because the referral presents an example of risk of harm (being introduced by research), which must be offset by use of public health resources and funds. The influx of research participants may adversely affect access to these services for patients who are not part of the research.

- anticipated harms should be minimised by preventing occurrence (i.e., mitigate risk of harm by having a plan to manage, eliminate, or limit setbacks) as far as possible. If the harm should occur, appropriate remedial interventions should be implemented.

The nature of anticipated 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. Importantly, the researcher should include a statement in the protocol that indicates a process of self-assessment of risk to self in conducting the study.

3.1.8 Reimbursements and inducements for participants

Reimbursements serve to repay proven costs of participants who must spend to participate, e.g., on transport or childcare, etc. Sometimes these amounts are given in advance of the study and sometimes proof of expenditure must be provided before a reimbursement is given. Inducements, on the other hand, are a tool to encourage participation by the intended target group. They may be healthy people less interested than those affected by the topic of the study, or they may be a bit reluctant because they regard the topic as sensitive and thus a bit scary.

3.1.8.1 Reimbursement payments

Participants should not incur expenses to take part in research. Consequently, researchers should budget to reimburse expenses incurred by participants, e.g., for travel, refreshments, cost of childcare, depending on the circumstances. Participants should be compensated also for the time spent on study activities, at an hourly rate equivalent to that for unskilled labour in South Africa. In addition, participants should receive modest increases in amount for degrees of inconvenience that are associated with participation, i.e., more inconvenience should merit a little more reimbursement than is given for minimal inconvenience.

A fair rate of reimbursement should be calculated using the Time, Inconvenience and Expenses (TIE)

[15] Benefit may be understood as the product of 'beneficence' i.e., something that produces good or helpful results or effects or that promotes well-being.
[16] Known as 'harm-benefit analysis' in animal research.

method[17] to determine the cost to participants for time expended, inconvenience and expenses associated with research participation. This method anchors payment for time at the current hourly rate for unskilled labour in the marketplace, regardless of whether the participant is employed. This means that not only employed people are eligible for reimbursement.

Note: If no travel or other expenses are incurred, reimbursement for expenses is not required; however, a time and inconvenience payment may be justifiable. Reimbursement of expenses should not be confused with a recruitment incentive or inducement.

Where reimbursement is justified, researchers must submit planned payment schedules and amounts together with a justification to the REC, when applying for ethics review. RECs should exercise caution against taking an unreasonably patronising view of the rate of reimbursement. In the context of endemic poverty, it is tempting to regard the reimbursement money as an inducement towards enrolment. RECs should be cautious about adopting this view which is potentially offensive to adults who are offering themselves to assist with research. The protocol and 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, payments for time could be paid to the party expending their time undertaking study procedures, where appropriate, and payments for expenses should be paid to the party incurring the expense where appropriate, e.g., the accompanying parent or guardian, with the input and guidance of the research ethics committee.

[17] NHREC (2012). Payment of trial participants in South Africa: Ethical considerations for Research Ethics Committees (RECs) [PDF]. With effect from 1 March 2024, the national minimum wage changed from R25,24 to R27,58 per hour - to be adjusted annually, as published.

3.1.8.2 Inducements

Inducements (also known as incentives) may be offered in justified circumstances where, e.g., recruitment is anticipated to be difficult, to encourage participation and to express appreciation by offering gifts over and above re-imbursement of expenses and compensation for time and inconvenience. Inducements are not necessarily cash but may take other forms like data or airtime vouchers, food vouchers, etc.

Importantly, an inducement should not unfairly influence an informed choice about whether to participate or undermine a potential participant's ability to assess the risk of harm. This is especially important for Phase I and First in Humans clinical trials where the circumstances may involve healthy people being offered significant payments over and above those outlined in the TIE method.

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. Respect for the autonomy of potential participants must be kept in mind, in addition to considerations of fairness. If the REC is doubtful about the situation, factual evidence of willingness to assume the risk of harm should be asked for from the researchers. In other words, preparatory work for such trials may be appropriate to ensure suitable protection of participants' interests. (See also 3.2.1).

3.1.9 Participants' interests in privacy and confidentiality

Every person has the constitutionally protected right to privacy. The right to privacy is an aspect of the principle of autonomy. In the research context, a participant retains the right to control access to their personal information, i.e., for their personal information to be private unless they give permission for others to access it, or if the law requires others to access it. This means that access to personal information for research purposes, whether directly or via third parties, without consent of the participant, is not permitted. Therefore, a protocol must explain how these constitutionally protected rights will be managed and protected during the research.

Management of information to protect participants' interests requires an assessment of whether and how research data might be disclosed carelessly or inadvertently by researchers or others, posing a risk of harm. Disclosure of research data that reveals a participant's identity or research category, could make them vulnerable to harm (see also 2.3.7).

The ethical duty of confidentiality is the tool for protecting the privacy interest of the research participant. The duty of confidentiality falls on the researcher to whom the personal information of the participant is entrusted, supported by the institution or entity that provides infrastructure. Researchers must make every effort to prevent anyone outside of the study being able to connect individual participants with their responses. Appropriate measures must be put in place to prevent disclosure of information that might identify the participant (inadvertently or not) either during the research period or afterwards, including when disseminating results or findings.

It should be noted that research records including informed consent documentation may be requested by interested parties via application in terms of the Promotion of Access to Information Act 2 of 2000 (PAIA).

It should be noted further that informed consent documentation may be subpoenaed during litigation.

3.1.9.1 The Protection of Personal Information Act

The Protection of Personal Information Act 4 of 2013 (POPIA) provides guidance on whether and how personal information may be processed. In so doing, it adds to the usual ethical principles that protect privacy and confidentiality interests. The Act seeks to balance the individual's right to privacy against the public interest in benefiting from locally conducted cutting edge research (based on the ethical principle of autonomy and section 71(1)(b) of the NHA).

POPIA stipulates that the right to privacy includes 'protection against unlawful collection, retention, dissemination and use of personal information' (Preamble to Act). Consent to processing of personal information in terms of POPIA requires a 'voluntary, specific, and informed expression of will' (section 1 of POPIA), separated from the consent to participate in research.

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.

In general terms, a participant should know what personal 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 participant, whether it will be shared with others and why, whether it will be shared with third parties inside South Africa and why, whether it will be sent outside South Africa and why. The participant should agree to these terms.

Note: The sections of POPIA that affect specific parts of the guidelines are discussed in those parts.

3.1.9.2 Anonymity and confidentiality

In principle, a study should not collect identifying information of research participants unless essential to the study protocol. Anonymous information protects confidentiality quite well but may still be 'interpreted' or 'inferred' by third parties and lead to partial identification of individuals by motivated parties.

Various methods of preventing identification of participants exist. A brief overview of some methods and associated terms is provided.

Anonymous data are collected without identifiers. Collection of anonymous data from research participants means that the study either does not collect any identifying information of individual persons, e.g., name, address, email address, etc., or it cannot link individual responses with participants' identities. This method is useful for some types of research but not for others, and especially not for studies where results or findings are intended to be shared with participants. Anonymity should not be promised if personal identifiers are collected.

Anonymised data are collected with identifiers but then permanently stripped of the identifiers, which means the data cannot be linked back to the participants. Clearly, the same sorts of limitations for feedback exist.

Coded data are stripped of identifiers, substituted by codes.

De-identifiable data are collected with identifiers, which are separated after collection and retained separately in the custody of a person not associated directly with the study. This is called de-identification. This method permits later re-identification and linking to participants for specific purposes.

Note: POPIA uses different terms; please consult the Glossary.

3.1.9.3 Participant-initiated waiver of anonymity

Sometimes participants want to be identified and acknowledged publicly for contributing to research studies. In some disciplines, e.g., history, participants may request to be identified because they want to be acknowledged for their role in an important event, or an elected public official is asked about how they are fulfilling their public mandate and it may be important to know who the participant is.

If a participant wants to be identified, this should be respected and considered, with due consideration of possible ethical and legal implications. However, if the research involves groups of participants, not all of whom hold the view that identification is desirable, then individual requests for identification should give way to protection of the group, as a manifestation of democratic reasoning.

3.1.10 Obtaining informed consent for research with human participants

The principle of respect (which includes autonomy) underpins the ethical requirement that a person should choose voluntarily whether to participate in research, based on information that allows an informed choice to be made. The process of providing the necessary information and of engaging with the person before they choose, 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 protocol is ethical. All the other elements discussed above (see 3.1) should also stand up to ethical scrutiny.

The type and nature of the planned research may necessitate different methods of obtaining informed consent. A characteristic of social science research is that informed consent is in most cases not a once-off event or action, but rather a trust-based process and relationship between the researcher and the research participants, groups and communities that extends over time; consent must be negotiated and renegotiated as the research continues and develops.

An important element of enabling an informed choice is the nature and quality of information made available to the potential participant, such as reading the information sheet and/or dialoguing with the participants, allowing for verbal consent, which is then recorded and transcribed or documented manually in the researchers' fieldnotes.

Adults, i.e., persons aged 18 years and older, may make independent decisions. However, they may wish to consult with family members or others in keeping with personal preference or cultural practices (see 2.1.1.3). Consequently, the process should permit sufficient time for consultation between the time recruitment is suggested and the time of deciding whether to participate. 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 3.2.5 and 3.2.2 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 free of bias
- the text
  - is in plain language and appropriate to the participants' level of understanding[18]
  - is translated into the language(s) best suited for the population and context of the study
  - has content, language(s) and procedures that are simplified and modified to accommodate any written or verbal language differences or impairments with which the participant may present
  - is free of jargon and unexplained acronyms

Note: If appropriate, the consent documents can be translated. Merely translating documents is insufficient to ensure that consent is informed, however: illiteracy is prevalent in some contexts, language dialects vary substantially across regions, some words and terminology are not easily translated, translated written materials may not be helpful to some participants, and professional translators are not content experts so mistranslation may occur. Consider whether it may be more useful to train a research assistant/interpreter who can explain information about the study verbally to potential participants in their language of choice and answer any questions they may have about the study.

  - is clear and explains technical terminology e.g., randomisation
  - 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 protocol
- 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 withdraw from participation at any time without explanation or prejudice
  - the purpose and nature of the research procedures and components
  - the research-related activities and procedures that the participant is being asked to consent to

Note: Social science research projects may use research designs that emerge during the research process rather than being fixed at the planning stage. This means 'the researcher cannot provide full information about the research design and process at the start of the project. It also means that social science researchers must be aware that informed consent is not merely a signature-on-a-piece-of-paper action, but a deep appreciation of the participants' contextual circumstances, including the use of culturally appropriate consent procedures. In some cases, oral consent may be more appropriate and/or acceptable than written consent'.[19]

  - 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
  - instances where a legal obligation to disclose information may arise
  - whether reimbursement for expenses is available
  - that sponsors of the research and regulatory authorities may inspect research records

[18] The Flesch-Kincaid 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.

[19] See Visagie R, Beyers S and Wessels JS (2019) Informed Consent in Africa – Integrating Individual and Collective Autonomy …for an in-depth discussion of informed consent and individual/collective autonomy for social science research in Africa. (In Nortjé N, Visagie R & Wessels JS (eds.), 2019. *Social Science Research Ethics in Africa*. Springer Verlag. pp. 165-179. DOI: 10.1007/978-3-030-15402-8_6.).

- who the researchers are and the nature of their expertise
- how the personal information of participants, including confidentiality of data collected during the research, will be protected
- who will have access to participants' information, biological samples and associated data, including whether samples will be shared with other researchers
- that participants may request that corrections to their information be made or that their information or samples be deleted or destroyed. In cases where withdrawal of samples and information is not possible, the potential limitations and consequences of not withdrawing samples and data from research should be explained
- whether feedback about the study will be provided and, if so, how it will be provided
- whether biological samples will be used for commercial benefit
- where relevant, whether incidental findings will be shared with participants
- 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)
- where relevant, information or resources relating to compensation for research-related injury of harm

Note: Consent alone is insufficient to justify processing of some types of personal information. Necessity must be evident too, e.g., information about a person's race or ethnic origin must be necessary for the research activity (section 29(a)) or for affirmative action purposes (section 29(b)); information about a person's health or sex life must be necessary for the research activity (section 27(1)(d)); information about a person's inherited characteristics (genetic makeup) must be necessary for the research activity (section 32(5)(b)); biometric[20] information about a person must be necessary for the research activity (section 27(1)(d)).

- a measure to probe understanding and comprehension of the information is planned (e.g., a teach-back method), and how it proposes to do so especially for very vulnerable potential participants.

It is sensible to ensure that the consent document includes a choice about whether data and/or samples can be used after the person's death, especially if it is possible that the person may die during the study. (See also 2.3.6)

The protocol should explain how data records (written, audio or visual) are to be secured, the length of time for which they will be retained and who will be responsible for storage and/or final disposal. The protocol 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 protocol. 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 confidentiality in a focus group is dependent on members of the focus group because they may disclose information outside the research setting, despite agreeing not to do so. For this reason, consent documentation should advise potential focus group participants to be cautious about disclosing personally sensitive information.

Where a clinical trial is proposed, additional information for prospective participants is required.[21] Any multi-phase studies or clinical trials involving lengthy, complex consent documents should adopt a thorough process of consultation with stakeholders to adapt the documents and to support research study

[20] Biometrics 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' (section 1 of the Act).

[21] See Department of Health (2020) South African Good Clinical Practice: Clinical Trial Guidelines 3rd edition (or its successor) at 2.5*ff*.

enrollers in explaining the study to participants in simple, understandable ways.

3.1.10.1 Waiver of informed consent

Sometimes the REC is requested to waive the requirement for informed consent or to alter informed consent requirements. 'Waive consent' means that the REC permits, by way of exception, the research to proceed without prior informed consent from participants, i.e., the usual requirement of informed consent is waived for specific reasons. Bear in mind that the REC is not obliged to accede to a request for a waiver. Any decision by the REC to grant a waiver of parental or guardian consent must be documented and must include the justification for the decision.

A waiver of consent (i.e., permission to conduct the research without consent) can be justified on two grounds:

a) if the waiver will not infringe any right of a participant, and obtaining consent is impracticable, or
b) if the rights infringement is minimal and is outweighed by the expected social value of the research, and obtaining consent is impracticable.

A waiver of consent is not automatic: it requires a researcher to apply to the REC for approval to use, for research purposes, someone's personal information or personal health information without obtaining consent from the individual. The application must explain why a waiver is requested and how one or other of the justification criteria above fits the circumstances described by the researcher. Commonly, waivers are granted for purely observational studies in public places and retrospective review studies of health care records where data are anonymous and no individual privacy or confidentiality interests are affected. Prospective observational studies might also be eligible for a waiver in circumstances that meet the required criterion.

A waiver of consent might be granted for research using archived human biological material (HBM) in circumstances where the HBM is anonymous and the data will also be anonymous and aggregated. However, waivers relating to genetic and genomic research should be approached cautiously, since re-identification of the original source of the HBM may be technically possible (see also 4.1.2), despite anonymity of HBM.

In the same vein, archived data (e.g., interview records, clinical records, etc) are also valuable research resources. A waiver of consent might be granted for such research in circumstances that include anonymity and aggregation of data.

A waiver of consent for preliminary or preparatory work to identify potential participants from records or other databases may be possible, including a waiver of parental permission in the case of potential minor participants (see also 3.2.2.2). The REC must assess the level of risk of harm associated with a waiver, which refers to the risk of harm flowing from researchers accessing identifiable private information and not to risk of harm concerning the whole research project.

An alteration of requirements for informed consent[22] (as opposed to a full waiver) is possible, e.g., when existence of a signed consent form might pose a risk of harm (breach of confidentiality) to the participant in studies involving illegal behaviour. The alteration may take the form of permitting unsigned informed consent documentation (see also 3.1.10.2c).

3.1.10.2 Formats of consent

The context of the research and surrounding circumstances are important considerations. The NHA requires written consent but does not consider circumstances that might not be suitable for written consent. To insist on written consent in all circumstances may sometimes present the potential for (social or legal) harm to participants, e.g., when sensitive research is to be conducted. The usual approach is to record written consent but, if it is ethically justifiable for the specific circumstances, then verbal consent may be approved. Usually, if verbal consent is permitted, a witness attests that the person did consent to participation after indicating his or her understanding of the information provided.

[22] See CIOMS 2016 p35 Modifications and waivers of informed consent [pdf].

Usually, the process of informed consent involves a face-to-face dialogue between the person designated to recruit participants and the potential participant, followed by the recording of written consent. Sometimes, however, the nature of the research requires electronic data collection, or the potential participants may have an impairment that prevents a personal face-to-face consent process, including provision of written consent.

Note: None of the alternatives to face-to-face personal consent discussed below may occur without sound justification approved by the registered REC. The justification for an alternate format of consent process must be evidenced by clear descriptions of why an alternative is justified in the circumstances (not based merely on convenience) and of how it will be managed so that the interests of the potential participant are properly protected.

a) Electronic consent

Research conducted electronically to collect the desired data uses methods of obtaining the equivalent of informed consent that have become settled in social and behavioural science research. The unique circumstances presented by the Corona virus pandemic served to accelerate use of digital processes towards virtual (online) data collection methodological approaches. This change has affected ways in which informed consent can now be obtained from potential participants.

Note: The nature of the research, e.g., large-scale national online social surveys, may propose means of providing consent not discussed below, e.g., by referring potential participants to a specific page where they indicate their consent by clicking a 'radio button'. If the REC is satisfied that this or another method is appropriate for the circumstances, then it may be approved. The reasoning of the REC leading to the decision should be recorded in the minutes of the meeting.

Where electronic consent is proposed, the research protocol must describe in detail the method and process for obtaining consent. Where relevant, methods of screening to filter out inappropriate participants must be described.

Electronic signatures are defined according to the Electronic Communications and Transactions Act 25 of 2021 (ECTA) as 'data attached to, incorporated in, or logically associated with other data and which is intended by the user to serve as a signature'. It represents an electronic functional equivalent of a paper-based signature with the same legal authority if it meets legal requirements and can include

- a typed name at the end of an email
- a scanned image of a handwritten signature embedded into a MS Word® document
- a digital signature.

Section 13 of ECTA creates an electronic signature accredited as authentic by the relevant authority, called an 'advanced electronic signature'.[23] This new concept is designed to reliably identify the person who made the signature now accredited. A handwritten (wet) signature is still valid. Only when an electronic signature is statutorily the preferred option is a person obliged to use an advanced electronic signature. [24]

A range of alternatives to deal with challenges to obtaining prior written informed consent has been proposed. Some international regulators have formally endorsed telephonic (verbal) and electronic informed consent as an alternative to paper-based informed consent. REC reviewers of research protocols must insist on a proper decisive description of how informed consent will be regarded as authentic.

The following electronic methods of obtaining informed consent are recommended:

- Telephonic recruitment for research that poses more than minimal risk of harm should be

[23] The Electronic Communications and Transactions Act (ECTA) creates a special type of electronic signature, known as an “advanced electronic signature” (AES), which is a particularly reliable form of signature. Section 1 of ECTA explains that an 'advanced electronic signature” means an electronic signature which results from a process which has been accredited by the Authority as provided for in section 37; “authentication products or services” means products or services designed to identify the holder of an electronic signature to other persons; section13(4) Where an advanced electronic signature has been used, such signature is regarded as being a valid electronic signature and to have been applied properly, unless the contrary is proved.

[24] E.g., the Credit Agreements Act requires an electronic signature, which indicates that an 'advanced electronic signature' (AES) must be used.

limited to screening for eligibility, followed by face-to-face informed consent, or virtual informed consent via an electronic platform.
- Telephonic research surveys are possible for minimal risk studies. Verbal agreement to participate serves as informed consent.
- For research that poses more than minimal risk of harm, different electronic platforms could be used to screen and obtain informed consent, on the one hand, and to collect data, on the other, e.g., electronic mail for screening and informed consent, and a different platform for data collection. Any suitably secure virtual platform could be considered.

Note: If more than one electronic platform is used, it is important to ensure that the link between the documents is maintained administratively so that the notion of 'a floating consent' does not occur. A floating consent is one that cannot be linked to its relevant research documentation. Whilst this may appear desirable for purposes of anonymity, it is most undesirable for purposes of audit and accountability.

- When using electronic/online platforms for research projects, always consider the availability of good connectivity, online security and accessibility, and the availability of funds for data amongst potential participants. If necessary, the budget must include provision of data for impoverished participants.
- Bear in mind that use of electronic/online platforms is potentially exclusionary for recruitment purposes and could lead to selection bias. Researchers should explain how inclusivity will be promoted.
- Compliance with the requirements of the POPI Act must be observed.

Whether electronic data collection always requires consent depends on the nature of the proposed research. Where data are obtained by observing online public electronic platforms, there is no expectation of privacy amongst those who communicate on the platform, which indicates that consent from individuals is unnecessary. Where access is gained to private electronic spaces – usually so labelled and requires permission from the domain-holder – individual admission to the space indicates that consent for data collection is necessary in line with the expectation of protection of privacy. Bear in mind, though, that social media platforms have different policies, especially for groups within, e.g., secret Facebook groups or WhatsApp groups, which means a 'blanket approach' is unwise.

b) Proxy consent

Proxy consent occurs when an authorised person provides consent on behalf of the potential participant (see 3.2.5*ff*). Proxy decision-makers for incapacitated adults are not permitted in South African law, unless the proxy is a court appointed curator or holds a statutory mandate to make health care decisions for the now incapacitated person in terms of section 7(1) of the NHA.[25] Neither the NHA nor the Mental Health Care Act 17 of 2002 (MHCA) makes provision for proxy decision makers for research purposes but both provide clear lists of proxy decision makers for treatment purposes.

Note: Incapacity may not be assumed but requires independent and objective assessment by appropriately trained persons (see 3.2.5*ff*).

The NHA specifies the sequence of legally appropriate treatment proxies as spouse or partner; parent; grandparent; adult child; brother or sister. The MHCA provides, in no specified sequence, that legally appropriate treatment proxies are spouse; next of kin; partner; associate (defined as 'a person with a substantial or material interest in the wellbeing of a mental health care user or a person who is in substantial contact with the user'); and parent or guardian.

[25] Section 7(1) of the National Health Act 61 of 2003: Subject to section 8, a health service may not be provided to a user without the user's informed consent. unless-
a) the user is unable to give informed consent and such consent is given by a person -
   (i) mandated by the user in writing to grant consent on his or her behalf; or
   (ii) authorised to give such consent in terms of any law or court order
b) the user is unable to give informed consent and no person is mandated or authorised to give such consent, and the consent is given by the spouse or partner of the user or, in the absence of such spouse or partner, a parent. grandparent. an adult child or a brother or a sister of the user, in the specific order as listed.

An ethical argument can be made to use the statutory 'treatment proxies' to give permission for the incapacitated adult to participate in research. Such argument complies with the principles for responsible conduct of research by relying on the constitutional principle of equality. To exclude a category of persons from research participation without adequate justification, would be unethical and unconstitutional (unfair discrimination). However, RECs must be careful to maintain the clear distinction between treatment and research. In unusual circumstances, e.g., major incident research (see 3.3.2), it may be ethically permissible to permit proxy consent also in a situation where no statutory proxy is available and the balance of risk of the likelihood of harm to potential for knowledge ratio justifies it. The proxy should be someone that the patient is likely to regard as suitable to make this choice e.g., an informal caregiver, a trusted friend, a pastor, or a relative (outside of the statutory categories).

Note: If the research participant regains capacity to make decisions, they must be informed that they have been enrolled in a research study. If they object to having been enrolled in the research study, this counts as a refusal to participate, and their data must be withdrawn. If the participant does not object, personal consent may be desirable depending on the length and complexity of the study.

Parents or guardians of children or adolescents with intellectual or mental impairments give permission for their children to choose whether to participate in research, i.e., the parent or guardian assists the minor child or adolescent. If the child or adolescent is unable to communicate at all or lacks the capacity to choose, then the parent or guardian should choose whether the child or adolescent may be enrolled. In other words, the parent acts as a proxy decision maker.

Where an adolescent remains intellectually or mentally impaired so that they cannot make a decision after reaching the age of majority, the situation is managed as for an adult with decision-making incapacity (see 3.2.5.2).

c) Deferred consent

Sometimes, the context merits use of deferred consent (also called delayed consent). Usually, the circumstances entail a temporary loss of decision-making capacity and a reasonably held prognosis that the person will regain the capacity within a predictable period, e.g., an unconscious patient in the Emergency Unit who is predicted to regain consciousness within hours. In cases where it is expected that the majority of patients will not recover and regain capacity (based on the existing data), deferred consent is not appropriate as a strategy. For example, resuscitation research where survival rates are typically low, or research with pathologies such as severe traumatic brain injury where a similar situation applies is not suitable for deferred consent.

Note: Deferred consent should be used only where the likelihood of obtaining personal informed consent after the research has begun is likely.
Deferred consent is personal consent, with an alteration of the requirement for prospective consent (see also 3.1.10.1).
Deferred consent is not an example of fully waived consent.

The REC may approve use of deferred consent if

- the proposed research is based on valid scientific hypotheses that support a reasonable possibility of more benefit than that offered by standard care, and
- the patient has a temporary loss of decision-making capacity, and
- there is a reasonably held prognosis that they will regain the capacity within a predictable period, and
- participation is not contrary to the medical interests of the patient, and
- when the patient regains capacity to make decisions, they must be informed that they have been enrolled in a research study i.e., deferred consent must be obtained. If they object to having been enrolled in the study, this counts as a refusal to participate, and they should be asked whether their data already collected must be withdrawn.
- If death of the participant occurs before deferred consent can be obtained, it should not be assumed that continued use of the data and/or samples is ethical. The deceased's wishes or those of their proxy or mandate holder should be ascertained.

RECs should ensure that a clear and full justification for the proposed used of deferred consent accompanies the research protocol.

Urgency is not by itself sufficient justification: all relevant principles must be observed as well as the individual circumstances of the patient to prevent inadvertent violation of personal or cultural values.

d) Consent for post-mortem research following natural death

The NHA section 66 permits post-mortem examination of the body of a deceased person if the person gave consent while alive or if a proxy (in accordance with the sequence of persons described in NHA section 66(1)(b)) consents, or the examination is necessary to determine cause of death. In other words, ordinarily, consent to post-mortem examination is required unless there is a societal or public health interest at stake, in which case the individual autonomy principle gives way to the collective societal interest. Protection for the individual interest remains in place because the post-mortem examination requires explicit written authority from the medical practitioner in charge.

The Guidelines on Post-mortem Testing for Natural Deaths were issued by the National Department of Health in October 2020 to facilitate collection of nasal swab samples immediately after death to obtain diagnostic cause of death information. However, the NHA section 67 read with section 64 clearly permits removal of tissue at post-mortem examinations 'for the purpose of the advancement of health science'. This would include collection of biopsies for pathogenesis research.

3.2 Vulnerability and incapacity

Vulnerability may be caused by limited decision-making capacity, or limited access to social goods, such as health care, education, or social support. Individuals or groups may experience vulnerability to different degrees and at different times, depending on prevailing circumstances. Minors (persons <18 years) are regarded as legally underage to protect them from their lack of life experience and knowledge. It is expected that life changing decisions for minors are made with the knowledge and assistance of their parents or guardians.

Persons may be factually incapable or less capable of understanding information and processing it to reach a decision about whether to participate in research. For example, this may occur because of brain damage or the effect of the aging process.

It is important to note the difference between legal incapacity and factual incapacity. No person may claim that, because a minor is factually capable, their legal incapacity should be waived. Legal incapacity prevails notwithstanding the existence of factual capacity.

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.

Historically, vulnerable groups and individuals in the research context have included children, the elderly, students, women, inmates, individuals with mental health problems, and those with diminished capacity for decision-making or self-determination. Vulnerable individuals or groups[26] require careful consideration to ensure that, where appropriate, additional precautions are put into place so that adequate protection of their rights and welfare interests occurs.

3.2.1 Contextual circumstances

Personal circumstances, such as mental or intellectual impairment, acute illness, advanced age, and pregnancy and childbirth may increase vulnerability. Vulnerability may be increased also by environmental circumstances, such as 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 having a properly considered understanding of the implications of doing so.

South Africa is home to many vulnerable communities. Where factors usually associated

[26] For further, more detailed, discussion on special classes of participants, see CIOMS International Ethical Guidelines for Health-related Research Involving Humans (2016) Guidelines 15-19 [pdf]; US Department of Health & Human Services, Office for Human Research Protections [portal].

with vulnerability are integral to the research, the protocol should demonstrate how vulnerability will be managed. In cases where the researcher is known to the community and speaks the local language and/or is accepted as part of that community, this may be seen as a positive element for the research context. Special care 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 the research merely because they are expediently accessible, while the research is feasible to undertake in a less vulnerable community, and
- the research is relevant to the needs and priorities of the targeted community, and that
- research participants know they will take part in research and that the research will be carried out only with appropriate consent[27] and
- careful attention should be given to the content, language(s) and procedures used to obtain informed consent.

To ensure optimal protection of vulnerable participants, the REC may impose additional protective measures for the informed consent process; or may require increased monitoring and interim reporting about participants' welfare; or may require post-recruitment reviews of the effectiveness of the protective measures imposed. Other measures may also be appropriate. If compliance with the additional measures is poor and participants' welfare is negatively affected, approval for the study may be withdrawn, temporarily or permanently.

Note: The decision to impose additional measures should flow from an assessment of the nature of the research and the factual circumstances of the potential participants and should be minuted. Additional protective measures should not be automatic just because a vulnerable group will be recruited; rather, the decision should be based on the circumstances of the protocol before the REC.
It is important not to conflate vulnerability of people with low-income areas or difficult socio-economic living conditions. Poverty does not necessarily make people prone to rash or reckless decision-making, e.g., an automatic assumption that poor people cannot choose responsibly whether to participate in research is disrespectful because it denies or at least doubts their autonomy. (See also 3.1.8) Factual evidence must support a decision that a community is too vulnerable to be invited to choose whether to participate in research.

Categories of participants discussed in this section are

- minors (children and adolescents)
- women
- adults with factual incapacity to provide informed consent
- persons in dependent relationships
- persons highly dependent on medical care
- persons with visual, auditory or mobility impairments
- inmates (called offenders when convicted)
- 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)

The legal status of minority protects young people under 18 years of age,[28] from their own emotional, cognitive, and physical immaturity and limited life experience. In other words, minors are legally incapable of performing legal transactions without assistance from a parent or guardian. However, children have the right to participate in matters that affect them. In terms of the NHA section 71(a)(iii) and (iv), a minor who is capable

[27] Note that the requirement of knowledge on the part of a participant does not mean that a REC may not approve a waiver of informed consent for types of research on retrospective reviews of records or such like (see 3.1.10.1).

[28] Section 28 of the Constitution; and section 17 of the Children's Act 38 of 2005.

of understanding 'consents' to treatment.[29] The Children's Act states that when a child is 'of such an age, maturity and stage of development, the child has the right to participate in any matter concerning that child'. [30] And that the child's views 'must be given due consideration'. 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.[31] 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 specific research procedures, without realising it could happen.

Note: RECs and researchers are strongly advised to pay careful attention to the use of terminology when describing potential research participants aged under 18 years, especially for research into sexual and reproductive health. As is discussed helpfully in the WHO's Guidance on ethical considerations in planning and reviewing research studies on sexual and reproductive health in adolescents (2018), a wide variety of terms is used to describe the same age range of minors (children and adolescents). It is important that a research protocol uses terminology that is appropriate to the local cultural context, so that ambiguity is avoided, and clear understanding is facilitated.[32]

Tension exists between the views that, in general, children and adolescents[33] 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 and adolescent population of South Africa, on the other. Resolution of the tension 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. Note that the parent or guardian does not choose for the minor who has factual capacity to choose,[34] rather, the parent or guardian gives permission for the minor to choose, i.e., to assent to participation (see also 3.2.2.2). Where a minor is very young (less than 7 years old) or is factually incapable of exercising a choice, then the parent or guardian chooses whether the minor should participate.[35]

In terms of POPIA, when personal information about a child (under 18 years) is to be processed

[29] Confusingly, the term 'consent' is used in the NHA, whilst it is well-established that a minor provides assent, unless there is a statutory exception to the rule, e.g. The Choice on Termination of Pregnancy Act 92 of 1996 (section 5(2)) permits a female of any age to terminate a pregnancy. See also 3.2.2.1 e).

[30] The Children's Act 38 of 2005, section 10.

[31] In some circumstances, e.g., when they are self-supporting and living away from home, a minor may be emancipated by their parents or guardian. This means that the minor is 'set free' to be legally and financially independent, despite not yet being 18 years old.

[32] The World Health Organisation (2018). Guidance on ethical considerations in planning and reviewing research studies on sexual and reproductive health in adolescents. J Adolescent Health, 64(4): 427–429. [article].

[33] **'Adolescent'** means an individual in their second decade of life. The World Health Organisation adolescent age range extends from 10 to 19 years, with 'early adolescence' ranging from 10 to 14 years and 'late adolescence' from 15 to 19 years. Definition of 'adolescent' based on Singh JA, Siddiqi M, Parameshwar P & Chandra-Mouli V (2019). World Health Organization Guidance on Ethical Considerations in Planning and Reviewing Research Studies on Sexual and Reproductive Health in Adolescents. Journal of Adolescent Health, 64(4), 427-429. [article].

[34] Section 10 of the Children's Act 38 of 2005. Note that a caregiver, a foster parent and a schoolteacher or principal are not guardians.

[35] 'Assent' describes agreement by someone who is legally incapable of providing consent. With minors, 'assent' refers to the child's agreement to participate in the research; with incapacitated adults, 'assent' has the same role: the person agrees to participate. In both instances, the person is assisted by a legally capable other: a parent or guardian agrees to their child's participation in research; a statutory proxy or a person with a mandate agrees for the legally incapacitated adult.

permission of a parent or guardian[36] is required before collection (section 35(1)(a)),[37] even when permission of a parent or guardian is not required for the activity that gives rise to the information, e.g., donating blood. A minor aged 16 years or more may donate blood without parental permission,[38] but POPIA requires parental or guardian permission to process the information.

The best interest of a child should be paramount in decisions that affect the child.[39] 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 easily accommodate a best interest analysis. Rather, the design draws on aggregates of information rather than focuses on individual interests. 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 using minors should be scrutinised carefully in case extra precautions or protective conditions are necessary.

In the research context, it has become convenient to ignore minority and to categorise young research participants as 'child' or 'adolescent'. While this categorisation is convenient, it is inappropriate to ignore the legal status of minority and its implications for the informed consent process, as described above. RECs must be alert to whether Informed consent documentation for minors includes documentation for parental or guardian permission. Exceptions to the requirement for parental permission are discussed at 3.2.2.4.

3.2.2.1 Minimum conditions for research involving minors

The following considerations are critical when RECs review protocols to involve child or adolescent participants:

a) Children and adolescents should participate in research when their participation is scientifically essential to the research. In the case of interventional clinical research, equipoise[40] should exist. Research should investigate a problem of relevance to children and adolescents. The protocol should provide sufficient information to justify clearly why children and adolescents should be included as participants.
b) Children and adolescents should participate in research only where such research poses acceptable risks of harm. That is, research involving children and adolescents should be approved only if:
    i. the research, including observational research, is not contrary to the best interest of the minor (child or adolescent), and
    ii. the research, including observational research, places the child or adolescent at no more than minimal risk of harm, where the probability and magnitude of possible harms implied by participation are not greater than those posed by daily life in a stable society or routine medical, dental, educational, or psychological tests or examinations; or
    iii. the research involves greater than minimal risk of harm but provides the prospect of direct benefit for the child or adolescent.

[36] Note a caregiver, a foster parent, and a schoolteacher or principal are not guardians.

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

[38] In terms of the Standards of Practice for Blood Transfusion in South Africa (7th ed. 2016).

[39] See also section 9 of the Children's Act 38 of 2005.

[40] '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.

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 child or adolescent, but has a high probability of providing significant generalisable 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

c) Research involving children and adolescents must be reviewed appropriately, including paediatric or child research specialists as reviewers. The NHA distinguishes research with children and adolescents as 'therapeutic' and 'non-therapeutic' research. The intention of this distinction is to place special emphasis on deliberation by the REC about the degree of risk of harm posed by a protocol and the likelihood of benefit to the child or adolescent participant. The 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 protocol 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 minors (children and adolescents) 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 (i.e., up to age 18 years) must include members with appropriate child research experience.

e) Children and adolescents should participate in research only when the required written permissions have been obtained. The general principle is that minors cannot agree to research participation without assistance of a parent or guardian because they are legally incapable (exceptions to the general principle are discussed in 3.2.2.4). This principle holds notwithstanding the exceptions created in the Children's Act for consent to medical treatment and surgical operations (section 129); consent to HIV-testing (section 130); and the exception for female minors created in the Choice on Termination of Pregnancy Act (section 5(2)). Consequently, in principle, the consent process for a minor's participation in research requires

i. Permission in writing from parents or legal guardian for the minor to be approached and invited to participate (in accordance with section 10 of the Children's Act)

ii. Assent from the minor in writing preferably (i.e., agreement to participate) if they choose to participate

iii. Permission in writing from parents or legal guardian for the minor's personal information to be processed (POPIA)

Note: Pregnancy and childbirth do not change the legal status of a minor mother. An unmarried minor mother may not agree, without assistance, to the participation of her child in research. 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, when the mother reaches the age of majority (18 years), she may consent to her child's participation in research. Marriage bestows majority and changes the legal status of a minor, even if the person is not yet 18 years old.

f) 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 or adolescent in the study.

g) The informed consent documentation must explain whether results of tests will be made known to child and adolescent participants and their parents. However, this does not mean that parents are entitled to know the outcome of all diagnostic and therapeutic interventions, especially as regards older adolescents. Whether this happens, depends to an extent on the socio-cultural context and the best interest standard.

h) The child or adolescent's interest in confidentiality, i.e., being identified or

identifiable without permission of the child or adolescent and their parent or guardian, must be respected.

i) 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 may be more important than those of adults who manifest a particular genetic condition.

j) Research involving children and adolescents must respect their evolving capacity to give consent. Adolescents who turn 18 years old during a study should be approached at the time of their birthday to confirm, as adults, that they consent to continue as participants. In cases where minors are permitted to decide independently whether to participate (see 3.2.2.4), the consent process should address how re-consent will be managed when they change status from minority to majority when they turn 18 years old. Similarly, in the case of large or 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. Nevertheless, the research protocol must evidence consideration of these matters.

k) 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 emphasises the right of a child (under 18 years) to participate in any matter concerning that child, provided they have sufficient maturity to participate appropriately and meaningfully (section 10), notwithstanding legal incapacity. This means that parents or guardians may not decide whether their minor child or adolescent should participate in research without their 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 child or adolescent to be approached to be invited to participate in the study. The factual decision whether to participate is that of the child or adolescent and not the parents.

Parental permission and the minor's decision must be consistent, i.e., if the child or adolescent 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 child or adolescent 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 (see 3.2.2).

Note: The fact that a parent is reluctant or withholds permission for their child or adolescent to choose to participate in a study, is not sufficient to persuade the REC to grant a waiver of parental permission. It is never necessary for an individual to be a research participant. (See 3.2.2.4.).

3.2.2.3 Children and adolescents without guardians

Many children and adolescents in South Africa do not have parents and very few have court-appointed guardians. Some of them are runaways who might be living on the street; others might be refugee or migrant unaccompanied minors. 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 for the informed consent process for research participation.

Note: For treatment purposes, substituted consent is based on necessity, it being in the child or adolescent's best interest to receive treatment. This reasoning is not applicable to the research context. It is never necessary for a child or adolescent to participate in research.

a) Justification for parent substitutes

Sometimes it may be ethically justifiable for a parental substitute to be part of the informed consent process. For example, important research that seeks to understand and improve

psychosocial, economic, and educational conditions for orphans and vulnerable children[41] to improve their future wellbeing usually involves no more than minimal risk of harm. Other research including clinical research may involve a minor increase over minimal risk of harm. To exclude a class of children and adolescents from research participation because, through no fault of theirs, they have no parent or guardian to assist them, seems unjust. Consequently, it may be ethical and reasonable to designate parental substitutes in such circumstances.

Note: Use of parental substitutes is not automatic and is not merely for convenience. Convenience is not an ethical principle. Careful deliberation and minuting of discussion must accompany any decision to resort to parent substitutes.

b) Pragmatic parental substitutes[42]

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 pragmatic guidance takes its lead from the Constitution, the Children's Act, the National Health Act, the Criminal Law (Sexual Offences) Amendment Act; the SA GCP 2020.

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

Note: If the proposed research holds out more than minimal risk of harm, there must be a compelling justification for why orphans should be included as participants, e.g., the research focus has special relevance for OVC and cannot be studied without their enrolment. The objective of considering a parental substitute in this manner is to ensure that a class of person is not unfairly excluded from what might be important research for persons in the class. That such a class might be excluded because of a lack of law on the point, is difficult to justify constitutionally. Hence, the ethical consideration of whether the spirit of the law might be followed (protection of vulnerability) while giving effect to the ethical justification for preventing unfair exclusion.

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

The child or adolescent expresses their will about whether to participate and thus expresses their will AFTER

i. the parent gives assistance with understanding (so the child or adolescent makes an informed choice);
ii. if no parent, then guardian: either court-appointed OR as indicated by the parent in a Will (section 27 Children's Act);
iii. 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);[43]
iv. if no foster parent (per iii above), then caregiver (section 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

[41] Arguably, OVC should be understood to include street children and runaways, both examples of vulnerable children.

[42] This pragmatic guidance is provided to temper the chilling effect of a literal interpretation of section 71 of the NHA, which otherwise might prevent important ethical research.

[43] Social workers should request that the Children's Court order expressly includes authority to give permission for a foster child to choose whether to participate in health research. Note a caregiver, a foster parent and a schoolteacher or principal are not guardians.

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');

v. if a minor is the caregiver in child-headed household and no supervisory adult (section 137 Children's Act), then a trusted adult nominated by the minor, including but not limited to social worker, community worker or teacher

Note: POPIA requires consent from parents or guardians for processing of personal information of minors (classed as special personal information). A separate consent document is required. POPIA does not address the vulnerability of OVC. Nor does the Act address the matter of independent consent by sufficiently mature minors.

3.2.2.4 Minors' independent consent

In special circumstances, e.g., for reasons of sensitivity, like discussion about sexual activities, substance or other forms of abuse etc., it may be desirable and ethically justifiable for children and adolescents (especially older adolescents 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. Reasons supporting the desirability of independent consent may include being able to recruit enough minors who otherwise would be unwilling to participate if they must tell their parents about the nature of the research to obtain parental permission.

Where researchers are planning an independent consent approach for minors, they should engage community stakeholders, e.g., community leaders, school leadership or even a community advisory structure such as a Community Advisory Board (CAB). Researchers should discuss the justification for independent consent based on the criteria above and seek to establish if this consent approach is acceptable within the community. Researchers should demonstrate to the REC that such engagement has taken place, e.g., a letter from the community stakeholder that confirms the view that independent consent is acceptable. The evidence sought is that independent consent from adolescents is an acceptable strategy to community stakeholders.

Preparation for evidencing an ethical justification for independent consent by minors may occur in the following manner:

- By prior engagement with participating community stakeholders, the PI or study leader can gather factual evidence of the community or relevant part thereof. Engagement could include outreach to relevant stakeholders such as canvassing the opinion of a representative body of parents (not the targeted parents), e.g., via schools.
- Factual evidence of such engagement must form part of the application to the REC. Factual evidence may be contained in a letter from a relevant stakeholder (like a community leader, school principal or a CAB) that confirms the view that independent consent is acceptable to the community.
- This evidence may ground a request for a waiver of parental permission (i.e., permission for older adolescents to choose independently whether to participate in research). Bear in mind that the REC is not obliged to accede to the request.
- If the REC accepts the ethical justification and the factual evidence of community 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 due to 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 *A2.1 Mandatory reporting of child abuse or neglect* for guidance.)

a) Reporting obligations for abuse and neglect

The Children's Act section 110 requires a broad range of persons who reasonably believe 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. This broad range includes especially medical practitioners, nurses, psychologists, social service professionals, social workers and members of staff or volunteer workers at drop-in centres or child and youth care centres. However, any person may report if they reasonably believe the child to be suffering abuse.

b) Reporting obligations for under-age sexual activity

The age at which a minor 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. Any adult (person older than 18 years) who engages in sexual activity with a minor younger than 16 years commits the crime of statutory rape and may be prosecuted. The Sexual Offences 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 early adolescents (12 to 15 years) and older adolescents (16 and 17 years). For adolescents, the situation is as follows. The Teddy Bear Clinic case[44] found criminalisation of consensual sexual acts between adolescents aged 12 to 15 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.

Consensual sexual acts are not criminal offences and are not reportable when they occur between adolescents aged 12 to 15 years, or between an adolescent aged 12 and one aged 16 or 17 and the age difference between them is not more than two years. Sexual acts with adolescents aged 12 to 15 years by an adult, even if consensual, are criminal offences and are reportable. Sexual acts with children younger than 12 years are always criminal offences and reportable as rape.

The Sexual Offences and Related Matters Amendment Act 13 of 2021 introduced changes to the reporting obligations towards 'vulnerable persons' that are important to note:

Sexual offences committed against 'vulnerable' persons must be reported by a person 'who has knowledge, reasonable belief or suspicion that a sexual offence has been committed'.[45] The report must be to a police official.

A 'vulnerable person'[46] is

a) a child or person with a mental disability
b) a female under the age of 25 years who-
   i. receives tuition at a. higher education college, higher education institution or university college...
   ii. receives vocational training at any training institute...or as part of their employment
   iii. lives in a building, structure or facility used primarily as a residence...for the entities mentioned in (i) and (ii)
c) person who is being cared for or sheltered in a facility that provides services to victims of crime
d) person with a physical, intellectual or sensory disability and who—
   i. receives community-based care and support services, other than from a family member or

[44] The 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 NDPP [2014] ZACC 13.

[45] In terms of section 54 of the Criminal Law (Sexual Offences and Related Matters) Amendment Act 13 of 2021.

[46] Described in section 40 of the Criminal Law (Sexual Offences and Related Matters) Amendment Act 13. of 2021.

ii. lives in a building, structure or facility used primarily as a residence or
iii. is cared for in a facility providing 24-hour care to, persons with physical, intellectual or sensory disabilities or

e) person who is 60 years of age or older and who—
i. receives community-based care and support services, other than from a family member or
ii. lives in a building, structure or facility used primarily as a residence or
iii. is cared for in a facility providing 24-hour care to such persons.

c) Sexual and reproductive health research with minors (children and adolescents)

When researchers encounter instances of abuse and underage sexual activity during research with minors, 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 or vulnerable person from abuse and sexual offences may have the unintended consequence of increasing harm (physical and social) for the minor or vulnerable person. Furthermore, careless 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 only a research interest in the life of the child or adolescent, but no further right of access or duty of intervention, ought to take on the role and responsibility of a social worker is unclear. Consequently, researchers should think very carefully about the anticipated consequences of reporting, considering the legal context. Reporting, especially to the South African Police Service (SAPS), may include unnecessary exposure of participants to the criminal justice system, which can be a very traumatic experience. It is thus strongly recommended that researchers should partner with child protection experts to carefully consider each case, especially the best interests of the child participant, and carefully balance the various considerations.

The protocol 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 appropriately and effectively. The consent documents should clearly inform the potential participants (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 childcare organisations may assist researchers to make appropriate and meaningful referrals.

3.2.3 Women

Routine exclusion of women as research participants has led to a dearth of data needed to promote women's health. To prevent further unjust exclusions, 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. But exclusion of women from drug trials may result in skewed results which put women patients at risk in the treatment context. Systematic class exclusion must be guarded against to avoid unfair participant selection (see 3.1.5).

Additional health concerns arise during pregnancy, including the need to avoid unnecessary risk to the embryo, fetus, or infant, however, automatic exclusion of pregnant women should be avoided to prevent data inequities for pregnant and nursing women.

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 embryo, fetus or infant and
b) if exclusion is scientifically supportable.

Note: The informed consent documents must explain carefully and fully what the effects of the research activities on the embryo, fetus or infant 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 embryos, fetuses or infants
- appropriate studies on animals and non-pregnant women have been completed[47]
- the risk of harm to the embryo, fetus or infant is minimal, when procedures or interventions have no potential individual benefit for the women or embryo, fetus or infant,
- the risk of harm is outweighed by the prospect of potential individual benefit, when procedures or interventions have potential individual benefit for the women or embryo fetus or infant, and
- in all cases, inclusion poses the least risk of harm possible for achieving the objectives of the research.

3.2.4 Elderly persons

The Older Persons Act 13 of 2006 sets out a framework that facilitates empowerment and protection of older persons to promote maintenance of their entitlement to respect and equality appropriate to their circumstances. Research is needed to improve understanding of a wide range of aspects of aging and the lives of elderly people. For example, this age category of people is the highest consumer of medicines (drugs), many of which have not been tested adequately on elderly patients. It is thus obvious that elderly persons should not be excluded from research based merely on age. Rather, they should be included in research to ensure that the care and treatment required are based on sound information rather than guesswork.[48]

3.2.5 Adults and decision-making incapacity

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 in this context is how to obtain informed consent, especially whether proxy consent is permissible. The best interest principle is often suggested in connection with decisions relating to whether incapacitated adults should be enrolled in research. However, as with 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 easily accommodate a best interest analysis. 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.

3.2.5.1 Capacity and communication

Decision-making incapacity may result from a variety of causes and take various forms.[49] The most important insight is that incapacity to decide is a question of fact to be determined on a case-

[47] Clinical trials involving pregnant women or nursing mothers should ideally involve products for which the toxicology in adults is established and is acceptable. In the case of pregnant or nursing 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.

[48] Canadian Institutes of Health Research, Natural Sciences and Engineering Council of Canada, Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (2022) [pdf].

[49] TCPS-2 (2022) Chapter 3 pp55-57; National Statement on Ethical Conduct in Human Research (2007; updated 2018) (Australia), Chapter 4.5 [portal].

by-case basis. Even if, for other purposes, a person has been declared legally incompetent, they 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 they can 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 them. The ability to communicate includes the ability to hear and to speak or otherwise signal or express their 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.

3.2.5.2 Minors and factual incapacity

Note: This paragraph addresses minors who are without factual capacity to make decisions in addition to being under the legal incapacity applicable to minors.

Parents or guardians of children and adolescents with intellectual or mental impairments should give permission for their minor child or adolescent 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 this instance, the parent or guardian acts as a proxy decision maker for the incapacitated minor.

When the minor reaches the age of majority, the person becomes an adult with decision-making incapacity.

3.2.5.3 Minimum conditions for research involving adults with incapacity

Research involving incapacitated adults should be approved only if

a) The research, including observational research, is not contrary to the best interest of the individual;
b) The risk of harm assessment shows that the research, including observational research, places the incapacitated adult at no more than minimal risk;[50] or
c) 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
d) The research, including observational research, involves greater than minimal risk, with no prospect of direct benefit for the incapacitated adult, but has a high probability of providing generalisable knowledge, i.e., the risk should be justified by the risk-knowledge ratio;
e) Greater than minimal risk must represent no more than a minor increase over minimal risk;
f) Where appropriate, the person assents to participation.

Note: The incapacitated person's refusal or resistance to participation, as indicated by words or behaviour, takes precedence over permission by a proxy. 'Assent' is the term for agreement by someone who is legally incapable of providing consent. With incapacitated adults, 'assent' refers to the legally incapacitated person's agreement to participate; with minors, 'assent' refers to the child's agreement to participate in the research. In both instances, the person is assisted by a legally capable other: a statutory proxy or a person with a mandate agrees for the legally incapacitated adult, while a parent or guardian agrees to their child's participation in research.

The NHA specifies the sequence of legally appropriate treatment proxies as spouse or partner; parent; grandparent; adult child; brother or sister. The MHCA provides, in no specified order, that legally appropriate treatment proxies are spouse; next of kin; partner; associate (defined as 'a person with a substantial or material interest in the wellbeing of a mental

[50] The 'everyday risk standard' means minimal risk, commensurate with 'daily life or routine medical, dental or psychological examinations and in social or education settings activities'.

health care user or a person who is in substantial contact with the user'); and parent or guardian. (See 3.1.10.2)

3.2.6 Persons in dependent relationships

This category of persons includes persons in junior or subordinate positions in hierarchically structured groups and may include relationships between elderly persons and their caregivers; persons with chronic conditions or disabilities and their caregivers; persons with life-threatening illnesses; patients and health care professionals; wards of state and guardians; students and educators (including university educators); 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

3.2.7 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 their 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 unfairly affect research participation decisions.

3.2.8 Persons with visual, hearing or mobility impairments

Recruitment strategies for research participation in general should be sensitive to the possibility that persons with visual, hearing or mobility impairments may wish to volunteer. Therefore, they should ensure 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 visual, hearing or mobility impairments should anticipate possible barriers and include measures to minimise them.

3.2.9 Inmates

The main reason to consider inmates[51] as a vulnerable category of persons is the potential effect of incarceration (imprisonment) on voluntariness of a decision to participate in research. Neither coercion (direct threat of negative sanction) nor unfair influence is acceptable in the informed consent process. Researchers should pay attention to whether their intended participants are awaiting trial inmates or convicted offenders. 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 unfair 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 inmates when deliberating on the protocol. The researchers must ensure that their protocols comply also with the requirements of the Department of Correctional Services as listed at http://www.dcs.gov.za (under 'Services' tab).

[51] Note that the term 'prisoner' is no longer acceptable; the Correctional Services Act 111 of 1998 prefers 'inmate' (applies to all who are incarcerated); and 'offender' (applies to those who have been convicted). The Act explains that 'inmate' means any person, whether convicted or not, who is detained in custody in any correctional centre or remand detention facility or who is being transferred in custody or is en route from one correctional centre or remand facility to another.

Research should be conducted amongst inmates only if

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

In the case of child and adolescent inmates, 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.

3.2.10 Collectivities

'Collectivity' is a term used to distinguish some distinct groups from informal communities, commercial or social groups. Collectivities are persons who participate in research in 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.

3.2.11 Consent to use of animals of private owners

Research involving use of animals of private owners requires consent from the animal owners. The objective is to ensure that the owner understands and gives permission for their animal to be used as described. Where relevant, the following aspects should be addressed:

- objectives of the research study
- expected benefits of the study for the owner and community
- contact details and community channels related to the study and use of the animals
- voluntary permission by the owner for participation of the animals
- language of consent in language of animal owner
- withdrawal of animals from the study
- if relevant, protection of owner anonymity as well as community represented
- expectations of owner of the animals
- whether feedback about the study will be shared and how it will be shared
- whether any remuneration will be provided
- details regarding access to the owner's property
- procedures to be carried on the animals, as well as which and how many animals will be used
- foreseeable risk of harm for the animals or property associated with participation in the study
- details regarding occurrence of active monitoring
- any insurance cover and veterinary or other care that may be provided as well as the applicable circumstances and limitations

- details regarding actions if the animal reaches humane endpoint or suffers other adverse event
- details regarding actions if serious incidents or property damage occur
- details regarding rights to data and collected biological samples
- details regarding rights to intellectual property resulting from the study

Note: The researcher is responsible for animals in the study. If other animals on the property appear to require care, the researcher should report this to the owner; when animals receive sub-optimal care or suffer from uninformed practices or naïve negligence, this may, depending on context, be an opportunity for education; cruelty or illegal activities involving other animals on the property, should be reported to SAPS or NSPCA.

3.3 Considerations specific to research methodologies or contexts

Different academic disciplines may use different research methodologies and different research contexts may present challenges for the review process. It is of critical importance, therefore, that RECs review different research methodologies appropriately in accordance with accepted standards of the different academic disciplines, and that different research contexts receive appropriate attention to ensure participant protection.

Research methods and contexts discussed are:

- Social science research
- Major incidents[52] and research
- Intensive care research
- Terminal care research
- Innovative therapy or interventions
- Traditional medicines and indigenous knowledge research
- Deception, concealment, or covert data collection
- Multinational collaborative projects
- Research using audio visual recording
- Complementary medicine and natural health products

3.3.1 Social science research

3.3.1.1 Introduction

Social science research uses a variety of methodologies, including qualitative and quantitative methodologies. It should be noted that quantitative social science research is different from laboratory and clinical quantitative research[53]. It is thus important not to see all quantitative research as similar and qualitative research as the outlier. Rather, the purpose for which the methodology and paradigm are deployed is important for identifying more appropriately the relevant reviewing lens. Thus, social science research requires appropriate review.

As indicated in Chapter 1: *Ethics in research*, perceptions exist that the 'medical model' of ethics review prevails and that RECs inappropriately apply it to research that uses qualitative research methodologies. As the acceptability of qualitative research has grown, many researchers choose designs that focus on qualitative approaches. Transdisciplinary research often includes qualitative research approaches to address complex research problems. Mixed method designs have also increasingly become popular to answer research questions.

Researchers and RECs must thus familiarise themselves with the principles, practices, and conventions of using qualitative research methodologies so that methodological issues are competently reviewed. If a protocol includes qualitative research, the appropriate attention must be given to ensuring inclusion in the protocol of the theoretical basis for this methodology as well as at least one team member with appropriate expertise in qualitative research.

Note: The composition of REC membership necessarily must include members who have appropriate disciplinary expertise, e.g., at least one scientist with experience and expertise in qualitative research should be included in the membership.

[52] Previously known as disaster research

[53] See Bryman A (2012) Social Research Methods 4th ed. Oxford Press : Oxford UK. 15 p. ISBN 978-0-19-968945-3. [PDF].

It is important to recognise that, although research methodologies and analytical paradigms may differ, all research protocols are judged against the same ethical principles. No philosophical justification exists for judging different methodologies against different ethical standards.

3.3.1.2 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'.[54] Individuals, organisations and communities and interactions between and among them may be seen as socially constructed[55] 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 apply specific criteria to determining the rigour as well as the trustworthiness of their data (analogous to reliability and validity of quantitative data). '[T]he aims of qualitative research are very diverse, both within and across disciplines. The intended goals of qualitative projects may include giving voice to a particular population, engaging in research that is critical of settings and systems or the power of those being studied, affecting change in a particular social environment, or exploring previously understudied phenomena to develop new theoretical approaches to research'.[56]

3.3.1.3 Methodological approaches and requirements

a) Diversity of approaches

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

b) Inductive understanding

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

c) Dynamic, negotiated, and ongoing consent process

Conducting research in specific settings may require the researcher to negotiate with the population of interest to gain access. Unlike with quantitative research, where the anticipated pattern of the study may be apparent and can be described, with qualitative research, this is not always possible, for reasons including establishing that access will be possible and that the population of interest is willing and able to co-operate with the design and testing of the desired project. In other words, the researcher may not be able to describe the process of the research project in advance, in part because the relevant contexts within which the research occurs evolve over time. In some cases, participants hold equal or greater power in the researcher-participant relationship, such as in community-based and/or organisational research when a collaborative process is used to define and design the research project and questions, or where participants are public figures or hold other positions of power (e.g., research involving economic, social, political, or cultural elites). In other cases, researcher themselves may hold greater power when access to prospective participant populations is gained through gatekeepers with whom the researcher has established a relationship (e.g., when a researcher engages with the police to do research with offenders).[57] In general, however, researchers should be clear on how they will gain entry to a community and how and why they will involve gatekeepers and mediators.

d) Dynamic, reflective, and continuous research process

During the research, questions, concepts, theories, strategies and ways to engage with and gather data may emerge, which may require the researcher to practise ongoing reflective, flexible

[54] TCPS 2 (2022) Chapter 10 p184.
[55] TCPS 2 (2022) Chapter 10 p184.
[56] TCPS 2 (2022) Chapter 10 p186.
[57] TCPS 2 (2022) p186.

and responsive approaches to ensure the rigour, credibility and trustworthiness of data collection and analysis are maintained. Due to this dynamism, it is important that the researchers communicate with the REC timeously and effectively to ensure that any issues or changes that arise during the research, are handled in a rapid and ethically appropriate manner.

e) Diverse, multiple and often evolving contexts

Qualitative research very seldom takes place at a 'defined research site'. Rather, it focuses on context and may occur in a variety of contexts, which may present different ethical issues. As knowledge is context-contingent in qualitative research, these studies tend to focus on individuals, sites or concepts empirically derived from other social settings. The researcher's priority is to answer the research question stemming from the study of those individuals in a specific social setting at a specific time.

Researchers sometimes engage in research that questions social structures and activities that create or result in inequality and injustice. Studies may involve participants whose circumstances make them highly vulnerable in the context of research because of the social and/or legal stigma associated with their activity or identity, and who may have little trust in the law, social agencies or institutional authorities. Regardless of the methodological approach, researchers who question social structures may face pressures from authority figures. Research may also involve participants, such as business executives or government officials, who may be very assertive in response to the researchers.[58] Research protocols should include discussion that demonstrates the researchers' awareness of these possibilities and explains what measures will address such imbalances and their consequences.

f) Data collection and sample size

Generally, qualitative research emphasises depth over breadth of research. Consequently, samples and research areas are selected for their usefulness as rich sources of data and vary according to the choice of qualitative design. Selection of participants may be guided by emerging patterns over the course of data collection. Sample sizes are usually smaller than those used in quantitative research, as the focus is usually on either representation or saturation of data. Some examples of types of samples are stratified purposive sampling, maximum variation sampling, criterion sampling, critical case sampling, snowball/network sampling, theoretical sampling, etc.

Multiple methods of data gathering may be used to elicit data from multiple sources. For example, unstructured or semi-structured interviews, participant observation, focus groups, and document analysis may be used. Increasingly popular but ethically challenging are research methods that involve audio visual materials, e.g., capture of photographic and video data of participants or contexts. The risk/benefit ratio and confidentiality considerations are especially but not exclusively pertinent. The REC should pay attention to the format of data and how it will be stored to ensure confidentiality.

g) Data analysis

The process of data analysis consists of making sense of text and image data. Researchers should be clear on what method of analysis will be followed i.e., thematic, semantic, or content analysis, pragmatic iterative approach etc. and that the method of analysis matches the chosen qualitative methodology.

h) Research findings

Qualitative research project findings are not uniformly generalisable from one setting to another; rather, they are contextual. Some commentators find this characteristic concerning and criticise research for not being generalisable. This attitude is unfortunate because small scale qualitative research projects are not intended to represent whole populations. If a large-scale project is desired, the design and theoretical basis must demonstrate the feasibility of generalisability as an outcome. Transferability of findings from one setting to another is often more

[58] TCPS 2 (2022) p185.

of a theoretical issue than a procedural or a sampling issue.[59]

3.3.1.4 Approach to ethics review of qualitative research

As outlined above, qualitative research is inherently dynamic and may be based on assumptions that differ from those that inform other methods of research.

Best practices, standards and expectations that exist in the different disciplines must be considered. However, as stated previously, the moral standards by which the ethical acceptability of planned research is judged, do not differ because a different methodology is to be used. Consequently, the principles outlined and discussed in Chapter 2: *Guiding principles for ethical research* 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. Like with quantitative research, RECs must consider ethical tensions arising from specific methodologies and analytic approaches competently, fairly and with open minds.

Similarly, to quantitative protocols, 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.

The key criteria for the review process are outlined and discussed above (see 2.3 and 3.1). These same criteria are relevant to review of qualitative research, with adjustments to emphasise aspects peculiar to qualitative research. An example of adjustment is the protocol description of the process of the research. For non-social science research, the expectation is that the protocol anticipates in detail what will happen, when, and to whom, what the expected outcomes are etc. This anticipatory regulatory regime is based on assumptions derived from the model of clinical trials or biomedical experimentation, with prior specification of hypotheses, design, instruments, and implementation in protocols that are finalised before the study begins. This model readily transfers to survey research, where it is possible to specify, in advance, exactly what a study will involve. This is not, however, true for ethnographic research.

By nature, ethnographic research[60] is important for its contributions to creation of more efficient, more effective, more equitable and more humane health care systems. Informed consent in ethnographic research is neither achievable nor demonstrable in the terms set by anticipatory regulatory regimes that take clinical research or biomedical experimentation as their paradigm cases. This is because of differences in the practices of ethnographic and biomedical research. These include the extended periods of time ethnographers spend in the research setting, the emergent nature of ethnographic research focus and design, the nature and positioning of risk in ethnographic research, the power relationships between researchers and participants, and the public and semi-public nature of the settings normally studied. Anticipatory regulatory regimes are inimical to ethnographic research and risk undermining the contribution of systematic inquiry to understanding whether institutions do what they claim to do, fairly and civilly and with an appropriate mobilisation of resources.

The general requirements for stakeholder engagement, social value, scientific validity and integrity, informed consent, risk/benefit ratio, protection of privacy and confidentiality are the same for all research.

Specific ethical issues may arise around gaining access and negotiating entry to the field, building rapport, conducting ethnographic observations, in-depth interviews and issues of disclosure during focus groups, using data, whether to include data shared 'off the record', debriefing, reporting results and being sensitive to the fact that not all

[59] TCPS 2 (2022) p186.

[60] See TCPS 2 (2022) pp188*ff* for helpful discussion.

qualitative data are eligible for sharing on Open Access data repository platforms.

Review attention should be given to issues of consent, privacy, confidentiality, social and psychological harms, as well as the anticipated relationships between researchers and participants as well as inevitable 'onlookers'. For example, observation research conducted in education settings where minors are present, focusses on educators' performance. Necessarily, however, the learners in the classroom are indirectly involved, but not as participants.

Researchers are expected to explain thoroughly to the REC, the school authorities, the parents, and the learners (to the extent possible) what is intended with the observations, how matters will proceed, whether recordings will be made the purpose of the recordings, who will have access as well as how and where they will be stored, what will happen to the recordings after completion of the research, and how learners' confidentiality will be maintained, etc. Further, it is important that the researcher should familiarise the class with their presence to avoid unnecessary disturbance with teaching and learning activities Parents and learners must be given enough time to consider the purpose of the activities and should be given enough time to contact the researcher should they have questions, concerns or specific requests.

Some issues 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, flexibility, and be able to consult, including with the REC. The basis for exercise of discretion and the degree of flexibility should be considered at the design phase. The REC should be consulted when doubt arises. Should amendments be required during the research, the REC should be approached for approval before changes are implemented.

3.3.2 Major incidents and research

3.3.2.1 Introduction

Major incidents entail any sudden event that occurs where local resources are constrained, so that responding swiftly and appropriately is difficult. Major incidents include acute disasters – natural or man-made – such as floods, tornados, earthquakes, outbreaks of deadly disease leading to a public health emergency, 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 type of emergency with consequent ethical implications for patient care.

Research during major incidents is important for advancing emergency health care interventions for prevention and treatment, and for refining resource allocation policymaking and implementation as well as for improving triage methods and procedures, and for developing effective treatments for life-threatening conditions and improving therapies for survival and quality of life. It is also important for improvement of civilian and local authority readiness planning.

Note: Sometimes researchers appear to assume that people caught up in 'emergency circumstances' in any context should be enrolled in research projects. For example, circumstances that include incapacitated patients, austere and under-resourced clinical environments (including pre-hospital patient care), complicating factors (for patients with capacity) such as acute pain, physiological derangements, anxiety, risky clinical contexts due to the pathophysiological effects of severe illness or injury, time-sensitive interventions and (often) no available proxy decision-makers within intervention time-frames present logistical and ethical challenges.
Researchers must remember that expedience is not an ethical principle and that sometimes the perceived opportunity for research is not appropriate due to challenges. The ethical and other regulatory requirements for sound ethical research are more important than a lost opportunity for a research project.

A public health emergency, like that driven by the Corona virus, revealed unanticipated methodology and ethical dilemmas for RECs and researchers. Ongoing research projects faced previously unknown challenges because of the mandatory lockdown periods, such as forced self-isolation, government-ordered research site closures, restrictions on travel, all of which affected whether and how ongoing clinical trials and other community-based research could proceed. Additionally, community transmission of infection increased vulnerability of participants,

many of whom chose to stay home rather than to report for clinic visits.

The focus here is on starting new research projects during a major incident, especially a public health emergency.

3.3.2.2 Research during a public health emergency

Signature elements of public health emergencies are uncertainty and the need for rapid but thorough decision-making, planning and allocation of resources. Uncertainty overwhelms especially when a sudden, new, and rapidly evolving cause of severe illness and high rates of morbidity and mortality occurs.

A powerfully stabilising influence in our context is the existence of a robust and flexible ethico-legal research framework and associated infrastructure in South Africa. It is important to remember that the principles and guidance outlined in NDoH 2024 and SAGCP 2020 guidelines remain relevant and helpful, even if specific SOPs are not provided. That a public health emergency prevails and necessitates rapid and thorough administrative processes, does not mean that the ethics review processes should differ from what is usually done, other than the need for rapid execution. It is vital that proposed research is conducted in a manner that complies as far as possible with the accepted principles that underpin scientific and ethical integrity of research involving human participants to ensure their safety and mitigation of risk of harm. Where compliance is claimed to be impossible, this must be explained fully and justified. Perceived urgency can never justify circumvention or dilution of the established ethics guidelines and statutory standards for thorough review, ethical conduct of research, attention to the safety and wellbeing of participants.

In what follows, the key norms for ethical research (see 2.3) are examined through the lens of uncertainty and public health emergency research. None of these norms is new but understanding of how to interpret each in this context may benefit from focused attention.

a) Rapidity required for administrative processes

Starting a new research project involving people who are healthy but at risk, or already very sick and vulnerable, in a public health emergency, may require certain adjustments to the usual procedures, e.g., planning the research and the ethics review processes necessarily should occur as rapidly as possible.

To achieve rapid but thorough processing, the REC and its administrators must speed up the usual processes. However, bear in mind that not all research proposed during a public health emergency is urgent. It is highly desirable that researchers and RECs communicate clearly as soon as possible about what will likely be regarded as urgent research in the emergency context and what will not.

Note: Rapid but thorough review processes should be available also in other situations, if the need for it can be well motivated i.e., emergencies on a smaller scale on district or provincial level.

b) Preliminary considerations

i. Necessity for research participation

Researchers and clinicians are reminded that it is never necessary for a patient to become a research participant. It is erroneous to think that a patient will benefit from being enrolled in a prevention or treatment trial. If it is already scientifically certain that a trial-related intervention will benefit patients, then the intervention should be administered as part of prevention or treatment, or an implementation study, not research (see 3.4.1).

ii. Diversion of resources

While the scientific and ethical rationale to conduct research during a public health emergency may seem obvious, research must not impede emergency medical responses. Additionally, resources allocated to research should not compromise routine delivery of health care and public health services required, notwithstanding the public health emergency.

iii. Therapeutic misconception

Where clinicians treat patients in health facilities and use their patients as research participants, great care must be exercised to avoid therapeutic misconception as an outcome of their dual role (see 3.2.6 & 3.2.7 of NDoH 2024 and 10.10 of SA GCP 2020). A therapeutic misconception prevails when a patient/participant believes that the primary purpose of a trial procedure or intervention is to confer preventive or therapeutic benefit rather than to generate knowledge, thus confounding the purposes of research and treatment. In a therapeutic (treatment) context, clinicians must act in the best interests of their patients. When a patient becomes a trial participant, this obligation becomes more complex. Necessarily, the trial context has a different focus, i.e., the systematic generation of new knowledge that may not include direct benefit for individual participants, as is the case in all clinical trials. This implies that the best interests of individual participants are not the focus and thus that researchers cannot simultaneously act in the best interests of the patient to change the trial protocol to suit an individual participant's interests. In research, the study protocol is designed to answer a research question, without focus on the best interest of individual patients.

iv. Conflict of interest

As in all research and as discussed elsewhere in these guidelines, researchers and REC members must take care that their research activities are free of undeclared conflict of interest.

The dual role of clinicians and researchers is an important consideration in research, but more so in a public health emergency. Researchers are reminded to separate these roles so that potential conflicts of interest can be better managed. Conflicts of interest can occur at various levels and at different points of the research process. Such conflicts of interest could be for financial gain in cases of industry-sponsored research involving drug companies, which could introduce possible researcher bias in how the study is conducted, analysed and reported.

Conflicts of interest could arise out of the desire for personal career advancement or to promote strongly held social views, or because of political pressure on researchers (at national or local levels) to drive a particular research agenda.

All conflicts of interest, including disclosures of such conflicts should be documented and managed accordingly. Apart from the disclosure of conflicts of interests, there should be institutional policies and processes for the management of these conflicts of interest (see 10.1 of SAGCP 2020).

c) Public health principles

A public health approach is appropriate for research to be conducted during a public health emergency. RECs must be familiar with and must use public health principles in discussions and deliberations. The values of social and health equity, distributive justice, and reciprocity feature strongly in public health approaches. The African philosophical concept of Ubuntu incorporates these values.

Conscious consideration of public health principles helps to maintain focus on public health priorities in the public health emergency. For example, instead of competitiveness being the strongly relevant element in the quest to find a vaccine, collegial and international cooperation across borders, and sharing of funding, knowledge and data could be prioritised.

Note: For specific guidance on conducting clinical trials during a public health emergency, see SA GCP (2020) at 10.11.

d) Novel virus considerations

Whether a novel virus or other cause drives the public health emergency, certain ethical principles and scientific integrity conventions informing development of appropriate evidence-based prevention and treatment interventions must be considered and implemented to ensure that research participants are treated humanely and respectfully.

Some principles and conventions concern the care of the patient, whilst others concern the rigour of the research that necessarily may affect the

wellbeing of the participant. In a public health emergency, nearly all research participants are patients, whereas, ordinarily, medical research, especially drug development, will involve healthy participants in the early phases of research.

Where it is difficult to describe and define the standard of care in a public health emergency – as was the case with the Corona virus pandemic (COVID-19) – standard of care is the best available treatment at the time. Rather than seeking to name and define a standard of care, it may be more useful to undertake continuous assessment of emerging data (scientific and clinical), as should occur in any other placebo controlled clinical trial, to determine an intervention based on good data (see also 3.4.1.3).

e) Ethical principles versus regulatory requirements and SOPs

An important distinction exists between ethical principles and guidance, on one hand, and regulatory requirements and standard operating procedures, on the other. Given the prevailing uncertainty, it is possible that, as new information becomes available during the research, regulatory requirements and standard operating procedures could require amendment. The ethical principles and guidance are unlikely to change, however, since they focus on the interests of research participants, which remain the same as they usually are for research.

The usual ethical principles that underpin sound ethical research (see Chapter 2: *Guiding principles for ethical research*) must be adhered to in public health emergency research. It is unethical to ignore certain ethical principles so that patients can be enrolled despite failure to meet all the legal and ethical requirements. Of high importance is the requirement to keep meticulous records (minutes) of decisions and the reasoning that led to the decision. This helps to build a body of knowledge for later review and possible incorporation into SOPs.

i. Social value

Even in a public emergency, the study design must be feasible, appropriate, and scientifically valid. If the design lacks scientific validity, the research will not have social value and should not be conducted. Social value exists in the responsiveness of the design to the health needs and priorities of the communities in which the research is conducted (CIOMS 2016). Research should be relevant and responsive to the needs of the people of South Africa (see 2.3.1). However, in a global public health emergency context, this principle may be relaxed so that the social value of the research extends beyond the South African context, e.g., equitable access to vaccines developed from research (CIOMS 2016). RECs should consider social value broadly, provided the risk of harm in the local context is balanced equitably. As indicated by the Nuffield Council on Bioethics, 'rigorous ethical safeguards should be in place', especially in respect of 'externally sponsored research, to prevent the exploitation of those who take part in the research'. In cases where research interventions have features that make them difficult to implement locally, the design should be adjusted or modified to allow implementation in the local context within available resources.

ii. Distributive justice

The ethical principle of distributive justice is of particular relevance in public health emergencies. Implementation of interventions developed during infectious disease outbreaks are usually limited initially. It may be acceptable to prioritise certain groups of people for enrolment in a trial based on the principle of utility, e.g., frontline health care workers first. However, extensive emergency use with inadequate data collection on patient outcomes must be avoided.

RECs and regulatory authorities should ensure that access to developed products is addressed by the researchers, including studies conducted during emergency situations. No part of the population should bear the burden of research but be denied access to benefits that may result from the research. If SA contributes to global good, then shared benefits should accrue from the research.

iii. Beneficence and non-maleficence

After authorisation for emergency use of an investigational product, ongoing pharmacovigilance and safety evaluations are necessary, without detracting from the mandate of SAHPRA, the regulatory authority.

RECs must act rapidly to evaluate reported side effects and whether to pause or terminate the use of the investigational product or recommend amendments to the information leaflet or make other interventions to minimise risk of harm to participants.

iv. Autonomy: Informed Consent

Infectious disease outbreaks cause great anxiety, distress and even mental unwellness in populations. These circumstances challenge obtaining informed consent, as many people may not be in a calm frame of mind to make informed decisions. Nevertheless, the principle of autonomy requires that both voluntariness and independence of choice prevail to ensure informed consent. Potential participants must be assisted to understand the research proposed and the implications of enrolment, despite the situational duress and anxiety. The notion that informed consent is a process does not change because the research is being conducted in pandemic circumstances (see 3.1.10).

Regarding research ethics principles, it is clear that research during a public health emergency must adhere to standard research ethics principles mentioned elsewhere in these guidelines, viz., Stakeholder/community engagement; social value, scientific validity, fair selection of study participants, informed consent, independent and competent ethics review, and ongoing respect for study participants best interests once the study is completed.

3.3.2.3 Rapid ethics review

In a public health emergency, preparations for research must occur quickly. Rapid but thorough processing of ethics review applications is desirable The REC should carefully assess the nature of the research to determine the appropriate expedited (for minimal risk research only) or full REC (for more than minimal risk or clinical trial studies) review process. Careful ethical reflection is essential, notwithstanding any perceived urgency.

Even for a full REC review (for more than minimal risk or clinical studies), it is possible to review and approve a protocol without undermining the substantive protections provided by the review process in about 36-48 hours if the REC's operational systems are in good working order and members are experienced. In other words, rapid full REC review process between scheduled REC meetings is feasible for processing of urgent ethics review applications, provided the usual quorum requirements are satisfied (see 5.5.1.6).

Furthermore, given that all registered RECs undergo a robust registration process and subsequent quality assurance audits, it follows that the procedures for documented reciprocal recognition of review decisions is useful in a time-pressured situation (see 5.5.1.4).

RECs must have done the appropriate planning and development of SOPs for these procedures to be beneficial: the REC should have a review SOP that allows the combination of rapid and thorough review and reciprocal recognition of reviews of other registered RECs. The possibility of reciprocal recognition of reviews should occur in a collaborative, harmonious manner, bearing in mind that each REC bears the responsibility of protecting the safety, rights and interests of participants enrolled in the studies it has approved.

Note: Rapid review is not the same as expedited review (see 5.5.1.5).

3.3.2.4 Information sharing

Rapid sharing of reliable scientific information generated during public health emergency research is desirable so that evidence-based decision-making can inform revised public health responses to the emergency. Researchers should not forget about necessary cautionary restrictions of ethical requirements such as maintaining confidentiality and protecting privacy of participants' personal information. It must also be

borne in mind that early results might be misleading, and researchers should always publicly acknowledge foreseeable limitations of their data or interim results. Translation of scientific information for laypersons should be prioritised so that the media are able to deliver accurate messages about new methods of clinical management or the availability of new treatments and vaccines.

3.3.2.5 Stakeholder engagement

Research during a public health emergency, requires fair and meaningful stakeholder engagement and inclusive decision-making. The most inclusive level of engagement is one where local stakeholders take part in decision-making processes with respect to research design, implementation, and evaluation. It requires that all reasonable steps are taken to ensure that all those concerned, including policymakers, relevant health officials and those who are vulnerable and marginalised are included. Researchers should engage also with relevant supportive social or healthcare entities working within communities. If possible, engagement should occur from initiation of the research planning and should endure through all phases if feasible. While solidarity and reciprocity are core principles, individual interests of participants should not be undermined. International collaborations should adhere to the principle of fairness.[61]

Established stakeholder engagement processes may be challenging during a public health emergency. Use of virtual platforms such as social media may exclude community members without access to such platforms, or who have poor internet connectivity or no data or funds for use of mobile phones. This requires review of how innovative, responsive stakeholder engagement can occur despite these challenges. The local context of research must be considered. Researchers must seek standard permissions, where applicable, to access fieldwork locations ahead of time to avoid delays.

3.3.3 Intensive care research

Characteristic features of intensive care research include difficulties in communicating with patients receiving ventilation assistance or heavy sedation leading to impairment of cognition.

Whenever possible, informed consent for planned intensive care research should be obtained from potential participants before admission to that care. If necessary, alternative formats of consent should be used, with due consideration of the potential participant's rights (see 3.2.5).

Research involving infants receiving neonatal intensive care should be conducted in strict accordance with the principles set out for minors. These principles do not permit research that is contrary to the child's best interest (see 3.2.2). The small size and extreme vulnerability of some infants are unique features of this category 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 accompany the application for ethics review.

3.3.4 Terminal care research

Terminal care research is distinctive for 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

[61] See Montreal Statement on Research Integrity in Cross-Boundary Research Collaborations 2013 and TRUST (2018) The TRUST Code – A Global Code of Conduct for Equitable Research Partnerships, DOI: 10.48508/GCC/2018.05.

wishes of participants to spend time as they choose, particularly with family members.

3.3.5 Traditional medicines and indigenous knowledge research

3.3.5.1 Traditional medicines research

In line with the constitutional guarantees for cultural and language rights,[62] indigenous cultures and traditional values of all communities must be respected. Accordingly, participants in research involving traditional medicines and beliefs must be accorded the same respect and protection as any other human research participant. 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) diagnosis, treatment or prevention of a physical or mental illness; or
> b) any curative or therapeutic purpose, including maintenance or restoration of physical or mental health or wellbeing in human beings, but does not include a dependence-producing or dangerous substance or drug.
>
> '**Traditional health practice**' means performance of a function, activity, process or service based on a traditional philosophy that includes utilisation of traditional medicine or traditional practice and which has as its object-
>
> a) maintenance or restoration of physical or mental health or function; or
> b) diagnosis, treatment or prevention of a physical or mental illness; or
> c) rehabilitation of a person to enable that person to resume normal functioning within the family or community; or
> d) 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 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 Departments of Agriculture, Land Reform & Rural Development (DALRRD); Forestry, Fisheries & the Environment (DFFE); Health (NDoH); Tourism (DT); Science & Innovation (DSI); and Trade, Industry and Competition (DTIC). International and domestic legislation, policies and regulatory guidelines applicable in these departments must be taken into account when conducting research on traditional medicinal plants and genetic material.

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

[62] The Constitution of the Republic of South Africa Section 30 *'Everyone has the right to use the language and to participate in the cultural life of their choice…'*

Benefits[63], 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 Companies and Intellectual Property Commission Property's policies on Intellectual Property[64]

Prior ethics review of proposed research is required to ensure that norms and standards for health research in South Africa are 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 proposed methodology carefully and make decisions on a case-by- case basis.

3.3.5.2 Indigenous knowledge

Research ethics guidelines have not commonly included guidance on how to respond to and manage use of indigenous knowledge in health-related research involving human participants. In recent years, though, it has become ethically and constitutionally necessary to address issues that arise so as to protect, promote, develop, and manage indigenous knowledge in South Africa and elsewhere in the world. This is due to the tendency amongst many entrepreneurs, including researchers, to appropriate 'useful' information or articles from people in less developed parts of the world and to turn them into commercial products for profit without involvement or acknowledgement of the indigenous knowledge holders.

The Protection, Promotion, Development and Management of Indigenous Knowledge Act 16 of 2019 explicitly recognises that indigenous knowledge is a national asset and accepts that indigenous innovation is a unique approach to social innovation and aims to encourage use of indigenous knowledge in the development of novel, socially and economically applicable products and services.

The Act does not specifically address research matters but provides a framework that is designed to operate in trade and industry settings where plant material, animal husbandry and related issues give rise to the need to separate the indigenous from the modern commercial to ensure fair treatment for indigenous knowledge holders in the marketplace.

It stands to reason that the values, principles, and norms that underpin these guidelines apply also to indigenous knowledge communities. Nevertheless, specific values may be emphasised more in indigenous communities than they are in urban contexts where populations are generally more diverse and from many different cultural backgrounds. For example, the values of reciprocity, community welfare concerns and social justice are usually elevated above individual concerns amongst indigenous communities. In the African context, these values form the basis of the philosophical concept of Ubuntu, which informs the view that the collectivity is generally more important than the individual.

It is important that the values, principles, and norms of these guidelines are thoughtfully considered in light of the above comments when engaging with the communities that researchers will invite to assist with research by participating, especially when their indigenous knowledge is to add value to the research. The statutory framework outlines expectations.

A useful discussion may be found also in TCPS 2 (2022) chapter 9 that addresses research with Aboriginal peoples of Canada.[65] Although they have unique and different traditions, an oral tradition for transmitting indigenous knowledge is

[63] Ratified by South Africa on 11 May 2011. For further information, see http://www.cbd.int/abs/.

[64] Department of Trade, Industry and Competition (DTIC) https://www.cipc.co.za/.

[65] TCPS 2 (2022) Ethical Conduct for Research Involving Humans (Canada) 2022, Chapter 3 (available at https://ethics.gc.ca/eng/policy-politique_tcps2-eptc2_2022.html).

common to the Aboriginal peoples of Canada and the indigenous peoples of Africa and South Africa.

3.3.6 Complementary and alternative medicines (CAMS)

In addition to African traditional medicines, several other medicine systems are used in South Africa, e.g., herbal medicine (phytotherapy), naturopathy, Chinese medicine and acupuncture, Unani Tibb medicine, and Ayurvedic medicine. Qualifications in these systems of medicine are offered at some tertiary institutions. It follows, therefore, that research in these fields of medicine occurs, conducted by both practitioners and students.

These guidelines do not provide focused and detailed guidance for these fields, since regulation of their practice is currently beyond the scope of the mandate of the NHREC. However, it is relevant and important to note that SAHPRA includes in SAGCP 2020 the following:

1.2.1 Specific types of clinical trials are not addressed separately unless a particular need is identified, i.e., 'clinical trials' includes trials involving complementary medicines, African traditional medicines, and non-pharmacological interventions including surgical procedures, medical devices, cell therapy, genetics and genomics, and imaging technology.

In other words, SA GCP 2020, read with NDoH 2024, provides guidance for any clinical trial involving human participants, especially those with experimental designs. This means that, in principle, to plan and conduct a research project that involves complementary or alternative medicines requires the same approach following the same ethical and procedural guidance as for other clinical trials.

3.3.7 Research involving deception or withholding information

Sometimes, to ensure validity of research, researchers withhold certain information about the study during the consent process. This may take the form of withholding information about the purpose of specific procedures. In most 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 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 minimal risk. RECs must be satisfied that deception is indispensable; that no other research method would suffice; that significant advancement of knowledge could result from the research; and that nothing has been withheld that, if divulged, would likely 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.

3.3.8 Research in South Africa with international collaborators

All international collaborative health research conducted in South Africa must undergo ethics review and approval by a South African registered REC. The proposed research projects and studies must comply with the ethico-legal requirements for health research as outlined in these guidelines and SA GCP 2020. In addition, if international collaborators are affiliated to a foreign research institution or university, they must provide evidence of ethics review and approval from their home institution.

International researchers are expected to demonstrate sensitivity to and understanding of the local socio-economic and political conditions of the research context, as these may indicate vulnerabilities of potential participants. This is important for collaborative partnerships so that

international researchers understand the nature and context of the local environment and the particularities of the research site(s) before determining the priorities and needs assessments of all relevant stakeholders in the collaboration. It is advisable to create appropriate memoranda of understanding (MOUs) and agreements to establish the expectations, roles and contributions of the various parties, as well as the limitations of the collaborative relationship.

An agreement should exist between the host research institution and the collaborating institution(s) regarding all aspects of the research, including management of the research itself; research data management that includes the fate of the data and samples after completion of the study; financial arrangements; approach to research output publications; infrastructure development; allocation of intellectual property rights; and dispute resolution mechanisms.

Selection of study participants is expected to be based on distributive justice and fairness (see 3.1). Risk of harm assessments must be properly conducted to ensure that foreseeable risks of harm are mitigated and that anticipated benefits of participation are distributed fairly. Regarding benefit-sharing efforts, researchers should engage with the local community and other relevant stakeholders when planning the study to establish how best to optimise the efforts.

3.3.8.1 International research using online. platforms

Where international research (multi-country studies) is conducted exclusively online or the online platform is used to recruit study participants, and the PI neither lives or works in South Africa, an exemption from ethics review and approval is possible. This is on the proviso that the PI can demonstrate to a local registered REC that permission has been obtained from the website owners and that a notice of research intent is posted on the relevant website. In addition, the PI must comply with the privacy policies and terms of website use, also with the requirements of POPIA regarding data curation and management, as well as any cross-border transfer of data that includes personal identifying information.

3.3.8.2 Research conducted in foreign countries

Where health research is conducted in a foreign country by researchers, including students, based in South Africa, the studies must comply with the host country ethics review and approval processes recognised in that country, and national laws, standards and regulations in that country. This is in addition to the ethics review and approval obtained from the relevant South African REC. Contact details for both RECs must be included in the consent documentation. The South African REC must ensure that the parallel ethics review and approval records are properly documented and stored.

3.3.9 Research that includes audio-visual recording

Sometimes researchers wish to make visual or audio recordings of participants, e.g., children and their caregivers in situ, faces for dental research, etc. The recordings may be for raw research data usage only but sometimes researchers wish to include them in training materials to be developed in future or for conference display, etc.

If the intention is for the audio-visual material collected to be used for purposes other than research (e.g., for posters or training materials), specific informed consent must be obtained from the participants, with a clear indication of how it will be used. In the case of minor children and their caregivers, note that it would probably be insufficient for the caregiver to provide consent for the children unless the caregiver is the primary caregiver. For example, parents of children in a day care or crèche facility would expect to be asked whether their children may be recorded.

Concerns arise about the clear invasion of privacy and the possible harms that may flow from publication of the audio-visual recordings. However, before coming to a negative conclusion, RECs must request clear information from the researcher as to the necessity for the recordings, what if anything their prior engagement with the community concerned has revealed about how potential participants feel about the possibility of their images being shown at conferences or in

training material. Use of child images should be very carefully considered before approval is given.

3.4 Special topics

3.4.1 Novel, innovative unregistered, and scientifically unproven therapies

Innovative treatment and health or health related research are both experimental in nature. However, the purpose of each is different. The aim of research is to accumulate a body of generalisable knowledge using a standardised protocol for the benefit of future patients. 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.

3.4.1.1 The treatment context

The wish to use a novel, innovative, unregistered or scientifically unproven treatment usually arises in a context dominated by the rule of rescue. In other words, a health care provider may face a situation where standard treatment options have been exhausted, but 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 provider takes primary responsibility to act in the best interest of the patient, in these circumstances, the health care provider 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, unregistered or scientifically 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 section 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 implications for accountability and responsible decision-making about resources in health facilities.

3.4.1.2 Legal and ethical contexts

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

The NHA makes provision for 'health services for experimental or research purposes' (Section 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 requires 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 (see 3.4.1.3). Where the intended novel therapy is classed as research, the REC must review and approve the research protocol 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.

3.4.1.3 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 for 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 protocol is conducted by peers and by persons with expertise in research ethics.

In the context of considering motivations for novel, innovative, unregistered or scientifically 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 ethical may require consideration also of whether a research study is called for to answer the ethical question. If so, then research ethics considerations are triggered.

Current health 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 the social sciences, however, a case study (n=1) is a valid research activity. For example, documenting an exception to a rule or theory is powerful research. Exemption from ethics scrutiny is thus unlikely. A biomedical case series (>3 cases) usually triggers the need for research ethics review, since generalisable knowledge can be generated.

3.4.2 Insurance against research-related bodily injury[66]

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 to treat 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 consider 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 because of interventions or investigational drugs. In the absence of pharmaceutical company sponsorship, no commercially sponsored insurance cover is available.

RECs must pay attention to the measures proposed for dealing with research-related injury in this context. To address this potential problem, some academic institutions buy insurance cover to address research-related bodily injury that eventuates during 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

[66] Detailed guidance for conducting clinical trials is provided elsewhere – see SA GCP 2020 or its successor. Because insurance cover is relevant also to other interventional clinical research, the topic is addressed here too.

offered. This section explains the relationship between research-related injuries and insurance cover.

3.4.2.1 Scope of insurance cover

The layperson's 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 case of *Venter v Roche Products (Pty) Ltd*[67] 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 SA GCP 2020[68] requires a clinical trial sponsor to provide insurance cover. If a trial-related serious bodily injury of an enduring nature occurs because 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 appropriate 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 the policy is in place and valid i.e., up to date.

Payment for medical expenses is made without acknowledgment of any liability and is thus to be understood as an *ex-gratia* payment.[69]

SAHPRA, 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 research participants who suffer bodily injury, including death, in accordance with these Guidelines.

3.4.2.2 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.

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 provide 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.

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 confirmed this view by dismissing Venter's appeal. These cases show that RECs must pay careful attention to the statements

[67] (12285/08) [2013] WCHC 7 May 2013; and on appeal (A11/2014) 22 October 2014.

[68] South African National Department of Health (2020) 'Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa' 3rd ed. (or its successor) 10.2.

[69] Paid 'out of grace', without any legal obligation.

in consent documentation that explain the nature and scope of insurance cover offered.

3.4.2.3 '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, e.g., for 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 A2.2 *Insurance against research-related bodily injuries: wording for IC document* for guidance about the consent document wording for insurance cover for research-related injury.)

3.4.3 Data science research

Data science is transforming the health sector at an unprecedented rate, through its use in a variety of contexts, including precision medicine, pharmacovigilance, digital epidemiology, accelerated patient diagnoses, home-based care, clinical research and drug development.

Health and health-related research projects seek to maximise unconventional data sources (e.g., social media, see 3.4.3.3), partially inscrutable data analytics tools (e.g., machine learning), and big volumes of data. The evolution of research practices and new methodologies such as post-hoc data mining have blurred the concept of 'human participant' and caused a shift towards the concept of 'data subject', as used in data protection regulations. Data science, however, raises legal, ethical, and security issues associated with collection, storage, use and sharing of these data.

3.4.3.1 Context for big data research and AI technologies

Because the amount of health-related information generated is enormous, and may be gleaned from unusual sources, privacy and autonomy in data science research cannot be assured with certainty. Furthermore, inherent to analysis of big data is finding unexpected correlations, associations, and trends due to the computational analytics, which could pose harm to individuals or biologically related groups of people or even communities.

RECs must consider the potential ethical implications, societal impact, and privacy concerns associated with data-related activities, and that data usage, sharing, archiving, and deletion are in line with relevant national, regional and international legal frameworks and ethical principles. Data ethics aims to ensure that data practices align with ethical principles and respect the rights and wellbeing of individuals, communities, and society. However, specific aspects challenge the application of the familiar norms and standards:

Major ethical issues arising from the collection and use of big data include:

- Informed consent

The tool of consent has limitations in big data research:

- Given the general nature of how big data are collected and processed, the requirements for individual face-to-face informed consent cannot always be met for these types of data. It is possible, thus, that participants or even the general public may be unaware that their information is being collected and used, or be unaware of the purpose of such use. For example, social media data collected by researchers or private companies using broad consent, can be reused (i.e., resold and repurposed, a phenomenon known as data brokering) by researchers to conduct

additional analyses without REC approval. It is not only reuse of the data that poses unforeseeable risks.
- RECs face the challenge of assessing the value of informed consent for big data projects.
- Information provided for the informed consent process cannot disclose all possible future uses of data, partly because these uses may be unknown at the time of data generation.
- Researchers can access existing datasets multiple times and reuse the same data for alternative purposes.
- Furthermore, to obtain fresh consent from participants can be impractical particularly when data sets include consumer generated data (e.g., social media data) for research purposes. This leaves 'participants' unaware of their participation in specific studies and makes them incapable of engaging with the research progress.

- Anonymity

It is unclear whether data in which the individual can be identified should be deidentified before storage or before subsequent data access.
Further ethical concerns associated with use of big data include the possibility of inadequate protection of personal privacy. Balancing data protection and privacy concerns with data sharing and open science is a persistent challenge

- Data resource reliability

In almost all cases, it is unclear
- who is collecting the data
- where it is to be stored (e.g., cloud, databank, hard drive etc)
- how it is to be stored
- the chosen format for storage
- whether data relate to individuals or are aggregated
- whether they are deidentified and if so how
- who has access to the data
- how long the data are to be stored
- whether data are periodically destroyed or wiped or overwritten

- Use of data for covert purposes

This includes use for surveillance, profiling or diagnostics. These data on human actions and movement can be used both positively (e.g., to deter public violence and hence advance public health) and negatively (e.g., to limit or stifle human actions, and to control public spaces).

- Unpredictability of emergent correlations

The nature of computational technologies used in big data analytics, make it difficult to anticipate all the correlations that could emerge from the analysis. This is partly why big data research proposals are often tentative in approach to research questions, rather than indicating a specific hypothesis. Difficulty with framing big data research clearly makes it harder for RECs to anticipate unforeseeable risks and potential societal consequences.

3.4.3.2 Application of research ethics considerations to data science research proposals

The current ethics review approach might not be suitable to assess some stages of the data lifecycle, such as deployment of machine learning algorithms. Rather than reusing data, some big data studies build models from existing data (using data mining and machine learning methods), creating new data, which are used to further feed the algorithms. Sometimes it is not possible to anticipate which analytic models or tools (e.g., artificial intelligence) will be used in the research.

Potential algorithmic biases, especially in selection of data sets or algorithms, could lead to stigmatising of certain groups or categories of people based on gender, health conditions, socioeconomic status, lifestyle, etc. A lack of equity in selecting data sets could exclude categories of people, leading to unbalanced analyses.

The initial gathering of data could have ethical implications if they were gathered unethically or for another purpose – i.e. through the common crawl dataset, by avoiding paywalls, or by copyright violations. Moreover, the data may

include unethical content (all of which may not be advertised to the would-be user).

Data protection measures should be aligned with the requirements of POPIA, including the conditions for cross-border transfer and sharing of health data. While POPIA provides legal provisions for data protection, the limitations of POPIA on big data research must be recognised. These include unavailable or lack of informed consent for the original collection of data, the possibility of future research, and deidentification of data. In addition, there can be challenges with transparency, sharing of information, public engagement, reciprocity.

Therefore, RECs should consider the following when reviewing studies related to data science research, including big data.

a) What are the data's availability and quality, and are they applicable to the local context?

b) How were the data sourced? Are the data in aggregate format, how are the rights of affected populations protected?

c) How has the proposed selection of data sets been identified? Has potential selection bias been addressed? Has the limitation of the data been demonstrated?

d) Informed consent: how is this facilitated, implemented and documented for project-specific studies (please see section on IC).

e) How are the participants' right to withdraw their stored data facilitated and protected?

f) Where secondary data is being used, how were the provisions for informed consent for the original data collection facilitated?

g) Where big data is used and consent for the use of the stored data is not available, how does the researcher balance issues related to participant privacy while acting in the public interest?

h) What measures are in place to uphold individual privacy and confidentiality? What measures are put in place to mitigate possible risks to reidentification of study participants? Is there potential for data to be re-linked to groups of individuals?

i) Are there processes in place for regular evaluation of biases especially in big data research.

k) Has the researcher considered the entire data cycle, from the source to where the data go, where and how it is stored, who has access, with whom and how data will be shared, how the data will eventually be disposed of, Was the data processing lawful, fair and transparent? For this purpose, researchers should submit a data management plan, which can include how data will collected, stored, accessed, shared and disposed of or retained (See 3.1.1). The data management plan should indicate how data security will be maintained and the processes for dealing with possible data breaches.

l) Has maintenance of confidentiality of and accountability for the data been discussed?

m) Does the data management plan indicate how data security will be maintained as well as the processes for dealing with possible data breaches?

n) Where stored data are re-purposed, how is unauthorised sharing of data with third parties avoided? Similarly, would unauthorised sharing of data inadvertently stigmatise affected individuals?

o) Does transfer and processing of data meet POPIA requirements?

p) If data sharing options include the use of open-access databases, do the selected databases meet the minimum legal, ethical, and security requirements?

q) Will the data be used for commercialisation?

3.4.4 Artificial intelligence (AI)[70]

Artificial intelligence (AI) refers to the automated tasks performed by computers through use of encoded algorithms to imitate human intelligence. AI technology includes machine learning applications based on statistical and mathematical modelling techniques used to define, describe and analyse data. An algorithm is a set of commands that must be followed in a specific order for a computer to perform calculations or other problem-solving operations. Machine learning can be categorised into supervised learning, unsupervised learning and reinforced learning. These categories highlight the extent and continuum of human involvement and control in machine learning applications, which in turn can give rise to ethical concerns. Despite the value of such technologies, associated ethical, legal, and social implications of AI-powered research must be reviewed by RECs to ensure that research participants' rights and interests are protected.

3.4.4.1 Application of research ethics considerations to AI research proposals

In addition to the usual research ethics considerations, research in AI technologies raises specific challenges with AI applications and their implementations in real world settings. These considerations include how the model performs, accuracy, calibration of the model, and the impact on real patient/participant care. Other issues include the extent to which applications of AI may cause loss of knowledge in the field, and where responsibility lies in real terms for implementation of the AI technology.

RECs, thus, need to consider the following ethical considerations when reviewing protocols related to AI using the framework below:

If the researcher is focusing on machine capability and there are no human participants, then no ethical review and approval is needed. However, if the researcher intends to apply such technologies in a clinical setting and involves human participants, then ethics review is required. RECs need to also be aware of such nuances when simulated data is used for research purposes.

a) Transparency

Transparency in the context of artificial intelligence (AI) necessitates openness and clarity at every phase of the research. This includes disclosure of AI development processes, methodologies, data sources, algorithmic functioning, and decision-making mechanisms. Transparency is crucial for fostering trust among stakeholders, including patient/participants, healthcare providers, researchers, and the general public. Transparency also includes who are the decision makers: and is it an appropriate method for use.

b) Explainability

Researchers should explain how interpretable these models are, how this interpretation is communicated to a user, and to what extent interpretation is possible.

c) Responsibility and Accountability

Given that there are multiple role players in the development, supply chain, and use of the AI products, accountability may involve many parties e.g., manufacturers, investigators, information processors etc. Researchers should have a sufficient understanding of the AI model / technology and take responsibility. Thus, information on technical engineering perspectives should also be made available for the RECs conducting the review. The ethical and responsible use and deployment of AI tools remains the responsibility of the Principal Investigator to ensure the protection of research participants' data.

d) Equity and fairness

AI tools must be designed and implemented equitably and without unfair discrimination against any individual or group. Diversity and inclusiveness is necessary to avoid bias in

[70] World Health Organization; 2021. Ethics and governance of artificial intelligence for health: WHO guidance. Geneva: Licence: CC BY-NC-SA 3.0 IGO. https://www.who.int/publications/i/item/9789240084759.

healthcare access and outcomes, and to promote equitable access to developments and knowledge in the field of AI.

Special attention should be given to vulnerable and historically underrepresented populations to avoid exacerbation of existing disparities. Researchers should actively involve diverse participant groups in the design and testing phases to ensure fairness and representation. Additionally, algorithms should be assessed regularly for bias, and any discovered discrepancies should be promptly addressed and rectified.

e) Benefit sharing

Benefit sharing, with particular attention to the needs and contributions of LMICs including LDCs, should be considered. Evidence of fostering equitable and collective sharing of the benefits and burdens of research must be presented.

f) Safety and security

Safety risks and well as vulnerabilities to attack (security risks) should be addressed, prevented and eliminated throughout the lifecycle of AI system.

There should be evidence related to the safety, accuracy and efficacy of the AI technology so as to avoid risk of harm to research participants.

Safe and secure AI should be enabled by the development of sustainable, privacy-protective data access frameworks that foster better training and validation of AI models.

g) Risk of harm, safety measures, and monitoring

Researchers must prioritise safety in the implementation of AI-enabled systems, with thorough assessments of the risk of harm and strategies for mitigation.

Automated machine learning models can make errors, e.g., producing false information not based on original training data, which can contaminate the integrity of evidence-based decision-making. Data that is predominately obtained from a single group based on race, ethnicity, socioeconomic class or country of origin, are likely to produce biased results that may perpetuate injustice and misrepresentation of groups in data-making. Studies using anonymised data should not be deemed oversight-free by default, as it is increasingly hard to anonymise data. Technological advancements might soon make it possible to re-identify individuals from aggregate data sets.

Ethical scrutiny of AI research projects should be continuous and adapt to evolving circumstances. Regular re-evaluation as new information emerges and as the technology progresses is expected.

RECs should consider the following questions for the review process:

a) Does the AI technology meet the current standards of scientific validity and accuracy applied in similar settings?
b) How have researchers prioritised safety in the implementation of AI-enabled systems, with thorough assessments of risk of harm and strategies for mitigation?
c) What measures are put in place to ensure that the rights and privacy interests of vulnerable groups included in AI research, are protected?
d) Is the AI technology appropriate and can this be adapted to the local context of health care?
e) How is diversity in language managed to promote understanding and interpretation of AI technologies?
f) Has the technology undergone a rigorous process of meaningful stakeholder consultation and engagement and that information is readily available?
g) Could the application of AI technology for predicting future health risks result in possible stigmatisation and marginalisation of individuals?
h) Deliberations of the appropriateness of AI method chosen, and where final human determination should apply.
i) There has to be attribution of ethical and legal responsibilities for any stage of the life cycle of the AI system applied in the research, as well as in cases of remedy related to the AI systems, to physical persons or to existing legal entities. Some decisions e.g., a life and

death decision, should not be ceded to AI systems.

j) In case of post-mortem use of data: What happens to the data after the person dies: how is safety of information maintained, and how is disclosure of the information facilitated? (See 3.1.10.2).

k) Are the benefits of the AI clearly articulated, and how will the research team be recognized as part of the benefit sharing agreement.

3.4.4.2 Novel issues for RECs

Although data science research is suffused with considerable novelty and technical sophistication, the principles, norms and standards for conducting sound responsible research remain much the same as for traditional health research. As was the case with the pandemic of 2019-2022, it is easy to become overwhelmed in the face of unfamiliar terms, ideas and complex protocols submitted to RECs by those who understand the new technologies, while RECs may need help to do so.

Researchers concerned should demonstrate to the REC that a protocol proposes a study that is sound, responsible and ethical that the usual expected standards are able to be met, that their data will be sourced ethically and sustainably, that the original persons who provided raw data will have their personal information interests protected.

RECs will face many novel and complex issues when dealing with data science. It is recommended that RECs should co-opt or appoint experts on data science, especially for technical input. Further, RECs should involve both researchers and data subjects in the assessment of big data research.

In addition, ongoing learning opportunities should be arranged to assist REC members and administrative support staff to learn the terminology and its contextual meaning as well as data ethics, so that administration and processing of applications to the REC will progress smoothly.

3.4.4.3 Oversight of data science research

Gaps in RECs' regulatory processes, together with increased sophistication of research contexts for data science, which now include a variety of actors such as universities, corporations, funding agencies, public institutes, and citizen associations, have led to an increase in the range of oversight bodies.

Specialised committees have already found their place alongside RECs when research involves international collaboration and data sharing. Among others, Data Safety Monitoring Boards Data Safety Monitoring Boards (DSMBs), Data Access Committees Data Access Committees (DACs), and responsible research and innovation panels serve the purpose of covering research areas left largely unregulated by current oversight mechanisms and regulatory frameworks.

Chapter 4

Human and Animal Biological Material and Data for Research

This chapter discusses use of human biological material (HBM) from living and deceased persons; collection of HBM, data;[71] consent for collection; storage and retention of HBM, data; secondary use; and repurposing of HBM, data. Use of databases, controlling access and managing stored HBM and data are examined. In the last part of the chapter, the unique features of genetic and genomic research are discussed.

4.1 Introduction

The NHA permits removal of HBM from living and deceased persons for diagnostic,[72] therapeutic, health research purposes[73] and for health care training and medicolegal purposes.[74] In line with these permissions, researchers often collect data, including images, or HBM from participants, or use data previously collected for other purposes, for research. Once collected, both HBM and data may be stored in repositories as future research resources.

Although HBM are separate from their source (e.g., a specific person), they symbolise that person. Hence, ethical considerations concerning access to collected materials, appropriate use, management of potential privacy concerns arising from information management, as well as how to address the special status some groupings of the population ascribe to the human body and its parts, should be managed carefully. RECs and researchers must demonstrate sensitivity to the values, beliefs, and attitudes of the persons from whom the materials are collected.[75]

Use of data and HBM 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 HBM, be meticulous in their deliberations, and should ensure the integrity and comprehensiveness of the informed consent documentation. Consent documentation must distinguish clearly between HBM and data collected for clinical purposes, and those collected for research purposes, as well as those collected for any other reason and later re-purposed for research.

4.1.1 Collection of HBM

HBM are collected for various purposes:

- specifically for research
- incidentally for diagnostic or therapeutic procedures
- for health training and medicolegal purposes
- for a combination of purposes, including storage for possible future research use
- some collected HBM comes from surplus or waste

Collection of HBM specifically for research use requires prospective informed consent, usually from the living donor/participant. In exceptional circumstances, where a donor/participant is not able to provide informed consent, proxy consent may be permissible (see 3.1.10.1*ff*). For deceased persons, section 62 of the NHA directs from whom consent should be sought.

[71] To clarify, 'data' refers to all sorts of research data and not only data associated with HBM. All data can be stored, shared and reused.
[72] NHA sections 55 and 62.
[73] NHA section 64(1).
[74] NHA sections 64 and 62.
[75] 'Human 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).

4.1.2 Different consent models

Note: 'Blanket' or unrestricted consent is not acceptable because it cannot sustain fundamental ethical principles.

Several models exist:

4.1.2.1 Specific (narrow) consent

This form is the most restrictive. It permits use of the HBM for the current research study only and excludes consent to

- storage of left-over HBM for later use
- sharing of data or HBM with other researchers

which means that the HBM (including left-over and waste) must be disposed of at the end of the current study. If further use for additional research is wanted, fresh consent must be obtained before disposal occurs.

4.1.2.2 Tiered (differentiated) consent

This form lets the donor/participant provide consent for the current study and to include consent to a small range of additional options if wanted, e.g., to permit storage of their HBM and associated data for specified future research use, or to permit data sharing, or both, etc.

4.1.2.3 Broad consent

This form is more flexible than tiered consent but still maintains limitations. It lets the donor/participant provide consent for the current study, and to include consent for storage, and for future research use that is within the scope of the current research. This is permitted even if the precise topic of future research is unclear at present.

For example, broad consent would indicate

- the types of secondary research permitted with the HBM and associated data
- the type of personal information or HBM that may be used in the secondary research
- whether sharing of the materials and data may occur, as well as
- whether HBM and/or associated data may be exported
- how long the samples and materials may be stored, maintained and used
- whether the donor/participant wants to be informed when subsequent research takes place
- whether results from subsequent research will be disclosed to donor/participants
- the contact information for donor/participants to ask about the storage or use of their HBM and data

The nature of possible further usage should be described as fully as possible even if the precise topics are unknown; and the consent document must stipulate that further prior ethics review of any new study is necessary, and that permission may be requested to re-contact the person for fresh consent if the future use is outside the scope of the current consent.

4.1.3 Restrictions on collection of HBM

Certain persons are specially protected: without Ministerial permission, HBM may not be taken from mentally ill or incapacitated persons; HBM that are not naturally replaceable may not be taken from a minor; no gametes may be taken from a minor; and no fetal HBM, except for umbilical cord progenitor cells, may be collected. These restrictions are absolute, which means that research with the categories of person mentioned requires Ministerial permission. Researchers must provide RECs with appropriate evidence that the necessary permission has been obtained.

4.1.4 Identifiability of HBM

The presence of hereditary elements in HBM implies that any biological sample can be re-identified, albeit more likely to a group of persons rather than to an individual. This biological fact has implications for the consent process, insofar as donor/participants should understand clearly what is being requested when asked for HBM samples. Use of Artificial Intelligence algorithms with big data has revealed that identifiability is more likely than was originally thought possible.

The researcher must explain the implications of anonymisation for the participant in the consent documentation, e.g., anonymisation

means that disclosure of material findings to the donor/participant is not possible; it also means that access to possible benefits of research findings is unlikely, and it means that the donor/participant cannot withdraw their HBM from research use. RECs must scrutinise consent documentation carefully to ensure that the proposed approach and its implications are adequately disclosed and explained.

HBM with direct identifiers can identify a donor/participant. Coded HBM may identify a donor/participant if security and confidentiality measures are not adequate. Anonymised HBM without any linkage to a donor/participant are unlikely to identify the person. HBM collected without identifiers of any kind are unlikely to identify a person. Genetic markers make it possible to identify groups rather than individuals. Researchers must pay attention to eliminating or at least minimising risks to privacy and autonomy resulting from re-identification. RECs should check that this element has been adequately addressed by the researcher.

4.1.5 Secondary use of HBM or data

HBM collected for diagnostic or therapeutic purposes are usually stored for future use, e.g., pathology samples. Secondary use means using HBM or data[76] originally collected for another purpose. Surplus HBM samples may have been stored in a biobank or another type of repository. The importance of stored HBM and data as research resources cannot be overstated.

The ethical dilemma is whether later unanticipated use for research necessitates new informed consent and, if so, what should be done when a donor/participant is no longer available to provide consent for the further use of the HBM or the data.

The content of the previously obtained consent determines whether subsequent usage was envisaged and, if so, whether the envisaged use falls within the scope of the current protocol. If so, new consent is not required based on the tiered or broad consent previously provided (see 4.1.2).

In the absence of previously obtained consent to future use for research purposes of stored HBM or data, the following considerations are recommended:

a) If the scope of the current protocol is different from the original protocol, new consent is required.
b) If the HBM samples or the data are anonymous or de-identified[77] and the results of the research are unlikely to place any individual, family, or community at social, psychological, legal or economic risk of harm, then new consent is not required.
c) If a link to the identifiers exists but is not provided to the research team and the results of the research are unlikely to place any individual, family, or community at social, psychological, legal or economic risk of harm, then new consent is not required.
d) Archived HBM collected for clinical or diagnostic purposes, including waste and surplus samples, wanted for use for research purposes, (subject to a) and b) above) must undergo HREC review.
e) In certain circumstances, the HREC may waive the requirement for new consent if justification shows:
    i. the research poses no more than minimal risk of harm to participants or to the group to which the participant belongs,[78] and
    ii. the research has important social value, and
    iii. the research would not be feasible or practicable to carry out without the waiver.

[76] Data are not limited to data associated with HBM but include all types of data, including questionnaires, interview records, images and audio records, collected for research or other purposes.

[77] See Glossary for explanation of terms used.

[78] CIOMS Guidelines (2016) Guideline 11 p41.

4.1.6 Responsibilities associated with storage and retention

Storage of records and research data is usually associated with legal obligations to do so, while retention of HBM samples occurs to preserve the samples for future research use.

Informed consent for storage and retention must be obtained in addition to consent to participate in research.

If the donor/participant provides a more flexible consent than specific consent (see 4.1.2.1*ff*), the consent document must describe in sufficient detail

- how and where HBM or data will be stored or retained to prevent breaches of confidentiality and unauthorised access
- that future use of HBM or data will be preceded by further ethics review of protocols
- that stored and retained materials will be labelled with a unique code not derived from information about the donor / participant
- how de-identification or anonymisation will occur
- how long storage or retention will endure. If the duration of storage or retention is unclear due to the nature of the research, this must be indicated clearly together with a best estimate
- how destruction of data and/or HBM (if applicable) will happen.

Custodians of stored data must protect confidentiality of the information linked to the data, by sharing only anonymised or coded data with researchers, and by limiting access by third parties to the material. Custodians involved with storage, retention and sharing of HBM and data (e.g., researchers, clinicians based in hospital departments, biobankers) should have clear governance structures that include conditions, as well as written agreements for access and sharing. For example, a material transfer agreement (MTA) is required for sharing of HBM or data between researchers or research institutions for health research or clinical trials. The key to the code must remain with the custodian of the data. 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 HREC.

Withdrawal of consent to storage and retention is permissible at any time if the effect of withdrawal is feasible. In response to a request for withdrawal, the samples and/or data must be destroyed or returned to the donor/participant. Further use is not permitted after withdrawal of consent. However, practical limitations may prevent withdrawal, e.g., samples in genomic research, genomic data, or health information. Withdrawal is complicated as stored HBM and data may already have been shared with secondary users not involved with collection of the original samples. Researchers should explain fully the potential limitations and consequences of withdrawing samples and data from research in the consent document and discuss these as part of the consent process. Contact details relevant to withdrawal of consent must be made known to participants. Withdrawal of consent includes withdrawal of remaining HBM samples, which should always be possible to destroy or return, even if associated data cannot be withdrawn.

In the event of closure of the biobank or databank, plans for appropriate transfer or disposal of the health-related data should be developed in collaboration with local health authorities.

4.1.7 Cell lines

Biosafety and ethical issues may arise from use of 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.

Note that ‘blanket approval’ for use of 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.

4.2 Databases, storage and access

4.2.1 Databases, registries and repositories

Databases (also known as data banks), registries and repositories may be created for research, diagnostic or clinical purposes.[79] They constitute valuable resources of stored information that allow researchers to pursue questions not anticipated at the time of data collection. Increasing access to research data 'has the potential to make the entire research system more effective, participative and productive by reducing duplication and the costs of creating, transferring and re-using data.'[80] In essence, data sharing can decrease the research burden on future participants, facilitate wider dissemination of research outcomes, improve opportunities for collaborative research, improve responsiveness to societal challenges and foster greater research integrity. In addition, re-use of research data can lead to greater transparency and social engagement. Collection and storage of data and human biological materials (HBM) should balance the need for adequate participant safeguards with optimal advancement of such research in line with the stated goal expressed above.

4.2.1.1 Data repositories

Data repositories are not uniform. They differ in terms of who holds the data as well as the nature of the data held. The repositories can be institutional, governmental, discipline or program specific, or generalist data repositories. The frameworks (i.e., workflows and resources) in place at different repositories will vary in terms of data handling, oversight and whether data versioning is provided.

Before uploading or sharing datasets, researchers should consider the ethical, legal and security protections offered by the repository to assess whether the repository is fit for purpose. For example, does the repository

- ensure that human data have been anonymised. Names, initials, addresses, specific dates (birth dates, death dates, examination dates), and contact information should not be shared
- protect individual participant data, which, even if de-identified, may trigger re-identification concerns, especially in the context of big data.
- aggregate data do not generally disclose information about individuals and are safer to share openly
- ensure the deposited data are complete and well curated, are of the highest quality and documented appropriately
- ensure the data are shared in accordance with the ALCOA++ principles (Attributable, Legible, Contemporaneous, Original, Accurate, Complete, Consistent, Enduring, Available, , Traceable) and CARE principles (Collective Benefit, Authority to Control, Responsibility, Ethics)
- provide detailed documentation that describes the dataset, including its sources, collection and processing methods, limitations, and potential biases
- ensure study participants have consented to permit their data to be publicly available
- ensure that the data were collected in accordance with NDoH 2024
- note that certain data may not be shared due to participant privacy violations, national security concerns, or patent restrictions

[79] The NHA 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.

[80] Department of Science and Technology. Draft White Paper on Science, Technology and Innovation. 2018. p. 12.

- ensure the repository is trustworthy

Different models of access restriction vary significantly but, generally, data access levels fall somewhere along the spectrum of open, restricted, and controlled.

a) Open data repositories

Open data repositories are platforms that hold research output that permit researchers immediate and free access to share and download original research datasets. Repositories holding research data about individuals and aggregates of individuals are expanding in size considerably.

Researchers can access them remotely and use large volumes of possibly sensitive data without communicating or actively engaging with any study participants. Consequently, participants become more vulnerable and subjected to the research itself. As such, the nature of risk involved in this new form of research changes too. In particular, it moves from the risk of physical or psychological harm towards the risk of informational harm, such as privacy breaches or algorithmic discrimination.

b) Restricted access repositories

Restricted access ensures that only bona fide researchers, bound by professional obligations and specific agreements, have access to the data under certain data security conditions

c) Data security mechanisms

A wide variety of data security mechanisms is deployed by repositories, often linked to sensitivity of the data. Examples include:

- various levels of control may be imposed by the repository developer and custodian often through formal data sharing agreements with explicit researcher and institutional obligations articulated, including a mandate not to attempt to re-identify participant data
- data may be shared over secure platforms and may not be downloadable
- some repositories require members of the data repository to collaborate on projects
- some use audit trails to provide greater accountability and protections

d) Trustworthiness of stored data

- Researchers require confidence that the repository data storage systems are reliable administratively, technically and secure from unwarranted exploitation or cyber-attacks.
- Research participants require confidence that their (personal) data will be adequately protected.

e) Responsibilities of repositories

Data repositories should have

- published clear Terms of Use information, which includes information for situations that may require removal of a dataset, as well as about how ethical violations will be managed, and how the data publisher will respond if it comes to light that public availability of a dataset presents a risk of harm to participants, endangered species, sites, specific communities, or society
- content preservation and archiving workflows that, where possible, include notifications to indexing or preservation services when a new dataset version is posted or a dataset is removed, and when a dataset is published, repositories assign it an identifier, such as a unique identifier or an accession number
- a clear data management plan
- clear descriptions of responsibilities and expectations that researchers who access data have for its responsible re-use in research
- access regulation to research materials that allows beneficial data sharing globally while protecting rights of the participants to whom the data pertains
- transparent governance that requires comprehensive and open description of the conditions of access so that data custodians can make responsible decisions about the level of access they believe is appropriate for their data and research output
- policies that address researchers' concerns about losing priority in future publishing

and potential commercial use of their work without their consent or participation
- policies that require explicit acknowledgement of the contribution of initial investigators by subsequent researchers who request access to the data
- policies that outline the ethical expectations for publication of data, and how breaches will be followed up
- a legal provision that sensitive data may be transferred to a foreign jurisdiction only if satisfactory or equivalent levels of data protection prevail in the receiving jurisdiction.

f) Fair attribution of credit/acknowledgement

It is a well-known principle of research integrity that failure to acknowledge the work of others used in one's own work is plagiarism. Yet, the act of making data available as a building block for other researchers to use, seems not to prompt acknowledgement of the initial investigators from those who are granted access to the stored data. Amongst the concerns are that there are no clear standards for citing others' data and that, if data are cited, there is lack of professional credit for having made the data available. In the current climate of expectation of increased data sharing practices, better acknowledgement practices and alignment of professional evaluation structures is desirable.

g) Rights in HBM and data

Claims to ownership of HBM and data are made frequently. Neither HBM nor data are capable of private ownership in South African law. To the extent that rights in HBM and data exist and are recognised and protected by law, they are likely to constitute intellectual property rights, if the requirements can be met.[81] For both HBM and data, responsibilities associated with safety, preservation, sharing, etc lie with the person (natural or juristic) in possession. The concept of stewardship is probably the most apt way to think about the responsibilities. However, a more familiar notion is custodianship, as used in the legislation governing water (National Water Act) and mining and minerals (MRPDA). Neither water nor minerals are open to private ownership. Instead, state custodianship forms the basis of governance of these scarce and valuable resources.

4.2.2 Sharing of Human Biological Materials and Data

Sharing of HBM and data can raise ethical challenges that relate, in principle, to protection of individual privacy and confidentiality. Decisions to share HBM or data trigger a tension between respecting individual autonomy by keeping personal information confidential, on one hand, and advancing the possibility of public benefit from increased research because of sharing HBM and data, on the other. A key imperative, thus, is how to achieve a balance between maintaining respect for individual autonomy and ensuring that society benefits from research findings.

POPIA states:

a) that transborder data sharing may not occur unless
   - the recipient is in a country that has similar legal protections for processing of personal information (section 72(1)(a) of POPIA)
   - the data subject has consented specifically to the intended transborder data sharing (section 72(1)(b) of POPIA)

[81] See Academy of Science of South Africa (ASSAf) and Department of Science and Technology (DST) (2018) Human Genetics and Genomics in South Africa: Ethical, Legal and Social Implications. ASSAf Consensus Study (2018) [Web] DOI http://dx.doi.org/10.17159/assaf.2018/0033 at 5.3 pp. 85-86.

– the transfer is necessary in terms of a contract or for the benefit of the data subject (sections 72(1)(c) to (e) of POPIA)

Sensitive personal information can be shared with a third party in a country that does not have an adequate level of protection, if prior authorisation has been obtained or if there is a code of conduct in place.

Section 11(2)(b) of POPIA and the usual research ethics principles permit a research participant to withdraw consent; however, the right to withdraw is limited with anonymised HBM and data.

RECs should consider the following in the review process, in addition to the points outlined above:

- Prior ethics clearance should be obtained before the envisaged HBM and data sharing
- The recipient of such data should have the necessary research approvals to use the data for research purposes
- The recipient should comply with POPIA requirements, have clear processes to deal with possible data breaches, and must inform the provider and REC should a breach occur
- The recipient must specify the timeframe for storage of the data, its destruction where relevant
- Any envisaged re-use of the data not specified in the protocols should be subject to REC review and approval, as well as approval from the provider
- Intellectual property rights must be specified
- If the HBM and data are shared only for research purposes, such HBM and data cannot be used for commercialisation
- The researchers involved in HBM and data sharing must ensure that proper updated records are kept
- Where data alone is shared, a Data Transfer Agreement (DTA) or Data Sharing Agreement (DSA) is necessary. A DTA/DSA may have similar clauses to the MTA, but the actual substance of the agreements may differ depending on the circumstances. This template may be used, with the necessary adjustments made to suit the circumstances and to ensure compliance with POPIA. However, it is noted that the MTA and DTA are considered as separate agreements and should be prepared and used as separate documents that comply with the respective legal and ethical requirements.

4.2.2.1 Material Transfer Agreements

Note: This guidance is not intended to prescribe provisions or conditions (i.e. clauses) in a Material Transfer or a Data Sharing Agreement but rather to provide guidance to researchers about their ethico-legal responsibilities, as well as to RECs regarding what to consider in the review process.

A Material Transfer Agreement (MTA) records formally the binding contractual agreement that governs sharing of HBM. It describes the arrangements between providers and recipients of HBM used in research, including clinical trials, which are required whenever HBM are transferred (shared). This includes the transport of HBM between institutions/organisations within the country and cross-border transfers to provide access by the Recipient to that Material.

The MTA should provide guidance on key issues such as

a) purpose of the transfer of the HBM
b) obligations of the parties
c) terms and conditions under which HBM may be used
d) whether modifications to the HBM are permissible
e) whether third party transfers may happen
f) what the benefit sharing arrangements are
g) the relevant intellectual property rights
h) the indemnity arrangements.

Research institutions may tailor the content to suit their individual contexts. Although some MTAs may include clauses governing sharing of data, it is advisable, as part of data management, to enter into separate data sharing agreements to regulate sharing of one

or more data sets from the custodian/provider to a third party.

4.2.2.2 Data sharing agreements

A Data Sharing Agreement (DSA) records formally the binding contractual agreement that governs sharing of data. It describes the purpose for the sharing and the measures put in place to safeguard against unauthorised sharing and misuse of the data. The DSA also protects rights and interests of donor/participants, as well as collaborating researchers.

The ethico-legal considerations discussed in 4.2.2 apply also to data sharing agreements.

For transfer of personal information outside the national borders Section 72 of POPIA must be complied with.

4.3 Genetic and genomic research

Human biological materials (HBM), whether collected directly from donor/participants or accessed from a repository/biobank, are commonly used in genetic and genomic research.

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

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

4.3.1 Ethical considerations

From an ethical perspective, genetic research may hold both positive and negative implications. While its purpose may be to shed light on causes of diseases and how to prevent or treat them, genetic information is not specific to one individual but reveals much about that person's relatives and others with shared ancestry. This means that the implications for biological relatives of a participant must be considered when seeking consent, depending on the nature of the study. It may be that the participant should discuss participation with known biological relatives who share their gene pool.

Researchers must provide detailed information in the protocol so that HRECs can conduct the ethics review appropriately. When assessing the ethical implications of proposed genetic research, HRECs must pay attention to multiple considerations, including the anticipated social value of the research, consent, privacy, confidentiality, as well as the potential effect of the research findings on families, communities and other social groupings. Because of the types of information that genetic research may reveal, including the range of consequences of this information for participants and their relatives (e.g., in the contexts of health, employment, insurance, and possible stigmatisation), HRECs should consider developing a plan to manage this kind of information. Often, follow-up clinical testing or counselling may be recommended.

The proposed plan to manage the information gathered from genetic research should indicate the clinical relevance of the study findings, the implications of the study findings for both participants and those involved in the study, as well as whether and how these findings will be disseminated. This plan must be explained to potential participants.

4.3.2 Heritable human genome editing

Given the ongoing debates on heritable human genome editing research, there is a need for further national stakeholder engagement to guide the update of ethics review in this area of research. These updates will be communicated to RECs accordingly.

4.3.3 Informed consent for Genetic and Genomic Research

Specific elements should be incorporated into the separate consent process for genetic and genomic research in addition to the usual information for appropriate informed consent for research participation (see 3.1.9). Common features of genetic and genomic research that must be explained include what genetic or genomic research means, that indefinite storage and future use and sharing of HBM and derived data is requested, that there are ongoing privacy vulnerabilities for participants as well as for third parties, that there may be social harms.

4.3.3.1 Informed consent considerations

The consent documentation should explain clearly

a) 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
b) consent documents must state that genetic or genomic research is intended
c) the conditions and requirements under which data or HBM will be shared with other researchers
d) the nature and extent of specific risks of harm related to use and storage of HBM or data, especially if identifiers are retained
e) in the case of genetic or genomic research, the implications of genetic testing (e.g., incidental findings like paternity determinations, insurance risks, reproduction decisions) and associated confidentiality risks and potential benefits (see also 4.3.3.4)
f) where applicable, that HBM may be
    i. used for future research not yet identified
    ii. shared with or transferred to other institutions
g) the freedom to withdraw consent at any time and to request withdrawal of data and that unused identifiable HBM be destroyed. If withdrawal is not practically possible, the information should clearly indicate this
h) the length of storage time
i) when the current consent to use HBM or data will expire
j) possible secondary use of stored material
k) possible creation of an immortalised cell line based on the sample
l) the REC may approve a waiver of consent for secondary use of HBM or data where no more than minimal risk of harm is likely; and the donor/participant's rights and welfare interests are unlikely to be adversely affected; and the research cannot be conducted if the waiver were not approved.

A collection of three broad types of information may be involved: personal information, clinical information and research data to be returned to a database, registry or repository from which the HBM was sourced. This should be described in the IC document. First, researchers might ask donor/participants to complete a questionnaire with personal information, including age, sex, self-disclosed ethnographic details, and personal and family history. Donor/participants should be informed about plans for future recontact to update the information, if appropriate.

Secondly, researchers might request permission to collect clinical information by accessing participants' medical records. Informed consent forms must describe the types of information required to be collected and whether access to medical records will be once-off or ongoing.

Thirdly, some databases, registries or repositories may ask researchers, as a condition of use of stored HBM, to return research data (e.g., genotypes, results of biochemical analyses) so they can be integrated into the collection.

HRECs must also consider the circumstances under which further consent from donor/participants should be sought, bearing in mind specific local or national needs.

Where data or HBM are shared with researchers in other institutions, the recipient

institution must agree to comply with the requirements of the donor institution. Furthermore, use of the data or HBM should comply also with any additional requirements of the recipient institution. Inter-institutional sharing agreements must be confirmed in writing (see 4.2.2).

4.3.3.2 Re-contact of participants

Several reasons determine why researchers might want to re-contact participants, including updating personal information; requesting donation of a further biological sample if the first has been depleted; to re-consent participants who have attained majority during the period of data or HBM storage; or inviting participation in another study. That re-contact is possible should be communicated to potential participants during the consent process. Consent documentation should include an option for participants to select if they are willing to be re-contacted about future research. The document should indicate the likely frequency of re-contact events and indicate how contact may occur, e.g., by telephone, email, SMS or WhatsApp.

4.3.3.3 Risk of harms

The risk of physical harm involved in genetic and genomic research is usually minimal. Potential harms associated with research involving HBM arise from misuse of information, which could lead to unfair employment or insurance discrimination, stigmatisation, psychological harm, group harm, and familial disruption. Thus, the extent to which data or HBM can be linked to specific individuals or groups of individuals is a central component in the assessment of risk of harm. It is also possible that donor/participants could be identified even when data are anonymised, which possibility must be discussed as a risk of harm in the study.

4.3.3.4 Return of research results

Individual return of results means the results of a specific study participant from a scientific investigation. For example, in genomic research, an individual research result could be whether a research participant possesses a particular gene variant. Incidental findings (also known as secondary findings) are a subset of individual research results that are not related to the objectives of the current study. An example of an incidental finding could be that a participant in a study looking at the genetics of heart disease is revealed to possess a gene variant related to Alzheimer's disease.

The research protocol must plan whether and when it will be appropriate to return results to the participants, whether the results are study specific or incidental, which types of results will be returned, and how results will be returned. A baseline guideline for balancing the rule of rescue with maintaining scientific integrity is to have a process that can validate the specific incidental finding and decide whether the finding is medically actionable (i.e., whether an associated action to reduce the risk of a disease or to treat the disease exists), and whether there are sufficient resources to support the medical intervention. Obviously, this process is undertaken only with the consent of the donor/participant who becomes a patient at this point.

The response to incidental findings is ethically and logistically complicated. It is critical, thus, that the protocol addresses the proposed plan of action so that discussions with the HREC and other appropriately skilled and qualified health care professionals and relevant regulatory bodies can assist to find the most humane and appropriate way to manage such findings. Determination of which findings are actionable is in itself a challenging process.

Researchers who plan to return individual research results must bear in mind that some donor/participants may choose to opt out of receiving individual results during the consent process. They cannot be forced to receive their individual results, based on the 'right not to know', which must be respected.

Researchers who plan an opt-out choice must ensure that a robust mechanism to track these choices is in place.

a) Considerations for families

Genomic research results may reveal unexpected information about family relationships, such as the presence of misattributed paternity or adoptive relationships where a biological relationship was previously assumed. Genomic research results about an individual's current or future health risks may also be relevant to family members. Where relevant, researchers should plan how such information will be managed; participants should be informed about the circumstances under which this information will and will not be disclosed to them or to their family members.

b) Considerations for identifiable populations

Identifiable populations, which include specific racial or ethnic groups, geographically defined communities, and members of ultra-rare disease groups, raise concerns about privacy, confidentiality, stigmatisation, and unfair discrimination. Researchers who recruit members of such groups should strive to understand and to reduce potential group risks and communicate about such risks during the consent process, especially regarding how groups will be identified when summary-level results are disseminated. Potential participants should be made aware of individual risks they might face because of being part of an identifiable population, and potential risks to an identifiable population to which they belong. Where possible, researchers should work directly with members of identifiable populations before recruitment and throughout the research study to help inform the study design and the informed consent process.

c) Considerations for studies involving children

Genomic research that involves children can reveal information that might raise concerns for children and their families. Specifically, genomic analyses could reveal the presence of specific conditions (including adult-onset conditions), disease susceptibilities, or carrier status, relevant to the enrolled children or their family members. Depending on the nature of the study, questions that may arise include whether it is appropriate to disclose the risk of adult-onset conditions to children and whether researchers must honour a parental decision not to inform their child about clinically significant information, even when the child attains majority. It must be borne in mind that there is no obligation for any person to receive research results. Researchers who believe that participants who attain majority have the right to decide themselves whether to receive the research results should understand that, as adults, the participants are able to request them independently. The important planning point is that the results should remain accessible to such participants.

4.4 Use of animal biological materials

4.4.1 Principle of reduction

As an integral part of the principle of **'Reduction'**, optimal use and sharing of animal biological materials derived from approved studies are strongly encouraged, to maximise the potential benefit of the use of animals for research purposes. Where practicable, surplus tissue and other biological material from euthanised animals must be shared among investigators (required by the SANS 10386:2021, §4.7.2.6) or deposited in a repository for subsequent distribution and use, subject to further ethics review and approval.

Potential sources of animal biological materials include:

a) surplus animal biological materials, either via extraction from live animals (e.g., withdrawal of blood, smears of body fluids

or excretes, milking of glands, biopsy of internal tissue, etc.), or from post-mortem dissection
b) surplus animal biological materials obtained from abattoirs, retrieved post-mortem, from animals legally slaughtered for meat production purposes
c) animal biological materials obtained from archived samples (e.g., a repository or museum)
d) animal biological materials derived from carcasses of animals that died naturally or accidentally, e.g., in road traffic collisions.

In addition, information from databases compiled from analyses of animal biological materials can be shared for re-analysis or new analysis.

4.4.2 *Secondary use of animal biological materials*

Ethical implications of secondary use of animal biological materials do not include the effect on living animals and their wellbeing. Nevertheless, the AREC must consider several important aspects with ethical implications for approval of secondary use studies.

4.4.2.1 *Considerations of the source or origin of animal biological materials*

a) whether the samples for secondary use have been obtained ethically, e.g., from a previous approved study, or ethically acceptable animal euthanasia or death

Note: Where sample provenance (history) is unknown or questionable, e.g., for museum samples, the possibility of the samples not having been ethically obtained in the past should be weighed against the anticipated benefit to be derived from the study.

b) whether the samples have been obtained with permission from the animal owner or the custodian of samples, e.g., study principal investigator as custodian of the samples
c) whether the samples have been obtained legally, e.g., with required permits, aligned with an applicable MTA or other contract, with consideration for applicable intellectual property rights, and with recognition of applicable indigenous knowledge systems
d) whether scarce or endangered species materials are to be used in a responsible and sustainable manner.

4.4.2.2 *Considerations of biological safety, with appropriate mitigating measures*

a) physical, chemical, or pathological risks for researchers and other who collect, transport, analyse and dispose of animal biological materials
b) the community, other animals and the environment regarding the collecting, transporting or analysing and disposing of the animal biological materials, for example to prevent the spread of disease from one to another environment (e.g., Section 20 permit of the Animal Diseases Act: 35 of 1984). Also see A3.3 *AREC regulatory framework*

4.4.2.3 *Considerations for the integrity of samples*

Samples must be fit for purpose, especially regarding

a) physical integrity, e.g., regarding storage conditions and duration, record keeping, etc. and
b) identity security, e.g., sample labelling, record keeping, access control and security

4.4.2.4 *Additional considerations for specific uses of animal biological materials*

Additional legislative provisions apply when certain uses of animal biological materials are to be conducted. These provisions may require authorisation, specifically appropriate facilities, additional training, as well as necessary safety and mitigating measures in place. In addition to ethics review and approval, a biological safety committee or officer must approve the usage. Examples of uses that trigger additional precautions include

a) genetic manipulation of animal biological materials
b) animal biological materials with existing infection with pathogens

c) experimental infection of animal biological materials with pathogens
d) use of radioactive or other controlled dangerous or toxic substances or materials.

Chapter

5 Research Ethics Committees

This chapter outlines and discusses the governance framework for Research Ethics Committees, their role, how they are constituted and the national and institutional expectations of REC members. In addition, the chapter explains the objectives and desired outcomes of research ethics training, as well as providing guidance and examples of standard operating procedures (SOPs).

5.1 Introduction

Health or health-related research must be reviewed by Research Ethics Committees (RECs) registered with the NHREC. If all relevant standards are satisfied, then the REC approves the protocol, with or without additional conditions (NHA section 71(1)(a) read with section 73(2)).

5.2 Governance framework

5.2.1 Statutory framework

Section 73 of the NHA requires every institution, health agency and health establishment at which health research is conducted, to establish or have access to a REC, which is registered with the NHREC (see 1.2).

Researchers without affiliation to an institution or organisation with a REC should approach a registered REC[82] to request it to review their health research protocols. If the REC is willing to review external applications, a fee for service may be levied.

5.2.2 Terms of Reference and Standard Operating Procedures

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

The ToR is a legal document that informs any interested party about how the REC fits within the institutional committee framework, describes the formal character of the committee, and usually combines institutional requirements with the NHA and NDoH 2024 requirements (see Appendix A1.2 *List of statutes, regulations and other instruments*). The ToR should include the delegated and inherent authority as well as the scope of the REC's authority[83] (i.e., the nature of its powers), its responsibilities, its relationship to non-affiliated researchers, its accountability responsibilities, bearing in mind its dual governance mode (see 5.3), the mechanisms for reporting and remuneration, if any, for members. Unlike SOPs, ToR are not usually regarded as 'living documents', open to frequent revision. They are expected to guide the life and operation of the REC on a semi-permanent basis.

An approval process for ToR must be in place within the institution, e.g., if the REC is a faculty-based committee, the ToR must be approved by the Faculty Board (or similar entity) and then by the Senate (or similar entity). If the REC is an institution-wide committee, the ToR must be approved by the appropriate committee at the appropriate level of the institution or entity. These processes assist with transparency and dissemination of information to relevant stakeholders.

The ToR document for a REC must be in a proper format, as per institutional policy, and at least contain a descriptive title, institution's name and logo, an approval and revision date version control and history, signatures authorising the approval at the appropriate level, and the appropriate subheadings or content which may include purpose, scope, authority and accountability of the REC and its relationship to the institution, administrative, financial and other support, training-related matters, communication and reporting

[82] A list of registered RECs is available on the NHREC website at https://www.health.gov.za/nhrec-registration/.

[83] Note that if the ToR do not indicate the existence of a power or authority to do or not do something, then the REC concerned does not have the power or authority concerned. For example, if the authority to appoint subcommittees or to co-opt members is not provided for, then the REC cannot do this.

channels, reference to code of conduct, REC composition and appointments, procedure(s) and resources, compliance of the REC with national legislation and relevant regulatory documents (including NDoH 2024 and SANS 10386:2021 or latest versions, and other relevant documents), and reference to resources.

SOPs set out systematically in detail exactly how the operations of the RECs must occur, including how to review protocols, identifying the various procedures and considerations that should be taken into account, as well as providing information or references to additional materials to assist with the process of review and application for ethics approval. (See also 5.5.)

An approval process must be in place for SOPs, e.g., via the institutional reporting system. SOPs are regarded as living documents and are open to being changed as and when needed, in accordance with the relevant SOP for amending SOPs. They are not open to unilateral variation on the basis of expediency. Their existence and content are important for purposes of transparency and information dissemination to relevant stakeholders. No institutional official, researcher or REC member should be able to claim ignorance of the SOPs.

SOP documents must be in a suitable SOP format, as per institutional policy, and at least contain a descriptive title, institution's name and logo, an approval and revision date (e.g., after 3 years, although it may be a living document), version control and history, signatures authorising the approval at the appropriate level, and the appropriate subheadings or content which may include purpose, scope, responsibilities, procedure(s) and reference to resources.

The institutional Research Policy, the REC ToR and SOPs, as well as templates and forms should be easily accessible to REC members, researchers, and other interested persons, usually via internet or intranet sites.

5.2.3 Expectations of institutions that have RECs

5.2.3.1 Code of Conduct

Each institution must have a Code of Conduct for REC members, which details the conduct and integrity expectations of members, including regular and punctual attendance at meetings, diligent performance of responsibilities, maintenance of confidentiality, and management of potential conflicts of interest. The induction process for new members should require that they sign the Code of Conduct to indicate they know and understand the expectations. (See *A2.6 Code of Conduct for REC members sample.*)

5.2.3.2 Administrative support and resources

Institutions must ensure that adequate administrative support and resources are provided for RECs so that their work can be done in compliance with the minimum standards as described in these guidelines and the statutory governance framework. It is the responsibility of the institution to oversee the system within which the research ethics review process must operate to ensure that all research protocols that must undergo ethics review before being conducted, can enter the process timeously.

Expected administrative support includes

- sufficient adequately trained administrative personnel to manage the office administration required to process research ethics applications, organise and service REC meetings, including agendas, minutes and the other regular record keeping and reporting tasks expected of RECs , support for other processes and activities expected from the REC as per these Guideline
- clear, transparent, and accessible procedures and criteria in place for recruitment and appointment of REC members
- structures and processes in place to deal with complaints, queries and appeals about REC operations and decisions internally, before escalating matters to the NHREC

- a formal appointment letter for REC members which sets out the term of office, and the assurance that members are indemnified from personal liability against claims that may arise in the course of ordinary business of the REC.

5.2.3.3 Indemnification of REC members

Institutions must indemnify REC members from personal liability and should ensure that adequate public liability insurance exists at institutional level. The institution should take legal responsibility for the decisions and advice of the REC, provided that members act in good faith.

5.2.3.4 Wellbeing of people involved in institutional animal care and use

Institutions should be aware of the significant mental-emotional challenges that can be encountered amongst people, due to exposure to animal suffering and death. The people include veterinary and para-veterinary professionals, animal facility managers, animal caretakers, researchers, students, AREC members, and others involved in the institutional animal care and use programme. Institutional awareness includes ensuring that appropriate psychological and other relevant support is or can be made accessible to all relevant personnel for their mental-emotional wellbeing.

5.3 Role and Scope of Research Ethics Committees

The primary role of a REC is to protect the interests (rights and welfare) of the research participants who volunteer to take part, or to protect the interests and welfare of the animals used, in scientifically and ethically sound research, respectively. Consequently, the REC is responsible for the review of the research proposal and the post-approval monitoring of the approved study. With respect to review, each REC member is to decide independently whether the proposed research would adequately protect these interests and keep to exemplary standards in research activities.

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

Independence of RECs means that the committees must be free to do their work as described in these guidelines and the governing statutory frameworks, without interference from others within the institution or entity. However, RECs must not regard themselves as outside of their institutional governance systems but must operate within their institutional committee system.

Institutions should recognise that RECs necessarily have a dual governance model: on the one hand, they are institutional committees and are expected to comply with the usual institutional committee reporting lines. On the other, RECs are also a national research integrity resource (in terms of the NHA) and must comply with the prescripts and reporting expectations, as outlined in the statute and associated regulations and these national guidelines. And ARECs must comply also with the SANS 10386:2021 2nd ed., the Veterinary and Para-Veterinary Professions Act 19 of 1982, and requirements of the South African Veterinary Council (SAVC).

5.3.1 REC Membership Composition

RECs should be independent (see 5.3), multi-disciplinary, multi-sectoral and pluralistic.[84] In general terms, membership should include

- as many disciplines, sectors, and professions as possible, appropriate to the remit of the specific REC
- members from diverse age groups and academic or professional ranks
- ethnically and culturally diverse members and an appropriate mix of genders
- lay persons [85]
- researchers who do not conduct human participant research (HRECs) or animal use research (ARECs).

Collectively, the committee should include sufficient members with the necessary skills, 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 assess the anticipated layperson's perspective. In the case of clinical trials, the REC should ensure that they have the training, skills and expertise, as well as understand the local context of the participant community and capacity for post-approval monitoring. REC members and researchers are expected to familiarise themselves with the institutional documentation as well as the national and relevant international research ethics guidelines and should have documented proof of such familiarity e.g., an assessment of training certificate, not a mere attendance certificate. (See 5.4 for detailed discussion.)

5.3.2 Appointment of Chairperson

Subject to institutional requirements, a chairperson could be appointed or elected at the first meeting of a newly constituted REC. Alternatively, the chairperson, suitably qualified, could be appointed as per the SOP for a period of three to five years, renewable once, if so specified in the ToR. The chairperson must have experience in research methodology and research ethics, should have at least two years' experience as a REC member and should have leadership experience. If the chairperson is an external appointee, the institution must provide the chairperson with the necessary support and authority to perform the role. A chairperson may serve for a period of three to five years, renewable once, in addition to the term(s) served as members (see 5.3.2.2).

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.

5.3.2.1 Additional considerations for ARECs

The chairperson must have relevant experience in research and training in animal research ethics or have been a member of the AREC for a minimum of two years. The chairperson is appointed in addition to SANS 10386:2021 categories A to D members and is expected to manage possible conflicts of interest within the committee.

5.3.2.2 Appointment of REC members

Institutions should be mindful of the need for RECs to develop institutional memory amongst the membership as well as to ensure succession planning. Members of RECs should be appointed formally for periods of three to five years, renewable once as ordinary member, after which the member should step down for at least one term. In addition to the term(s) served as an ordinary member, a three-to-five-year term, renewable once may be served as a chairperson and/or vice-chairperson. A chair may serve for not more than two terms as a chair. A motivation can be

[84] Plurality or diversity of REC membership refers mostly to ethnicity, culture, and gender of members.

[85] A layperson is someone who has no affiliation to the institution, is not currently involved in medical, health care-related, legal or scientific work and is preferably from the broad community in which research takes place.

made to the institutional authority for further renewal of membership. Appointments should overlap so that no more than half the committee membership is new at any one appointment time. This practice allows knowledge and experience to be shared appropriately, efficiently and effectively amongst new appointees.

RECs should have an SOP that spells out meeting attendance expectations, possible sanctions if attendance is poor, expectations for promptness of reviews, preparation for meetings, etc. The appointment letter should also spell out the essential expectations of membership.

RECs should provide induction training for new members, that includes discussion of the role of ethics committee members, the code of conduct, expectations of integrity and confidentiality amongst members, their responsibilities and how to manage conflicts of interest. It should also introduce the new member to the REC's key SOPs, forms/templates and review processes. Such training should be documented by the REC.

5.3.2.3 Review responsibilities of REC members

It is important that RECs have clear SOPs that clarify the expectations about their review responsibilities. Operational expectations must be widely communicated and adhered to, e.g., review turnaround times, prompt completion of meeting minutes, feedback correspondence to applicants, etc.

In general terms, RECs are encouraged to strive for improvements in efficiencies, e.g., streamlining review processes, and considering the use of new technologies to improve review and approval cycles.

5.3.3 Human Research Ethics Committees

The composition of HRECs should promote optimal human participant welfare, research integrity (including data robustness and scientific validity), defendable significance of proposed research questions (including translatability of scientific findings into practice, where applicable), as well as legal, professional, and regulatory compliance.

All HREC members should have documented proof of recent research ethics training. Documented proof means evidence of appropriate training/learning. (See 5.4 for detailed discussion).

HREC membership[86] should consist of

a) a minimum of nine members with a quorum being a simple majority
b) where the number of members is more than 15, the quorum may be 33%
c) at least one layperson[87]
d) at least one member with knowledge of, and current experience in, the professional care, counselling, or health-related treatment of people, e.g., a social worker, nurse, psychologist, pharmacist or medical practitioner
e) at least one member with professional training and experience in qualitative research methodologies
f) members with professional training and experience in quantitative research methodologies
g) a member with expertise in biostatistics[88]
h) a member with expertise[89] in research ethics
i) at least one member who is legally qualified and has extensive knowledge of

[86] Based on the Regulations relating to the National Health Research Ethics Council R.839 23 September 2010, clause 2.
[87] A layperson is someone who has no affiliation to the institution, is not currently involved in medical, health care-related, legal or scientific work and is preferably from the broad community in which research takes place.
[88] Need not be a professional biostatistician.
[89] Expertise means with great skill and knowledge in a particular field.

family law, health law, and research ethics.

Note: All members, including those with special expertise, are expected to review applications. The objective of requiring specific expertise is to ensure the expertise is specially brought to bear on the applications.

5.3.4 Animal Research Ethics Committees

The composition of ARECs should promote optimal animal welfare, research integrity (including data robustness and scientific validity), defendable significance of the proposed research questions (including translatability of scientific findings into practice, where applicable), as well as legal, professional, and regulatory compliance.

All AREC members should have documented proof of research ethics training, refreshed at least once. Documented proof means evidence of appropriate training/learning. (See 5.4 for detailed discussion.)

In addition to the minimum stipulations of SANS 10386:2021, membership of registered ARECs requires:

a) a minimum of nine members with a quorum being a simple majority, provided the quorum members always include at least one member from each category of member (i.e., A to D, see below) and the SANS 10386:2021 balance between membership categories is maintained throughout the meeting (i.e., Cat C + D members must number at least 33% of all AREC members present at all times)
b) where the number of members is more than 15, ensure a quorum of 33%, provided the quorum members always include at least one member from each category of member (i.e., A to D, see below) and the SANS 10386:2021 balance between membership categories is maintained throughout the meeting (i.e., Cat C + D members must number at least 33% of all AREC members present at all times)
c) at least one member with veterinary qualifications, who is legally permitted to practice as a veterinarian in South Africa (*cf* SANS 10386:2021 Category A) and is registered with the South African Veterinary Council (SAVC) as a veterinarian or veterinary specialist
d) at least two members with substantial and recent experience in the use of animals for scientific purposes (*cf* SANS 10386:2021 Category B)
e) at least one member with expertise and experience in quantitative research methodologies
f) at least one member with expertise and experience in translating the relevant basic sciences to the corresponding applied sciences or practice, where:
    i. animals are used for the purpose of human health, the expertise in translation is from pre-clinical to human clinical sciences
    ii. animals are used for the purpose of animal health, the expertise in translation is from pre-clinical to animal clinical sciences
g) at least one member with active membership of, and endorsement by an independent animal welfare organisation, with knowledge of the welfare and husbandry of the animal species used (*cf* SANS 10386:2021 Category C). In cases of more than one Category C member, members should be from different animal welfare organisations, to encourage a diversity of views also from the animal welfare sector
h) at least one layperson, who has no experience or past or present involvement with the care or use of animals for scientific purposes, who is independent of the life sciences, biological sciences and health sciences, or any departments, faculties, schools, or other units that use animals for scientific purposes (*cf* SANS 10386:2021 Category D)
i) at least one member who is entirely independent of the institution, i.e., who has no association with the institution other than membership of the AREC (Note:

this member may be the same person as the member listed in h) above)

j) a member with daily hands-on contact with the animals and responsibility for the daily care, procurement, production, and maintenance of the animals (*cf* SANS additional member)

k) a member with expertise in biostatistics, with competencies to confirm appropriate statistical methodologies and power analysis (i.e., number of animals, Reduction), to allow the scientific hypotheses to be validly tested

l) a member with relevant expertise in animal research ethics

m) a member who is legally qualified is recommended.

Note: Members who serve as Category A, B, C, or D members (*cf* SANS 10386:2021), should be appointed formally in a specific, single membership Category capacity, i.e., they may not serve in more than one category, and they may not change membership Categories between or during meetings. The SANS 10386 requirement for balance amongst AREC membership Categories (i.e., Categories C plus D versus other members) must be maintained.

5.4 Education and Training in Research Ethics

It is expected that all REC members, REC administrators, researchers, and students who will undertake research with human participants, or that involves use of animals, will ensure they complete assessed theoretical research ethics training (education) at least every three years, to ensure they are familiar with expectations, especially those set out in NDoH 2024 3rd ed., SANS 10386:2021 and, for clinical trials, SA GCP 2020. The expectation is that researchers, and especially students, should complete the institutional required research ethics training, and demonstrate applied or practical competencies (e.g., applicable communication skills or interview techniques in case of studies with human participants, or applicable physical animal handling and procedures course in case of study with animals) before commencing with any research activities.

Ultimately, RECs are expected to verify, and researchers are responsible for ensuring, that they have the appropriate knowledge, skills, expertise, competence, including discipline-appropriate scientific background and research ethics training to conduct studies involving human participants or the use of animals.

5.4.1 Minimum norms and standards for education and training of REC members in research ethics

a) Health research ethics training is additional to discipline- or profession-specific and GCP training, and must include an assessment to provide evidence of more than mere attendance at training.

b) Additional training courses or learning opportunities, such as conferences, workshops, informal training at REC meetings, continuing professional development, (co-)authoring peer reviewed publications, and other learning opportunities that are not assessed can be valuable.

c) Institutions and research organisations must provide the necessary support and resources to enable and empower REC members to undergo assessed ethics education and training to achieve the required competence.

5.4.2 Expectations of training outcomes

Following research ethics training, REC members are expected to

a) be familiar with and have a good understanding of the ethical principles as described and discussed in NDoH 2024., SA GCP 2020, SANS 10396:2021

b) have a contextualised understanding of research, socio-cultural and public health implications, as well as scientific integrity (see Chapter 1)

c) have an understanding of the principles of research integrity and responsible conduct of research, consequences of non-compliance and misconduct, available structures for complaints and whistleblowing, etc.

d) have an understanding of the interdependence of scientific integrity, research ethics, social values and legal compliance
e) have an understanding of REC governance principles, structures and documentation, REC composition and function, REC roles and responsibilities, oversight, induction and other training of REC members, REC administrative support, REC procedures, confidentiality agreements, management of conflicts of interest, code of conduct, meetings, review process, expedited process, monitoring, complaints and whistleblowing, relationship with the NHREC, and relevant statutes
f) AREC members are expected also to have an understanding of concepts such as harm severity categories, harm-benefit analysis, analysis of the degree (magnitude and likelihood) of harm, justification of harm, identification of aggravating factors, mitigation strategies, end of the study, humane endpoints, and options (e.g., rehoming, introduction into breeding programmes, re-use if appropriate, transfer to other facilities, public adoption, euthanasia, etc.), and acceptable options, practices, legal requirements, ethical considerations and emergency options for and euthanasia
g) REC members must be mindful of the need for additional appropriate institutional expertise and attention for other study-related considerations with ethical implications that include
    - biosafety and other safety measures
    - proper study design and statistical analysis
    - requirements for legal authorisation or registration with applicable authorities
    - how to check for other legal requirements of studies
    - management of conflict of interest
    - gaining access to animals of private owners
    - environmental impact issues
    - multi-institutional collaboration, both national and international
    - maintenance and calibration of equipment

Note: The REC is not responsible for ensuring this array of expertise and skill amongst its membership. The institution must establish appropriate committees to provide the necessary oversight and scrutiny.

5.4.2.1 International collaborators with existing training in research ethics

a) International collaborators in studies based in South Africa must demonstrate appropriate recent research ethics training and GCP training where applicable, including a basic understanding of applicable South African legislation and regulatory framework and the NDoH 2024
b) For South Africa-based studies involving human participants, there must at minimum be a local PI or research supervisor
c) For South Africa-based studies involving the use of animals in research, appropriate research ethics training of international collaborators should also include and introduction to the SANS 10386:2021 2nd ed. or latest version

5.4.2.2 Student researchers

a) Student researchers must always be supervised by a supervisor within the tertiary institution or organisation. Students from abroad (foreign) must also be under the oversight of a local supervisor.
b) Supervisors must sign off on research protocols and research ethics review applications, accepting responsibility for

ensuring compliance with research integrity and ethical conduct by the student.[90]

c) Student research is often subject to severe time constraints which affects the ability to complete a research study with appropriate statistical power and depth of analysis. RECs should therefore be mindful of the academic status of the student when reviewing their protocols. The principle is that the sophistication of research should match the available resources, which are constrained by the academic level. It would not be appropriate, e.g., to have an undergraduate student or group of students attempting research at a level of sophistication that requires more expertise, experience, time or funding than they have access to.

d) Undergraduate and honours student research projects must have research ethics approval before commencement of the research. Depending on the approach of the tertiary institution, sometimes supervisors may obtain a group approval for the project, e.g., when all the students do the same project.

5.5 Standard Operating Procedures

SOPs are intended to convey the steps to be followed for purposes of achieving a review or administrative objective (see also 5.2.2).

SOPs should cover topics including

- institutional operations and procedures (e.g., institutional lines of authority and responsibility, reporting obligations, channels for escalation of problems)
- REC administrative operations and procedures (e.g., 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 timelines for reviewers, definitions as appropriate
- Structures and processes in place to deal with complaints, queries and appeals about REC operations and decisions, before escalating matters to institutional research integrity system or to the NHREC, guidance and specification of REC procedures required for expedited and full REC review; if the REC reviews US federally funded research protocols, the procedures must comply with the US Common Rule (45 CFR 46), quorum requirements.

5.5.1 Examples of SOPs

Some examples of SOPs are provided. RECs may customise to suit their specific needs but must maintain the essential standards, bearing in mind the need for national harmonisation of best practices to permit reliability of procedures across the country. Reliability of procedures is especially important to facilitate reciprocal recognition of reviews in appropriate circumstances.

5.5.1.1 Role of SOPs

a) RECs must have written standard operating procedures (SOPs) to ensure
   - standardised best practices for health and health-related research
   - compliance with national, institutional, and international ethical and regulatory requirements
   - consistent processes about ethical issues in health and health-related research
   - declarations regarding confidentiality and conflict of interest for each meeting

b) Ethical issues in research often require case-by-case deliberation, following independent review by more than one REC member. The ethics review process should not be mechanical. Although consistency of review outcomes for similar studies may be

[90] Note that not all student interview and writing assignments count as 'research'. Some disciplines require practical face-to-face interactions with informants, e.g., anthropology, history, psychology, journalism, sociology etc.; the outputs from these interactions are seldom regarded as research outputs. Institutions should give careful thought to how their curricula can meet the goal of conducting high quality teaching and learning within a rigorous ethically sound context. Appropriate SOPs should be drawn up.

desirable, it is not always possible or appropriate in light of the details of an application. Reviewers new to the discipline must receive assistance to develop their ability to analyse and deliberate on the necessary elements.

c) 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 can be difficult to achieve and that divergence enriches deliberations
   - accept that consensus is not a strict requirement; sometimes a majority vote is appropriate, minuted properly with sufficient detail
   - be mindful of the influence that the context (social, cultural and economic) has on how to prioritise principles
   - be reflective and thoughtful in discussions about how to balance ethical considerations.

d) SOPs should be regarded as living documents, to be reviewed, revised, and updated at regular intervals.

e) REC members and researchers should ensure that they use the most recent versions of documents.

5.5.1.2 Applications for ethics review

a) The REC must develop an Ethics Review Application form that is designed to capture the essential ethical elements. It should ask for an explanation of the proposed research in plain language and for information about potential participants (age range, vulnerabilities etc), ethical implications of the research, etc. The objective is to standardise the review process by providing access to the research protocol in a systematic manner. Having some context makes it easier to read the detailed protocol. The application form should avoid a tick-box approach, but also ask the "how" questions (e.g., not only indicate that participants are protected, but also ask an explanation of "how" they are protected).

b) Sub-studies are regarded as separate studies and must be reviewed individually. That a 'parent study' has been reviewed and approved does not imply that to associated sub-studies can go ahead without also being reviewed thoroughly and approved. There are numerous ethically relevant differences between a parent study and an associated sub-study.

c) Researchers who are not affiliated to a South African institution with a NHREC-registered REC, may approach such an entity requesting it to review their research protocols. Provided that its ToR authorises it to do so, the institution may exercise its discretion on a case-by-case basis to decide whether to review the protocol, or whether to refer the applicant elsewhere to access appropriate expertise and capacity to evaluate the application. In fact, when agreeing to review an external study implies that the REC also takes on the responsibility for monitoring and overall ethical oversight until the conclusion of the study. A fee may be levied for such a service.

d) The applicant must demonstrate adequate consideration of human participants' welfare, rights, beliefs, perceptions, customs, and cultural heritage.

e) The protocol must include a risk/benefit analysis of the risk of harm to human participants and how harm will be diminished if cannot be prevented, the likelihood of benefit and how this will be achieved.

f) The application must include all documents and other material to be used to inform potential human participants, such as information sheets, consent forms, questionnaires, advertisements, videos, dramatisations and letters.

g) Researchers must ensure that plain language adapted to anticipated literacy

levels is used in the human participant documentation. An indication of the readability level should be included.

h) Where research is to be conducted in community settings, evidence of community engagement and plans for ongoing consultation should be included.

i) Where appropriate for the context of the study under review, RECs should create awareness about benefit sharing by asking the PI about any plans to implement such.

j) Animal research applications should explain comprehensively how the welfare interests of the animals will be attended to, which should always take precedence over scientific interest.

k) Animal research applications should include justification for the use of animals, potential scientific or societal benefits of the research/teaching exercise, description of animals required, experimental design and procedures, housing conditions, animal welfare monitoring schedules, humane-endpoints, harms-benefit analysis, listing the responsible persons and their contact numbers, the schedule, and indicators for analgesia delivery etc.

l) Animal research applications should include welfare monitoring schedules listing the responsible persons and their contact numbers, the schedule, humane endpoints and indicators for analgesia delivery etc.

m) Protocols for clinical trials and studies involving a moderate increase over minimal risk should include monitoring schedules, the responsible persons and their contact numbers.

n) Researchers should disclose conflicts of interest, financial interests and information that may result in perceptions of conflict of interest.

5.5.1.3 REC decision making and feedback to applicants

a) After the deliberative review process, the REC should approve, require amendment to, defer, or reject a research protocol.

b) 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.

c) Decisions of the REC should be recorded in writing and appropriately minuted.

d) A decision to approve should include the conditions, e.g., the duration of the approval (maximum 12 months, renewable), the reporting requirements, etc.

e) A decision to require amendment or to reject, should record reasons for the decision (i.e., minutes in a narrative format describing deliberations, and not merely the final decision) and provide sufficient feedback to the applicant.

f) Outright rejection should be avoided if a researcher can be advised to improve the protocol.

g) 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.

h) Feedback should be sufficiently detailed so that the concerns of the REC are understandable to the researchers, and instructive to assist the researchers to improve the application of appropriate.

i) Feedback should include the expected return date to minimise delays to finalise the approval process. The maximum time for a return date should not exceed six months. Should the applicant exceed the stipulated return date without communication to the REC, the application should be removed from the agenda. A new application must then be submitted if the researcher still wants to conduct the study. If not, it is advisable that the REC requires of the researcher to formally withdraw an application.

j) RECs must require researchers to report immediately anything that might warrant reconsideration of ethical approval of the protocol, including but not limited to

   i. Serious or unexpected adverse effects on participants

   ii. Proposed changes in the protocol

iii. Unforeseen events that might affect continued ethical acceptability of the project.

k) RECs must require researchers to report immediately if a project is terminated or suspended before the anticipated date of completion.

5.5.1.4 *Reciprocal recognition of review decisions*

a) The South African ethico-legal framework requires that PIs or research leaders must obtain approval from their institutional REC. In principle, this means that RECs have the authority to review and approve research protocols only for research sites or geographic areas within South Africa[91]. Thus, when a protocol proposes a research study or project that is to collect data from multiple sites or geographic areas within South Africa, more than one REC may be involved in the review and approval processes.

b) To prevent unnecessary duplication of work, RECs may, at their own discretion, recognise the review and approval of a research protocol granted by another registered South African REC.

c) Reciprocal recognition means that two or more registered RECs decide to recognise each other's review.

d) This arrangement may involve formal agreements between the RECs explaining how the workload and responsibilities is shared and the basis on which recognition occurs. Alternatively, the committee may decide to use reciprocity recognition on a case-by-case basis.

e) RECs that recognise reciprocal review in this manner must determine the nature of the documents to be filed at each office. The expectation is that, at minimum, copies of the approval letter from the other REC, the protocol, and the ethics review application as well as the notes of the local REC member whose review led to the REC decision to use reciprocal recognition must be on file. Further, the decision must be tabled for minuting at the next REC meeting.

f) RECs that recognise reciprocal review in this manner may reverse their decision to do so if justifying circumstances arise. The reasoning supporting a reversal of recognition should be documented.

g) The roles and responsibilities of each REC involved in the reciprocal review process should be clearly described and agreed in writing by the participating RECs. These guidelines deliberately do not impose use of reciprocal recognition of reviews on any REC; nor is there a prescribed method for agreeing to reciprocal recognition. The expectation is that RECs should communicate with each other, through their chairpersons, and agree on a way forward regarding review of a multi-site protocol when it is desirable to avoid duplication of effort. The possibility of reciprocal recognition of reviews should occur in a collaborative, harmonious manner, bearing in mind that each REC retains the responsibility of protecting the safety, rights and interests of participants enrolled in the studies it has approved.

h) Matters to be considered include which RECs are participating in the particular reciprocal recognition arrangement, how protocol amendments will be managed e.g., a site-specific logistical amendment may not lead to amendments at all sites, but only noting by the others, how adverse events or unanticipated problems will be managed e.g., it might be decided to report AEs in the usual way only to own REC and SAHPRA but with Serious Adverse Events (SAEs) to notify the other participating RECs.

[91] Any research site or facility has the right to require ethical approval by its designated REC, or to accept the approval of another NHREC-registered REC. Also, whichever REC approves a study at a particular site, must ensure that they have the necessary understanding of the study participants at that site, and takes full responsibility for all monitoring, site visits, reporting, etc. arising from the study

i) It is important too that SA GCP 2020 be followed consistently in case of clinical trials. It is possible that some RECs already have SOPs in place for reciprocal recognition of reviews. The agreement might be reached by sharing the SOPs to ensure that all participating HRECs understand and can participate on the basis of a shared SOP.

5.5.1.5 Expedited review

a) Expedited review applies, in principle, only to research that poses no more than minimal risk of harm.
b) Generally, expedited review means that no fewer than two REC members review the protocol and that deliberation in the full committee meeting is foregone, unless the reviewers believe there are issues that the REC should discuss.
c) The nature of research that may be expedited should be described in the relevant SOP. For example, undergraduate student research (which ought to pose no more than minimal risk of harm) could be expedited to prevent overloading of the agenda for the full committee.
d) The outcomes of the expedited review process must be reported to the full committee, at least by being noted on the agenda, so that the record is complete.

5.5.1.6 Rapid review

a) Rapid review process permits rapid but thorough processing of ethics review applications in circumstances that require accelerated preparation for a research study or project. The usual example of such circumstances is a major incident of significant, wider impact. However, accelerated preparation for research could be justifiable in a localised emergency context too, e.g., an outbreak of cholera in one geographical area (see also 3.3.2.3).
b) Rapidity of review processes refers to the speed at which administrative processes are carried out, and may never compromise the thoroughness, or lead to a cursory process.
c) The REC should carefully assess the nature of the research to determine the appropriate review process, bearing in mind that not all research during a major incident is necessarily urgent.
d) Careful ethical reflection is essential, notwithstanding any perceived urgency. All the usual ethical norms and standards must be considered.
e) The REC should have a review SOP that allows a combination of rapid but thorough review and reciprocal recognition of review (see 5.5.1.4) by other NHREC-registered RECs.
f) The SOP might stipulate that a small group of reviewers (3-5 persons) with appropriate expertise reviews the protocol. The deliberations and outcome of the process must be minuted and reported to the full REC at its next meeting.

5.5.1.7 Joint reviews

Joint reviews occur when two or more RECs review a multi-site research protocol together. The sites may be within South Africa or may include sites elsewhere on the African continent.

A joint review is not the same as a reciprocally recognised review. A joint review entails members of the RECs concerned communicating virtually or face-to-face to discuss their respective reviews and queries and come to conclusions.

The joint review process permits efficiency of reviews, facilitation of capacity building, development of trust, and avoids unnecessary repetition of administrative work.

a) Ethics review of multi-site research protocols, e.g., where an identical protocol serves at several research sites in South Africa may benefit from the joint review process.
b) When deliberations are completed and a decision to approve has been reached, each REC uses its own approval SOPs and processes.
c) Joint review does not exempt any of the RECs involved from their responsibilities,

including monitoring and looking after the interests of participants at their respective designated sites.

d) The PIs concerned are responsible for informing their institutional REC of the fact of multi-site research, as well as the names of the other RECs with jurisdiction over other research sites.
e) This information enables the Chairs of the RECs to arrange a joint meeting of the RECs involved to review, deliberate on and to approve the protocol concerned simultaneously.
f) Sometimes research is conducted in various African countries. Joint reviews involving South African and other African RECs can be used in similar manner to facilitate the ethics review and approval processes.
g) An MoU between the RECs involved that outlines the process, the expectations and the responsibilities is desirable.

5.5.1.8 Archiving

a) 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: Electronic records are acceptable, provided the signatures, especially on the finally approved documentation, are properly documented and included in the record.

b) 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.
c) The record should include at least the following:
    - Name of principal, co and sub investigator
    - Names of all sponsors, collaborators and other team members, including students
    - Protocol identification number
    - Title of the project
    - Date of approval or rejection
    - Duration of approval period (maximum 12 months, renewable)
    - Conditions of approval, if applicable
    - Whether approval was via normal processes, reciprocal, expedited, rapid of joint
    - Copy of the signed final protocol or protocol approved
    - Site or facilities where the research will be conducted
    - Whether and how consultation occurred
    - Records of protocol deviations
    - Records of amendments
    - Reports of adverse and serious adverse events and all incidents, and action taken
    - Other relevant information, including complaints from participants
d) RECs should correspond primarily with the principal investigator or a delegated signatory, and not with the sponsor unless dictated by specific circumstances.

5.5.1.9 Conflicts of interest

a) REC members should disclose information that may lead to potential, actual as well as perceptions of conflict of interest.
b) REC members should not review or make decisions about research protocols in which they are involved personally (including as supervisor of a student) or financially , or can otherwise benefit from, or where any material matter can affect their unbiased judgement. When such a protocol is to be discussed, the member concerned must declare the potential conflict and offer to recuse themselves from the meeting for that time. Should the member be permitted to remain for the discussion at the discretion of the chairperson, e.g., to facilitate clarifications, the member must leave the meeting for the duration of the final decision-making discussion concerning the application in question.
c) REC members and ad hoc reviewers must not use the ethics review process to impose personal biases, professional jealousy or territorial protection conduct about an applicant's protocol, including about research methods or the topic.

d) That applicants pay fees to benefit from the ethics review service, must not be allowed to negatively affect the rigour of reviews, the integrity of the process or the capacity to monitor the research that the REC approves. The attraction of earning fees must never outweigh the capacity of the REC to perform its work as expected.

5.5.1.10 Advocacy

The REC should be alert to whether an advocate for special interest groups of participants proposed for specific research would add value to the review process for informed responsible decision-making in the context. This is especially relevant when appropriate expertise is not found amongst the membership.

5.5.1.11 Translators and interpreters

a) 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 by interpreting.
b) A translator deals with written words, while an interpreter translates spoken words.
c) The REC should be alert to the potential for poor consent processes in the absence of appropriately translated materials and the availability of interpreters.
d) If an interpreter 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.
e) An interpreter should not influence potential participants unduly during the interpretation process.

Note: It is unnecessary to have formal certified translations for consent documents. The objective is to facilitate understanding of the information at the local level.

5.5.1.12 Monitoring

a) RECs have the right and responsibility to monitor the research it approves (Declaration of Helsinki 2013 par 23).[92] Researchers are expected to 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.
b) Monitoring types include passive and active measures. Whilst it stands to reason that monitoring can take different forms, the distinction between active and passive monitoring is necessary to maintain currently.
c) Active monitoring requires a site visit. Passive monitoring is generally paper-based, using self-reporting and other information provided by the researcher/PI. A site visit is expected also for investigation of adverse events, serious adverse events for high-risk research, as well as other occurrences that prompt concerns for RECs.
d) A site visit for active monitoring would include an evaluation of the protocol and investigational plan's adherence to the REC-approved research protocol:
    - application of the study selection criteria (inclusion and exclusion criteria)
    - documentation of the informed consent process
    - type of data collected
    - date of enrolment for study participants
    - documentation of adverse and serious adverse events
    - evidence of HREC-approved amendments to the study
    - any protocol deviations
    - date of most recent certification

[92] This statement evidences the ethical authority for HRECs to inspect and monitor sites for research approved by them.

- application of the data management plan (data security and confidentiality)
- any challenges experienced at the research site
- sharing of best practices

Such an evaluation would include criteria for categorising the findings, such as

- compliance
- acceptable; no serious or urgent concerns
- minor concerns requiring attention
- serious concerns about participant safety/animal welfare/protocol adherence

e) The REC should ensure that appropriate feedback is given to the PI, with an opportunity to address any identified gaps within a negotiated timeline.

f) 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.

g) RECs should request regular, at least annual, reports from PIs 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)
- 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 in the case of clinical trials
- list all adverse events or incidents in the past 12 months
- list all amendments made in the past 12 months

h) RECs should inform PIs in writing of concerns arising from such monitoring activities.

5.5.1.13 Suspension or discontinuation of research projects

a) Where circumstances indicate that a project is non-compliant with the approved protocol and the interests of participants are at risk of harm, the HREC or AREC may withdraw approval, after due process has been followed.

b) 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.

c) If the decision is to withdraw approval, the REC should inform the PI 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.

d) In the case of suspension, the PI must comply with the recommendations and any special conditions imposed by the REC.

e) A study closure report or other communication must be submitted to the REC, especially regarding student projects to facilitate the process leading to graduation.

5.5.1.14 Complaints and queries

a) 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 at REC level, it should be escalated via the institutional complaints process, e.g., research integrity office or other channel.

b) An SOP should detail the procedures to be followed.

c) Internal (domestic) remedies should preferably be exhausted before the matter is brought to the NHREC. If the matter cannot be resolved at institutional level, it should be escalated to the NHREC. However, if the matter cannot be expeditiously resolved at REC level and has significant implications for the integrity of the review process under consideration, the situation may ground an earlier approach to the NHREC. The REC must, however, consult with the relevant person in the institutional complaints channel before escalating the matter to the NHREC.
d) The NHREC is empowered to adjudicate complaints about RECs and to hear a complaint from any researcher or other interested party (including a participant) who believes that they have been discriminated against unfairly by a REC. Typically, the NHREC will be approached after all internal processes as per institutional policy have been exhausted.
e) A framework for the management of complaints and ethics related health research misconduct has been developed by the NHREC [homepage].
f) The NHREC adheres to the following principles when investigating a complaint: fairness, confidentiality, integrity and prevention of detriment.
g) All research study-related information and consent documentation must include contact details for a participant to make a complaint 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.
h) The NHREC also provides guidance on queries regarding ethical governance of health research in South Africa. Such queries are handled in accordance with the framework for management (See e above).

5.5.2 SOP Topics for consideration

Note: This list is not exhaustive; merely illustrative.

- decisional analysis guidance
- the protocol review process
- continuing review and re-certification 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
- whistle blower protection
- conflict of interest and of confidentiality regarding researchers
- protocol amendment procedures.

5.6 Compliance reporting to the NHREC

a) The NHREC is responsible for registering and auditing RECs.
b) RECs should make relevant records available for inspection and audit by the NHREC (or its delegate) upon request.
c) The execution of the NHREC responsibility is dependent on the appropriate and responsible cooperation of RECs regarding timeous submission of Annual Reports, containing accurate and up to date information that is detailed and complete.

Note: Copy and paste submissions containing recycled and inaccurate information are unacceptable and are amongst the grounds for suspension of registration.

d) 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
   - any other matters regarded important to promote REC functioning and compliance

e) Each REC annual report must be submitted using the form provided on the NHREC website and must be signed off by the relevant person in the institution with the authority to take responsibility for the contents of the report. For example, the Authorised Institutional Officer might be the relevant Deputy Vice Chancellor, a specifically designated administrator in the institutional research office or other person.

f) Information provided by registered RECs and their organisation/institution is used to confirm compliance with the requirements for continued registration. Information collected from the annual reports is used also for the following purposes:
   - promote constructive communication between RECs and the NHREC
   - update contact and other details in the NHREC's database
   - maintain a record of REC activities, queries, and complaints
   - support and advise RECs and organisations/institutions
   - monitor and review HREC and AREC compliance with the National Health Act 61 of 2003, SANS 10386 requirements for ARECs and compliance with these Guidelines
   - gather information of national status of all registered RECs
   - maintain an updated and publicly accessible database of registered RECs.

Annual Reports are due by 28 February annually on the REC Reporting Template [homepage].

Chapter

6 Health Research Ethics Infrastructure

This chapter presents an overview of the statutory infrastructure and systems designed to regulate and oversee health research.

6.1 Introduction

The infrastructure framework includes the National Health Act 61 of 2003, the National Health Research Strategy: Research Priorities for South Africa 2021-2024,[93] and the National Department of Health Strategic Plan 2020/21 – 2024/25,[94] the care and use of animals for scientific purposes SANS 10386:2021 2nd ed.[95] International guidelines also inform governance of the conduct of health research.[96]

The NHA authorises the establishment of the National Health Research Ethics Council (section 72(1)) and mandates the Minister of Health to appoint members of the Council (section 72(2)(a)).

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

6.2 National Health Research Ethics Council

6.2.1 Establishment

The National Health Research Ethics Council (NHREC) was established in terms of the NHA (section 72(1). The Council's core responsibilities are to set ethical norms and standards for health and health-related research, to register and audit RECs, and to advance research ethics in South Africa, by promoting compliance by researchers and RECs using existing and new regulations and guidelines. It is also expected to advise the national and provincial departments of health about 'ethical matters regarding research'. In addition, the Council has responsibility for adjudicating complaints, for advising institutional committees, researchers, and members of the public, as appropriate.[97]

6.2.2 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. Nominations are called for by notice in the Government Gazette and the press.

6.2.3 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 (NDoH) about research ethics matters. In addition to the four statutorily required meetings, several ad hoc meetings of the NHREC as well as an annual face-to-face stakeholder meeting for REC chairs and others take place with the NHREC. Ad hoc meetings often take the form of virtual meetings. Established committees facilitate efficiency in performing council functions. The NHREC is supported by a secretariat in the NDoH, 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, but also via the annual workshop mentioned above.

6.2.4 Committees

Various committees deal with the Council's responsibilities in a systematic manner. They include

i. Executive Committee (EXCO)
ii. Complaints and Advisory Committee (CAC)

[93] Available online at https://www.health.gov.za/wp-content/uploads/2021/04/NATIONAL-HEALTH-RESEARCH-STRATEGY-2021-2024.pdf.

[94] https://www.health.gov.za/strategic-plans/.

[95] https://www.doh.gov.za; South African National Standard 'The care and use of animals for scientific purposes SANS 10386:2021 2nd ed. (or later version) www.sabs.co.za.

[96] The Declaration of Helsinki (2013) http://www.wma.net.

[97] See https://www.health.gov.za/nhrec-home/.

iii. Quality Promotion and Enhancement Committee (QPEC)
iv. Norms and Standards Committee (NASC)
v. Animals in Research Committee (AiR-Com)

6.2.5 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.

6.3 Research Ethics Committees

Every institution, health agency and health establishment at which health research is conducted must establish or have access to a REC (NHA section 73). The main responsibility of each committee is to conduct rigorous ethics review of research protocols to ensure that the welfare and other interests of participants, researchers and animals used for scientific purposes 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 protocols meet the ethical standards of that health research ethics committee*'.

6.4 Registration and audit of committees

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

6.4.1 Introduction

Health and health-related research is intended to improve health practice and, consequently, the health and wellbeing of South Africa's people and animals used for scientific purposes. Part of the framework that facilitates this process includes standardisation of infrastructure and SOPs for RECs, with a strong emphasis on guidance, training, support and feedback. To this end, the NHREC conducts a comprehensive quality assurance assessment and administrative audit of RECs on a five-year cycle to check compliance with the various administrative and record keeping standards. Follow-up contact is designed to facilitate improvement and compliance with the expected standards. When a REC persistently fails to comply with expected standards, the NHREC is required to enforce the standards, e.g., to suspend operations until compliance is achieved or, in extreme cases, to revoke registration of the committee (see 6.4.3). Capacity evaluation and enhancement for committees are important functions of the NHREC.

6.4.2 Registration

All RECs must follow the registration process as outlined on the NHREC website. Once the administrative registration and audit processes are completed, the registered REC is included on the list on the website.[98]

6.4.3 Quality Assurance Assessment and Audit

The criteria for the administrative registration assessment process and the eligibility audit are based on this guideline and other internationally recognised guidelines. Members of the NHREC undertake the assessment and auditing to ensure that RECs comply with capacity and operational requirements.

After the first pre-registration audit, guidance and recommendations for improvement are provided as appropriate. A follow-up audit is carried out to ensure that required revisions have been completed, before the registration is completed and an NHREC registration number is issued.

[98] See https://www.health.gov.za/nhrec-home/.

A critical part of the ongoing quality assurance review process is the Annual Report from RECs (see 5.6). Quality assurance assessment and audits can be done as the need arises and undertaken on a five-year cycle to review the capacity and operational status quo of each REC. Criteria for registration and auditing of RECs may change, as determined by the NHREC, to reflect new ethical concerns or standards arising from national or international ethics dialogue. RECs are informed of any changed or additional requirements. Following the audit, detailed feedback is provided to each REC, specifying the timeline for required improvements. Failure to respond to the feedback or to carry out the requested improvements can lead to the REC being suspended.

When a REC is suspended, the NHREC informs the REC of the suspended registration status and outlines the steps to be taken to rectify matters so that registered status may be reinstated. During the period of suspension, the REC concerned may not review new protocols for health research and may not permit another registered REC to review on their behalf and should refer applicants to another registered REC. An assessment of the implications for harm to participants will determine whether ongoing monitoring of approved studies is acceptable to the NHREC. The onus to find a solution for the situation lies with the REC and the institution to rectify the shortcomings.

Failure by the REC to respond to the required measures to reverse the status of suspended registration can lead to registration being revoked. In other words, the REC can be involuntarily deregistered by the NHREC. A fresh application for registration will have to be made if re-registration is desired.

Voluntary deregistration can occur when a REC is no longer active and closes.

6.4.4 Capacity building for RECs

As indicated above, the audit process strongly emphasises 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 be confident that the health research ethics infrastructure conducts itself with integrity, according to the highest ethical standards.

6.5 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.

6.5.1 The South African Health Products Regulatory Authority

The South African Health Products Regulatory Authority (SAHPRA) is the statutory body tasked with ensuring that the pharmaceutical medicines, medical devices and IVDs[99] available for use in South Africa are safe, are of the requisite quality, and have the required efficacy (effect) or performance. To carry out this mandate, SAHPRA must decide, based on sound scientific evidence and other relevant information, whether the decision to permit registration of a particular medicine, medical device or IVD for specific uses is in the interest of public health.

Additionally, SAHPRA 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 Clinical Trials Committee of SAHPRA. Clinical trials are conducted in accordance with these guidelines and the South African Good Clinical Practice: Clinical Trial Guidelines (SAGCP 2020). Breaches of the guidelines may lead to termination of the trial by

[99] IVD stands for in vitro diagnostic and means a test conducted in a test tube in a laboratory to detect or identify a disease, a condition or an infection. WHO https://www.who.int/health-topics/in-vitro-diagnostics.

SAHPRA. This means that SAHPRA and the NHREC have concurrent jurisdiction over clinical trial research: SAHPRA focuses specifically but not exclusively on the scientific aspects, while the NHREC focuses specifically but not exclusively on the ethical aspects.

6.5.2 South African National Clinical Trial Register

Sponsors of clinical trials must register all South Africa-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 South African Good Clinical Practice: Clinical Trial Guidelines (SAGCP) for more information.

6.5.3 Provincial Health Research Committees

The White Paper on the Transformation of the Health System in South Africa[100] 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[101] as important mechanisms for coordinating health research and facilitating efficient use of limited research resources. Provincial Health Research Committees are not mentioned in the NHA, which establishes the National Research Coordination Committee, but they are clearly integral to the system. Research, especially those using state or provincial facilities and resources, should be linked to health care system priorities, and findings should be integrated into policy planning and management of health programmes.

Provincial Health Research Committees (PHRCs) were established to liaise with researchers to ensure that the greatest health needs of each province are being addressed. Their role is assisted by access to the National Health Research Database. 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. Whilst, they accept ethics approval granted by a registered REC, they need to consider applications to use their facilities to manage potential interference with or interruption of services. It is thus important that PIs respect this role of the PHRCs. Some provinces have also established separate provincial research ethics committees, which register with the NHREC following the usual registration process. These committees are important in areas of the country where other RECs are not active.

6.5.4 National Health Research Committee

The National Health Research Committee (NHRC) determines the health research priorities to be carried out by public health authorities. The determination considers the burden of disease, cost-effectiveness of interventions aimed at reducing the burden of disease, availability of resources to implement interventions as closely as possible to affected communities, and also the health needs of especially vulnerable groups. Its role is assisted by the National Health Research Database.

6.5.5 National Health Research Database

Developed by Health Systems Trust (HST) in collaboration with the NDoH, the National Health Research Database (NHRD) is a searchable, electronic repository of health research studies conducted in South Africa. Its core function is to track research trends in the national health research priority areas. It is used by the NHRC to monitor and track health research being conducted in South Africa. In addition to being a repository of health research, it allows PHRCs to manage research applications by researchers to conduct research in health facilities.

Note: See A3.3 AREC *regulatory framework*.

[100] Published 31 December 1997.

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

Appendix 1

A1.1 Glossary of terms used in these guidelines

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

Active monitoring – see *Monitoring*

Adolescent – a child between 12 and 17 years of age

Animal – live, sentient non-human vertebrate, including eggs, foetuses and embryos, that is; fish, amphibians, reptiles, birds and mammals, and encompassing domestic animals, purpose-bred animals, farm animals, wildlife and higher invertebrates such as the advanced members from the Cephalopoda and Decapoda (SANS 10386:2021 2nd ed. definition)

Anonymous – see *Identifiable*

Audit – subset of research; not clinical practice but a review of clinical practice against an appropriate or prescribed guideline (e.g., SA GCP 2020 or OECD GLP) or standard (e.g., SANS 10386:2021)

Authorised institutional official – The authorised institutional person of the institution or organisation with the authority and ultimate responsibility for governance of research endeavours conducted under its auspices, and for alignment, allocation, implementation and assurance of necessary support and resources for institutional research stakeholders

Authorised signatory – The person with responsibility for specified functions related to RECs, in terms of institutional policy

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

Big data – no international standard exists for 'big dataset', but, unlike traditional health

research data, very large data sets (also called big data) are characterised by very high volume, variety, velocity (the speed at which they are processed), their variability, veracity, and the computing power required to interrogate, analyse and process the dataset. Because health data are also personal information, the sensitivity of these data is specially protected

Biobank – see *Repository*

Biometrics – see *POPIA*

Broad consent – see *Consent*

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 (section 1 Children's Act, 38 of 2005); a caregiver must safeguard the child's health, wellbeing 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 (section 28 Constitution; section 1 Children's Act)

Child-headed household – a household per section 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 trial – research investigation involving human participants intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product, to identify any adverse reactions to an investigational product(s), to study absorption, distribution, metabolism, and excretion of an investigational product with the object of ascertaining its safety (that it is not harmful or dangerous to human health) and is effective (that it works to diagnose, treat, prevent, or cure a disease condition) and has efficacy (that it is better when compared with other treatment or medicine for a similar condition). The terms clinical trial and clinical study are synonymous.

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 also *Undue influence*

Collaborative research – involves co-operation of researchers, institutions, organisations 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; see also *Stakeholder engagement*

Community engagement – a collaborative process whereby researchers involve community stakeholders in an early and sustained manner across the study lifecycle to enhance the scientific and ethical quality of a study; the degree of collaboration may vary depending on the circumstances

Confidentiality – management of information that an individual has disclosed in a relationship of trust and with the expectation that it will not be disclosed to others without permission in ways that are inconsistent with the understanding of the original disclosure. Management of information includes whether and how research data might be disclosed carelessly or inadvertently by researchers, thus revealing the individual's identity or category, making them potentially vulnerable to harm

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; may be perceived rather than actual incompatibility

Consent – indication of agreement to participate in research, based on adequate knowledge and understanding of relevant information, freely given and revocable; documented in writing, signed by the participant and dated; see also *POPIA* for consent to process personal information

- **Narrow consent** – also called specific consent; donor/participant permits single use only of biological materials; no storage; no sharing of data or specimen; new consent if further use wanted
- **Tiered consent** – donor/participant permits use of biological materials for current study; and chooses whether to permit storage for future use, sample and data sharing
- **Broad consent** – donor/participant permits use of HBM or data for future similar but as yet unspecified studies, subject to further prior ethics review and approval

Data – information usually comprised of facts and numbers used to analyse something and to decide, or reach a conclusion or infer further information

Data curation –means the process of creating, organisation and integration and maintaining of data sets so that the value of the data is maintained over time, and the data remain available for reuse and preservation. It involves collecting, annotating, structuring, indexing, cataloguing, publication and presentation of the data for users.

Data Science Research – use of computer-based algorithms to sort and interpret information into data sets, looking for patterns from which meaningful inferences can be drawn for the benefit of health and health-related research (or other field of enquiry).

Data Sharing – the process of sharing available data resources with multiple third parties, facilitating data access without compromising data integrity

Database – a collection of information including images (data) arranged to facilitate swift search and retrieval; see also *Registry* and *Repository*

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

De-identify – see *POPIA*

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

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

Ethics review – review of research protocols (all the documents to be used for the proposed research) by RECs prior to commencement of the research, as well as of amended documentation as necessary

Everyday risk standard – see *Risk*

Expedited review process – applies, in principle, only to research that poses no more than minimal risk of harm.

Experimental treatment – 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

Explainability – a term used in Data Science; means that a machine learning model output can be explained in terms that 'make sense' to humans at an acceptable level

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

Harm-benefit analysis – see A3.1 *Harm-benefit analysis for research using animals*

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

Health-related research – research that indirectly seeks to respond to health problems, to benefit health and wellbeing; includes systems research, quality assessment, efficiency improvement in the health context, etc.

Human biological materials (HBM) – '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)

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

- **Anonymous data or samples** – data or HBM collected without any direct identifiers or link to a specific donor/participant
- **Coded data or samples** – identifiers removed, substituted by codes; link to donor/participants maintained separately
- **Directly identifying** – direct identifiers e.g., name, identity number
- **Indirectly identifying** – combination of indirect identifiers e.g., date of birth, address, unique personal characteristic
- **De-identified data or samples** – data or HBM collected with identifiers but permanently stripped thereof; data or samples cannot be linked to the donor/participants (see *POPIA*)

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

Incentive – anything offered to encourage participation in research

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

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

Intervention – 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, counselling, behaviour change, complementary health modalities, and management or economic policies

Jurisdiction – in the health research context, this word indicates the scope of authority exercised by each NHREC-registered REC. For tertiary institutions, the employees and students who conduct research under the auspices of the institution are directly under the jurisdiction of their institution. A non-affiliated researcher, whose protocol has been reviewed and approved by a tertiary NHREC-registered REC, is also under the jurisdiction of the institution for purposes of the research study

Layperson – someone who has no affiliation to the institution, is not currently involved in medical, health care-related, legal or scientific work and is preferably from the broad community in which research takes place.

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).

Memorandum of Agreement (MoA) – records parties' agreement to work together co-operatively on an agreed upon project

Memorandum of Understanding (MoU) – describes a broad outline of an agreement reached or to be reached by two or more parties

Minimal risk – see *Risk*

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

Monitoring – observe and systematically check the progress or quality of research activities over a period of time

Active monitoring – post-approval onsite monitoring of research; typically involves active validation of compliance to ethical aspects of the approved protocol, including onsite observation of execution of the study

Passive monitoring – post-approval monitoring of research; typically involves regular (minimum annually) written reporting by the PI about research involving human participants, including progress and problems encountered

Narrow consent – see *Consent*

Neonate – a new-born child

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

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

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 specific outcomes, without intervention, i.e., no treatment is given)

Observational research in education settings – study on educator's performance; conducted in education settings where minors are present; focus of research is on teacher's performance but necessarily learners in the classroom are indirectly involved but not as participants. Researchers are expected to explain carefully to the REC, the school, the parents and the learners (to the extent of practical feasibility) what is intended with these observations, how they are to be achieved, whether any recordings will be made, the purpose of the recordings, who will have access to the recordings and where they will be stored, what will happen to them after completion of the research, how learners' confidentiality will be maintained, etc. It is important that the researcher spends time familiarising the learners to their presence to avoid unnecessary distractions and interference with teaching and learning activities. Parents and learners must be given enough time to consider the purpose of the activities and enough time to contact the

researcher should they have questions, concerns or specific requests

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 them (section 1 Children's Act)

Passive monitoring – see *Monitoring*

Policy – High-level governance or operational principles formally adopted by an institution

POPIA –

Biometrics – a technique of personal identification that is based on physical, physiological or behavioural characterisation including blood typing, fingerprinting, DNA analysis, retinal scanning and voice recognition (section 1 of POPIA)

Consent – any voluntary, specific and informed expression of will in terms of which permission is given for the processing of personal information

De-identify – in relation to personal information of a data subject, means to delete any information that—

a) identifies the data subject;
b) can be used or manipulated by a reasonably foreseeable method to identify the data subject; or
c) can be linked by a reasonably foreseeable method to other information that identifies the data subject,

and ''**de-identified**'' has a corresponding meaning

Re-identify - in relation to personal information of a data subject, means to resurrect any information that has been de-identified, that—

a) identifies the data subject;
b) can be used or manipulated by a reasonably foreseeable method to identify the data subject; or
c) can be linked by a reasonably foreseeable method to other information that identifies the data subject,

and '**re-identified**' has a corresponding meaning;

Unique identifier –any identifier that is assigned to a data subject and is used by a responsible party for the purposes of the operations of that responsible party and that uniquely identifies that data subject in relation to that responsible party

De-identifiable data are collected with identifiers, which are separated after collection and retained separately in the custody of a person not associated directly with the study. This is called de-identification. This method permits later re-identification and linking to participants for specific purposes.

Personal information – information relating to an identifiable, living, natural person, and where it is applicable, an identifiable, existing juristic person, including, but not limited to—

a) information relating to the race, gender, sex, pregnancy, marital status, national, ethnic or social origin, colour, sexual orientation, age, physical or mental health, well-being, disability, religion, conscience, belief, culture, language and birth of the person
b) information relating to the education or the medical, financial, criminal or employment history of the person
c) any identifying number, symbol, e-mail address, physical address, telephone number, location information, online identifier or other particular assignment to the person
d) the biometric information of the person
e) the personal opinions, views or preferences of the person

f) correspondence sent by the person that is implicitly or explicitly of a private or confidential nature or further correspondence that would reveal the contents of the original correspondence
g) the views or opinions of another individual about the person, and
h) the name of the person if it appears with other personal information relating to the person or if the disclosure of the name itself would reveal information about the person

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

Proposal – initiates research by describing what is to be researched, why it is important, and how it is to be researched, sometimes in great detail (used interchangeably with **protocol** in some disciplines)

Protocol – documents that explain in detail the background, rationale and objectives of planned research; describe its scientific and social importance, its design, methodology, organisation and conditions under which it is to be conducted and managed, including all documents to be provided to potential participants; see also *Proposal*

Pseudonymisation – personal information is processed in such a way that the personal information can no longer be attributed to a specific research participant without use of additional information, provided that the additional information is kept separately, confidential and secure from unauthorised access

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

Rapid review process – permits speedy but thorough processing of ethics review applications in circumstances that require accelerated preparation for a research study

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

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

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 – a systematic investigation or study designed to produce generalisable knowledge based on conventional scientific and ethical standards appropriate for the context. It 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

Research data – Research data is any information that has been collected, observed, generated or created to validate original research findings. Research data may be arranged or formatted in such a way as to make it suitable for communication, interpretation and processing.

Right not to know – usually recognised but sometimes controversial; a donor/participant may choose not to receive information relating to incidental findings from research-related tests.

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

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

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

for risk of harm to animals see '*Severity Classification*'

Risk mitigation – strategy to diminish or avoid circumstances that threaten risk of harm

Rule of rescue – the strongly felt desire to intervene to prevent further harm to or death of an identified person, usually in situations of constraint, especially resources

Secondary use – use of HBM or data originally collected for a different purpose

Serious adverse event – (SAE) relates to an unforeseen harmful event related to the study (e.g., injury/death due to an experimental intervention), thereby negatively affecting the research participants or research animals, and requiring an intervention

Serious incident – (SI) relates to an unforeseen harmful event unrelated to the study itself (e.g., unexpected patient life event, or infrastructure failure in a research facility), thereby negatively affecting the research participants or research animals, and requiring an intervention

Severity classification – for studies using animals, as defined by the SANS 10386:2021

Stakeholder engagement – a process of involving and collaborating with the people who have an interest or stake in the research at an early and in a sustained manner, for the duration of the study, to enhance the scientific and ethical quality of a study. It involves implementing actions to meet the needs and expectation of the different role players and stakeholder groups and aims to achieve accepted outcomes for all the parties with the level of collaboration dependent on the circumstances.

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

Tiered consent – see *Consent*

Unanticipated problem – Relates to any obstacle that negatively affects a study and the possibility to achieve the outcomes, other than due to a SAE or SI

Unscheduled event – Typically refers to an adverse event or serious adverse event

Undue influence –may occur where an offered good is regarded as sufficient to impair decision-making, or to undermine the comprehending of risks by potential participants; an inherently subjective inference; should be considered mindfully with awareness of the dignity of participants

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

A1.2 List of statutes, regulations, and other instruments

Note: This list is not exhaustive.

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

Domestic Violence Amendment Act 14 of 2021 with effect from 14 April 2023 as per Proc R117 *GG*48419/14-4-2023.

Electronic Communications and Transactions Act 25 of 2021

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

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

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

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

Prevention and combating of Corruption Activities Act 12 of 2004

Prevention and combating of Torture of Persons Act, 2013

Promotion of Access to Information Act 2 of 2000

Promotion of Equality and Prevention of Unfair Discrimination Act 4 of 2000

Protection, Promotion, Development and Management of Indigenous Knowledge Act 6 of 2019

Protected Disclosures Act 26 of 2000

Protection of Personal Information Act 4 of 2013

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Appendix 2 Resources

A2.1 Mandatory reporting of child abuse or neglect

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

Note that arrangements and negotiations with organisations with expertise in children 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 of abuse or neglect should trigger a meeting of relevant study staff including the Principal Investigator to explore the details on a case-by-case basis, including the engagement of relevant child agencies and organizations.
2. Disclosure of consensual but unlawful sex should also trigger a meeting of relevant study staff to explore the details on a case-by-case basis. This should include how to engage relevant child protection agencies, such as Childline (Childline Western Cape. Tel (+27) (0) 762 8198. 38 Fleming Road, Wynberg, 7800. Email: info@childlinewc.org.
3. Future follow-up on such cases by the study team to ascertain the outcome should be carefully considered and discussed.
4. [*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.	Balance legal obligations to report with social harms. Discuss with child protection expert.
An 11-year-old reports 'having sex' with 19-year-old neighbour.	Report to Childline Police.

Examples in practice	Action by researcher
A 10-year-old tells of a previously reported incident of 'bad touching' by adult aunt that went to court.	Ask whether the child wants to talk to someone. Engage social worker involved.
A 15-year-old relates rape by father.	Engage child protection expert, e.g., Childline, for further support. Report to police.
A 13-year-old boy relates anecdote of sex with 15-year-old girlfriend.	Within the two-year age difference, so no need to report. Offer counselling or referral to services.
A 13-year-old says she is 'having sex' but does not disclose who the partner is.	No reporting action. Offer counselling and support.
A 17-year-old brags that he has 'forced' many girls into having sex with him.	No reporting action. Offer counselling.
A 17-year-old learner speaks of having become pregnant by a schoolteacher who she does not identify.	Engage partner with child protection expertise regarding abuse of the learner. Offer counselling to the learner or refer for counselling.

5. Disclosure by any adolescent of sexual abuse (under 16 years) or other abuse (under 18 years), 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.
6. If there is a clear statement that the parties involved in the abuse include an adult or anyone who is more than two years older than the adolescent in the case of sexual abuse (section 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.
7. 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*]

A2.2 Insurance against research-related bodily injuries: wording for IC document

Notes for researchers

i. Research study insurance does not substitute for 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 recognise symptoms of side effects or have ready means to take action

The IC document should have separate paragraphs to explain whether insurance cover is provided, as well as how it may be used in the event of a bodily injury suffered by a participant. The relevant paragraph heading could be:

'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 company/institution] to assist you if 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 (2020 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.

A2.3 Novel, Innovative, Unregistered, or Scientifically Unproven Treatment

<*Insert hospital name*>

NOVEL, INNOVATIVE, UNREGISTERED, OR SCIENTIFICALLY 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) – see 29 Jan version

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 SAHPRA 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	Date

A2.4 Genetic and genomic consent documentation samples

A2.4.1 Sample language for potential risks of harm associated with genetic and genomic research

We want to tell you that there are some risks of harm associated with this study:

- Most of the time when we take blood, it is safe and nearly painless, but sometimes a person may feel a bit faint or may develop an infection at the site of the blood draw. Sometimes a person develops a bruise at the site of the blood draw. If any of these occurs for you, please let us know and you will be attended to by a healthcare professional.
- A very small chance exists that information about you may become known to people who are not part of this study. Your genetic information is unique: you are the only person who has your genetic information, similarly to the uniqueness of your fingerprint. While it hardly ever happens that your genetic information becomes known to others, you should be aware that it could happen.
- We will keep all your data confidential, whether or not you choose to participate in this study.

A2.4.2 Sample language for considerations for research results for family studies

- Before you decide whether to join this study, you may want to discuss your plans and this study with your family members. This study is recruiting biologically related family members, because certain conditions and traits can involve your parents or your children (they are passed on biologically).
- The study will compare family members who have [name of condition/disorder] and family members who do not have [name of condition/disorder]. This means you may learn something new about your genome or the genomes of your family members that relates to your health.
- You may be referred to a doctor for extra tests or medical care.
- While this does not happen very often, each person chooses whether they wish to have the information shared with them. It is your choice whether to receive the information. We will respect your choice, even if you later change your mind.
- It is possible that the information will show that assumed family relationships are genetically misattributed (i.e., they do not match as expected) e.g., the information may show a child is adopted or has a different father.
- We will not share these results with you, unless you choose to receive them OR We will share these results with you only if they are relevant to your health.

A2.4.3 Sample language for considerations for identifiable groups or populations

- This study has been developed in consultation with [representatives of the community, describe]. These community representatives have been / are involved in [describe involvement].
- Although we will not give researchers your name, we will give them basic information such as your race, ethnic group, geographic region, age range, and sex [specify demographic variables]. This will be limited to the personal information relevant to this study.
- This information may help researchers to study whether the factors that lead to health problems are the same in different groups of people. It is possible that in the future, these findings may help people in the same groups as you.
- However, it is also possible that some people may use research findings against members of the same groups as you, which might result in unfair discrimination.

A2.4.4 Sample language for studies involving children

- As part of the study, your child's samples, genomic data, and health information will be stored and used for this research.
- When your child reaches age 18, we will contact them to ask whether they want to continue to participate and to obtain new consent.
- If we cannot locate your child, we will remove identifying information but, with your permission, we would like to continue to use their samples, genomic data, and anonymised health information in research.
- We may learn Information relevant to your child's or your family's health. [customise based on guidance for return of research results]. If this happens, we will share only information directly related to diseases and disorders that affect children. If your child would like additional information, they can request this when they reach 18 years.

A2.4.5 Sample language for return of results and incidental findings

- Individual results
  - You will have the option to receive your individual results from the study. If we find something of medical significance for you, we will inform you only if you wish us to do so. This is likely to be a very rare occurrence.
- Aggregated results
  - When the study is completed, if you wish, you will receive a summary of the results of the study and what they mean.
  - We will not share your individual results from this study.

A2.4.6 Sample language for considerations for study withdrawal

- It is your decision whether to participate in the study. If you choose to participate, you can change your mind later and decide that you no longer wish to participate and that you no longer want your [biological specimens] to be used in the study.
- Please tell us and we will arrange to destroy the specimen.
- If, when you decide to withdraw (stop participating), your specimen has already been tested, it may be that your results and data have been shared with other investigators. This means the data cannot be destroyed but it can be stored electronically and not made available to any new researchers.

A2.5 Terms of Reference sample

This sample guides construction of Terms of Reference for institutional RECs. It outlines the necessary elements, [*square brackets indicate where contextual changes are likely to be needed*]. This sample is not intended to be a prescriptive template; it is intended to assist institutions so that the Terms of Reference are appropriate in style and content and differ appropriately from Standard Operating Procedures.

The sample may be used also to inform construction of Terms of Reference for other discipline specific RECs, including ARECs, Social Science or Arts RECs and Science RECs. The essential elements are very similar.

A2.5.1 Introduction

The University of XXXX [Faculty of Health] Research Ethics Committee's Terms of Reference are aligned with the University of xxxx Research Ethics Policy [must exist and be accessible] as well as with the National Health Act 61 of 2003 and the National Department of Health's 'Ethics in Health Research' Guidelines (NDoH 2024). The National Health Act per section 73 requires institutions to establish RECs which register with the National Health Research Ethics Council (NHREC) and requires all 'health research' involving human participants to undergo prior ethics review by a registered research ethics committee. Committees are registered by the NHREC after an assessment of their eligibility and compliance with the relevant legal and ethics framework.

A2.5.2 Authority

The University of xxx [Faculty of Health HREC – name of REC] is established as a [explain whether a Faculty committee or a Senate level university-wide committee] and derives its authority from the [Faculty Board or Senate as the case may be]. It functions as [a sub-committee of the Faculty Board of the University of xxx Faculty of Health Sciences – amend according to contextual detail]. Administrative support is managed by the xxxxx [describe whether faculty-based or university-wide]. The University of xxxxx [name of REC] is registered with the NHREC in accordance with the National Health Act 61 of 2003. Its registration number is xxxxxxxx.

Note If the REC is a university-wide committee, the authority, the scope of work, the expertise of members etc must be appropriate for that level. Such a committee is not the equivalent of a faculty-based REC.

A2.5.3 Mandate

The University of xxxx REC is mandated to fulfil its functions in accordance with the National Health Act 61 of 2003 as outlined in the NDoH 2024. It reports annually to the NHREC) and to the University of xxxx [Faculty of Health Faculty Board].

The University of xxxx [FHS REC] reviews health or health-related research protocols for members of the Faculty or elsewhere in the University. [Researchers with no affiliation to the University of xxxx may approach the University of FHS REC to review their research protocols. The University of xxx FHS REC may exercise its discretion on a case-by-case basis to decide whether to review the protocol or whether to refer the applicant elsewhere to access appropriate expertise and capacity to evaluate the application. A fee may be levied for such a service.]

Note Describe the process and fee in an SOP.

A2.5.4 Scope of operations

The University of xxx [FHS REC] is authorised to

- conduct independent rigorous ethics review, prospectively, of all health or health-related research protocols to ensure that welfare and other interests of participants and researchers are properly protected and that the proposed research complies with the ethical norms and standards outlined in the national ethics guidelines

Note retrospective review is not permitted.

- ensure that research protocols are scientifically sound and feasible within available resources
- decide whether to approve, to require amendments or to reject the protocols for lack of compliance with scientific or ethics norms and standards
- ensure appropriate reporting occurs to fulfil the oversight obligation of the [name of REC] to monitor welfare interests of participants

The University of xxxx [FHS REC] should establish an EXCO to deal with matters between meetings, duly authorised by the full committee. [Need SOP to describe how EXCO works and what sorts of matters can be dealt with in this way e.g. renewals, final approvals after gatekeeper permissions received etc]

The University of xxxx [FHS REC] may establish subcommittees to deal with specific aspects of the work of the REC, e.g. undergraduate student ethics review applications. The subcommittee must be authorised to approve the applications and to report to full committee for noting. [Need SOP to describe how the subcommittee is constituted and how it does its work; note that the subcommittee must be authorised to make decisions.]

The University of xxxx [FHS REC] must establish and make accessible a Code of Conduct for its members that describes what is expected of members, a Confidentiality Agreement and a Conflict of Interest Declaration. [Note that the

confidentiality agreement and conflict of interest declaration should be completed at each meeting of the REC – it can be part of the register of attendance. The SOP about meetings must describe the process.]

The University of xxxx [FHS REC] must establish and make accessible a transparent and inclusive recruitment and appointment process for members of the REC that includes paying attention to achieving demographic representivity and succession planning. [Note the SOP about recruitment and appointment of members must explain the process.]

The University of xxxx [FHS REC] must establish and make accessible Standard Operating Procedures (SOPs) that systematically describe all the processes and procedures involved in its work including the institutional arrangements and reporting obligations. The REC must ensure that the SOPs are systematically reviewed every three to four years or more frequently as necessitated by research ethics changes.

The University of xxxx FHS REC must establish and make accessible appropriate documentation, including application forms, guidance documents, review guidance, information & consent document guidance as well as report templates amongst others) to facilitate appropriate processing of applications and to assist researchers to comply with requirements.

Note The SOPs and the administrative and governance documents should be made available to all interested parties by placing them on the institution's website. This practice facilitates transparency and compliance.

A2.5.5 Approval process for Terms of Reference

These Terms of Reference were approved by [*Faculty Board*] on [*date*] and by [*Senate*] on [*date*].

Note Approval of a faculty REC ToR must go through Senate as other committee ToR do. This transparency assists the institution to know about and to support the faculty REC.

Signed by [*Dean*] on [*date*]

Signed by [*DVC Research*] on [*date*]

Note ToR are likely to be reviewed only infrequently (in line with institutional patterns) unless changed circumstances require a change.

A2.6 Code of Conduct for REC members sample

[*Last updated xxxx*]

Note this Code applies to all Research Ethics committees at [*name of institution*].

All committee members at [name of institution] have a fiduciary responsibility to serve the interests of the university and of the public generally. In accordance with [name of institution's Conflict of Interest Policy], all decisions are to be made solely on the basis of a desire to promote the best interests of the university and the public and, in the case of research ethics-related matters, the interests of research participants and researchers must be protected.

Note promoting the best interests of the institution does not mean that it is the responsibility of the REC to defend or protect the reputation of the institution. The primary responsibility of the REC is to the research participants.

Upon appointment to a Research Ethics Committee, all committee members, including external members (e.g., lay persons) have responsibilities, including

- To attend meetings on a regular basis and, as far as possible, to remain until the meeting is adjourned. This is important to maintain a quorum and thus have valid decision-making throughout the meeting.
- To maintain confidentiality, where necessary, regarding research protocol or protocol information, reviews and decisions and all matters discussed at committee meetings.

- To disclose conflicting interests, including any personal involvement or participation in the research or in competing research, and, in the event of such a conflict with respect to a protocol, not to review the protocol and to recuse him or herself during the decision-making process.
- To review independently, impartially, and objectively whether the proposed design and conduct of research are likely to protect participants' safety, rights and welfare.
- To serve as a main reviewer in their area of expertise.
- To serve as a general reviewer of all research discussed at committee meetings.
- To keep up to date with research ethics and regulatory guidance.
- To contribute to ethics-related continuing education.

Consultants or ad hoc reviewers might be called upon from time to time to assist with research protocol reviews. The obligation to maintain confidentiality, where necessary, should be made known to these reviewers.

Observers or guests may attend committee meetings at the Chair's discretion or invitation. Such persons have an interest in research ethics and the review process but are not committee members. Observers and guests must maintain confidentiality, where necessary, regarding the business of the committee.

All persons who attend REC meetings are free to make observations, ask questions but only REC members may vote on decisions. Anyone without a vote who disagrees with the resolution of the issues under discussion and/or the outcome of the vote should take the matter up with the Chair of the REC in the first instance. The Chair may call a special meeting to discuss the substance of the disagreement or to debate more fully issues raised in this way.

Note Members should confirm that they will conform to faculty guidelines on the confidentiality of applications and proceedings at each meeting. When non-members attend, they should confirm that they will maintain confidentiality. Confirmations to be minuted.

Appendix 3 AREC Examples

A few examples for use by ARECs are provided in this appendix. The examples may be adapted for use according to own need and context.

A3.1 Harm-benefit analysis for research using animals

Acknowledgement of the North-West University's generous permission to use the harm-benefit analysis template in their NWU-AnimCareREC application form. The inclusion of this template in the Guidelines is for information purposes, as an example of best practice.

IMPORTANT! For benefit to outweigh harm, the researcher must consider thoroughly harms, justification, mitigation strategies and other considerations during the planning of a study and address same in the protocol. A proper harm-benefit analysis requires contextualisation and deliberation by the REC, and cannot be performed by a mere algorithm.

A3.1.1 STEP 1: Interventions and associated harm

Identify all key interventions on live animals in the study (i.e., withholdings, handling, exposure, procedures, methods, procedures, tests, etc.). Then consider associated animal experience, stressors, risks, and justification of these interventions:

Note: Whereas for human studies we estimate risk-benefit, or for projects we estimate cost-benefit, in animal studies we estimate harm-benefit. Benefit should outweigh harm, for a study to be approved.

Discuss all key interventions on animals, one by one, each entered on a separate table indicating animals/harm/benefit/outcome #1, #2, etc. Keep in mind and consider

a. the **Five Domains**[102], namely (1) Nutrition, (2) Environment, (3) Health, (4) behaviour and (5) mental state.
b. the **Five Freedoms**[103] for animals, namely freedom from hunger and thirst, freedom

[102] Mellor, D. J., & Reid, C. S. W. (1994). Concepts of animal wellbeing and predicting the impact of procedures on experimental animals. Improving the wellbeing of animals in the research environment, 3-18. https://www.wellbeingintlstudiesrepository.org/cgi/viewcontent.cgi?article=1006&context=exprawel/.

[103] More information on the origins of the universal Five Freedoms can be accessed at the National Archive of the Farm Animal Welfare Council [html], with a 1st press release [pdf].

from discomfort, freedom from pain, injury and disease, freedom to express normal behaviour, and freedom from fear and distress.

For each table (intervention), provide the following as indicated in the table:

i. Identify and briefly describe the particular intervention to be analysed. This may include, but is not limited to, animal handling, drug administration, e.g., injections or oral gavage (also called force-feeding), device implantation, surgery or other invasive procedures, infliction of pain or discomfort, exposure to stress or fear, social isolation, withholding of food, water and/or normal husbandry, behavioural testing, euthanasia, etc.
ii. Identify which animal species, number of animals and experimental test group(s) (as reflected in the study layout) are involved in this specific intervention.
iii. Identify and describe briefly the specific harm[104] associated with this particular intervention.
iv. Indicate the context of the harm, i.e., whether it is physical (including sensory, physiological) or psychosocial (including anxiety), and whether it is repetitive or of long duration (typically >30 minutes).
v. Describe the probable experience of the animal. Indicate the severity category of the harm (i.e., impact on animal wellbeing, considering the degree of discomfort or suffering, as specified by the severity categories 0, 1, 2, 3, 4 or 5 (or whichever severity category system your REC uses) as in the table below.
vi. Explain how the justification for the intervention. Describe the aggravating factors (i.e., cause and nature of the harm, or factors that make the harm worse).
vii. Describe any mitigating factors (i.e., precautionary measures in place to minimise the harm, and to optimise animal wellbeing. These could include use of painkillers, anaesthetic, intra-operative and post-operative care and/or euthanasia at the end of the experiment, proper training, and even how the 4Rs are implemented.

In this harms analysis, ethical considerations and measures taken, the 12 Rs framework (see Brink & Lewis, 2023) may also be helpful and informative.

[104] More information on harm-benefit analysis can be found in Laber et al. (2016) Recommendations for Addressing harm-benefit analysis and implementation in ethical evaluation – report from the AALAS-FELASA working group in Harm-benefit analysis – Part 2. Laboratory animals, 50(1S):21-42. DOI 10.1177/0023677216642397.

Tables for analysis of harmful interventions (one table per intervention separately):

Inter-vention #1	**Description of intervention**	Type details here.									
	Which species, test group?	Type details here.									
Harm #1	**Description of harm (what?)**	Type details here.									
	Context (i.e. nature of the harm) … *choose one or more options*	**Number of animals**	**00**	**Physical** ☐		**Psycho-social** ☐		**Environ-mental** ☐			
		Acute ☐		**Chronic (lasting)** ☐		**Repetitive** ☐		**Long duration** ☐			
	Animal experience	Type details here.									
	Severity category	**0** ☐	**1** ☐	**2** ☐	**3** ☐	**4** ☐	**5** ☐				
	Justification (necessity?)	Type details here.									
	Aggravating factors	Type details here.									
	Mitigating factors	Type details here.									

Inter-vention #2	**Description of intervention**	Type details here.									
	Which species, test group?	Type details here.									
Harm #2	**Description of harm (what?)**	Type details here.									
	Context (i.e. nature of the harm) … *choose one or more options*	**Number of animals**	**00**	**Physical** ☐		**Psycho-social** ☐		**Environ-mental** ☐			
		Acute ☐		**Chronic (lasting)** ☐		**Repetitive** ☐		**Long duration** ☐			
	Animal experience	Type details here.									
	Severity category	**0** ☐	**1** ☐	**2** ☐	**3** ☐	**4** ☐	**5** ☐				
	Justification (necessity?)	Type details here.									
	Aggravating factors	Type details here.									

Note: Describe one intervention plus associated harm per table. To add for more tables, copy the whole table #2 plus its paragraph mark below (to view, unhide non-printing symbols), and paste a third, fourth, etc. table beneath, indicated with #3, #4, etc.

A3.1.2 STEP 2: Benefit, scientific integrity and translatability of the study

Reflect on the likely benefit from the study (by referring to and considering your Research Protocol (i.e., the problem statement, hypotheses & expected outcomes), the matters related to research integrity, as well as the translatability of the study results and findings to real-life practice (for example the human condition or treatment in the case of pre-clinical studies, or environmental sustainability in the case of environmental studies, or food production in the case of agricultural studies).

Note: Benefit (and the robustness thereof), should withstand the "*Why is this important?*" question on relevance, and will be used to ensure that benefit outweigh the harm, for a study to be approved.

More information
The SANS 10386 discusses "governing principles in the care and use of animals for scientific purposes", and then explains what can be seen as the "justification of the use of animals" for this purpose. It then states that (in brief summarised here) there should be evidence to support a case to use animals by demonstrating scientific merit, with the potential to benefit humans, animals or the environment. It also explains that projects using animals may be undertaken only when it is essential to obtain and establish such information, maintain and improve human and/or animal health and welfare, improve animal management or production, understand, maintain or improve the natural environment, achieve educational outcomes.

Description of benefit

Click or tap here to enter text.

A3.1.3 STEP 3: Overall harm-benefit analysis

This question describes the overall outcome of the respective harm analyses of all individual interventions in the previous question, as compared to the overall benefit analysis.

Using the table below, indicate and describe the overall harm associated with this study as follows:

a) Indicate the cumulative severity category plus degree of overall harm associated with this study, considering all the specific harms in the previous question. The cumulative severity category refers to the overall experience of the animal resulting from all interventions. This should be estimated/deduced/projected, either from the most severe intervention, or when multiple consecutive (combination of) interventions per animal would cumulatively aggravate the experience of the animal, it may be higher than the category for the most severe single interventions.
b) Indicate the degree of overall harm associated with this study on a scale from 0 to 5.
c) Indicate and describe the overall benefit associated with this study:
d) Give a brief description the specific benefit (theoretical or practical value) associated with this specific intervention. Indicate the domain of the benefit (i.e. who or what will benefit), e.g. social benefits (including human health from a better understanding of a particular phenomenon or treatment; animals directly when the animals in the experiment will benefit from, for example, a treatment; animals indirectly when the representative species will benefit, but not the animals being used, or the environment, socio-economic benefits, scientific benefits, educational benefits or enhancement of safety and efficacy.
e) Indicate the degree of overall benefit associated with this study on a scale from 0 to 5.
f) Indicate the final outcome of your analysis, as applicable to this study:
g) Consider from the cumulative severity factor, overall harm and overall benefit of the study, whether overall the benefit of the study outweighs the overall harm of the study. Add a brief motivation and comments to support your final analysis.

Overall Harm	**Cumulative severity category (overall degree of harm)**	0 Negli-gible ☐	1 Low ☐	2 Mild ☐	3 Mode-rate ☐	4 High ☐	5 Ex-treme ☐				
Overall Benefit	**Description of the benefit (what?)**	Type details here.									
	Domain (who/what will benefit?) … choose one or more options	Humans (e.g. health) ☐	Animals (direct) ☐	Animals (indirect) ☐	Environ-ment ☐						
		Socio-economic ☐	Scientific ☐	Educational ☐	Safety and efficacy ☐						
	Overall degree of benefit	Negli-gible ☐	Low ☐	Mild ☐	Mode-rate ☐	High ☐	Very high ☐				
Analysis outcome	**Benefit outweighing the harm?**	Yes ☐	Equal ☐	Unclear ☐	No ☐						
	Motivation and comments	Type details here.									

Note: Benefit should outweigh harm for any study to be approved.
It is particularly important to motivate your analysis outcome clearly. For example, in a case of "extreme harm" (e.g. severity category = 5), with "very high" benefit, it may still be that the benefit outweighs harm when benefit is in multiple domains and/or of extreme/critical significance and/or with critically important impact. Keep the motivation concise and to the point.
The overall harm cannot be less that the most severe individual harm indicated in any table of the harms analysis (compare A3.1.1 *STEP 1: Interventions and associated harm* above). However, the cumulative harm may be more than the highest individual harm.

A3.2 AREC Memorandum of Understanding (MoU)

Acknowledgement of the University of Cape Town which developed the draft MOU and scenarios, from which the examples below have been extracted, adapted and reproduced with permission

Status of the MoU examples below

Reference to normative clauses in these guidelines (NDoH 2024), must be followed. However, the MoU example between two or more ARECs to conduct collaborative research, is informative and, therefore, may be customised.

ARECs must ensure appropriate review, approval, and oversight of research involving animals. Additional complexity emerges when ARECs must oversee research that is occurring at or otherwise involves multiple institutions. The division of responsibilities between institutions must be clear and unambiguous so that the parties concerned share a common understanding of the responsibilities and expectations. The MoU covers the responsibilities for the care, use, ownership, transport, and transfer of all animals and addresses regulations as set out in the SANS 10386:2021, the NHA, NDoH 2024 and applicable legislation.

An example of an MoU between ARECs for cooperative animal ethics research oversight and monitoring of multi-institutional or multi-party studies is outlined below.

A3.2.1. the MOU presents an opportunity for the animal research oversight groups at each signatory institution to discuss best practices jointly and to align common expectations, while simultaneously building relationships to facilitate future collaborations.

A3.2.2. All aspects of the collaborative research must comply and align with the relevant norms and standards for ethical and human care of animals used for scientific purposes (i.e., for research, field trials, testing, diagnosis, teaching & training activities).

A3.2.3. International collaborations must comply with national legislation, regulations and other relevant requirements for all signatory, including the local requirements for the RAF or site, the ethical standards of all collaborating parties. In addition, protection of personal information, intellectual property interests, MTAs, DSAs must receive appropriate attention, and necessary regulatory import and other permits must be obtained.

A3.2.4. All ARECs involved in the review and approval of the collaborative research retain full responsibilities and accountability for ethical oversight of the study using animals. These responsibilities include, but are not limited to, all onsite animal care, research activity and researcher oversight and animal facility/site inspection (see NDoH 2024 section 2.4). These direct responsibilities remain in force for all ARECs, unless:

i. the MoU includes delegation of a specific responsibility to the registered AREC that oversees the appropriately registered and properly managed animal research facility or site where the research will be conducted. Where more than one RAF or site is involved, the MoU must specify which AREC takes responsibility for which facility or site;

ii. the MoU must stipulate that all signatory ARECs must be kept fully and timeously informed of all matters that affect the study, including matters related to animal housing, care and welfare, transport of animals, oversight reports such as adverse events or incidents, study amendments or other changes related to the approved study, as well as all passive and active monitoring reports and study closure reports as applicable;

iii. the MoU must provide reasonable mechanisms to permit any signatory

AREC to withdraw ethics approval for the study responsibly when a breach of the MoU occurs.

A3.2.5. Sample MoU

MEMORANDUM OF UNDERSTANDING

between

Name of Institution A

(Hereinafter referred to as "AAA")

and

Name of Institution B

(Hereinafter referred to as "BBB")

1. The AAA, incorporated under the Higher Education Act, 1997 (Act No 101 of 1997), having its principal office at [physical address], and BBB incorporated under [applicable legislative framework], having its principal office at [physical address], wish to collaborate on a pre-agreed basis, in order to benefit their respective use of animals for scientific purposes (including for research, field trials, testing, diagnosis, teaching & training activities) , and to comply with SANS 10386 2021 and applicable legislation.
2. The purpose of this Memorandum of Understanding (MoU) is to outline the basis on which the co-operation and collaboration may occur.
3. Co-operation between the institutions is based on the Department of Health's Guidelines on Ethics in Health Research: Principles, Processes and Structures of 2024 (NDoH 2024) and the South African Bureau of Standards' South African National Standard (SANS 10386) to establish legal compliance and promote best practices for the care and use of animals for scientific purposes, to:
   i. ensure minimum uniform national standards regarding animal care and use are adhered to;
   ii. emphasise the responsibilities of researchers, teachers, institutions using animals and their institutional Animal Research Ethics Committees (ARECs);
   iii. ensure that the dignity and welfare of animals are always appropriately considered;
   iv. ensure that the use of animals is justified and adheres to the principles of Replacement, Reduction, Refinement and Responsibility (the 4 Rs), and within the broader 12 Rs framework;
   v. prevent or minimise pain, suffering or distress, where possible, for each animal used for scientific purposes;
   vi. minimise the number of animals used for scientific purposes without jeopardising the validity of the studies or activities; and
   vii. promote development and use of techniques and monitoring instruments which adhere to the 4 Rs for the care and use of animals for scientific purposes.
4. Specific programmes, projects or services will be undertaken under this MoU only after a separate written agreement has been concluded by the institutions. Subordinate agreements must align with prevailing policies of partner institutions. The initial pre-agreed requirements are attached hereto as Annexure 1 and initialled by the signatories for identification purposes.
5. All signatories must designate a liaison officer for this MoU and for any subordinate project agreements under this MoU. For AAA, the authorised liaison officer must be […designation and name of the officer] and for BBB the authorised liaison officer must be […designation and name of the officer].
6. The rights in research materials and research findings must be clearly described in the separate project agreements. If collaborative research activities in terms of this MoU lead to potential intellectual

property interests, the institutions must seek an equitable and fair understanding as to the nature and scope of the interests that may arise.

7. The parties may disclose certain confidential information to each other regarding future projects in terms of this MoU. Each party therefore agrees that the contents of this MoU and the negotiations in relation to any future projects is strictly confidential and each party hereby undertakes not to disclose same to any third party, save for its professional advisers, without the prior written consent of the other party except where such disclosure is required by law (including, without limitation, in terms of applicable freedom of information legislation).
8. The Parties must ensure compliance with data protection laws.
9. This MoU comes into effect when the last signatory signs. It remains in effect for a period of five (5) years from that date. Not less than six (6) months prior to its expiry, the institutions must review its operation and collectively decide whether to renew it. Such renewal, which may include variations to the MoU, must be signed by the appropriate authorised officer of each institution.
10. This MoU may be terminated by written mutual consent of all the signatory institutions, or by any one institution giving sixty (60) days' written notice to the other institution(s).
11. All parties agree that prior written approval is required before using another party's name, logo, or other intellectual property rights in any advertising or associated publicity.
12. This MoU may be amended or modified only in writing, signed by the appropriate authorised officer of each institution.
13. This MoU places no financial obligations on the signatory institutions, nor does it bind any signatory institution to a particular undertaking. It constitutes a platform from which they may pre-agree in writing on any of the fields of co-operation as referred to in clause 1 hereof; set out more specifically, in Annexure 1 and subsequent Annexures.

Signed on behalf of Institution BBB

NHREC reg. no. AREC-###

_____

(*Name, designation and office of the authorised liaison officer*)

Date: _____

Signed on behalf of Institution AAA

NHREC reg. no. AREC-###

_____

(*Name, designation and office of the authorised liaison officer*)

Date: _____

ANNEXURE 1

Note: This Annexure should clearly and explicitly explain the onsite responsibilities at the research animal facility (RAF), which will be at one of the two institutions. Also, the respective responsibilities of, and reporting lines between AAA and BBB should be clear and explicit.

For example, when the study of researchers from BBB will be undertaking the study at the SAVC-registered RAF of institution AAA[105], it may include the following:

BBB may agree to

i. the study taking place at AAA;
ii. members of BBB (and CCC, DDD, EEE, etc.) taking part in the study at AAA

if and only if the following conditions are met:

1. AAA has a suitable SAVC-registered RAF
2. Both AAA and BBB have a NHREC-registered AREC

[105] More complex scenarios will require additional agreements to explain respective responsibilities.

3. AAA, through its AREC, has approved the study and makes the full study-proposal/protocol/protocol documentation available to BBB
4. BBB's AREC satisfies itself that the study protocol fully meets its own standards/requirements
5. AAA submits to BBB, and obtains approval of BBB's AREC for each amendment to the study proposal/protocol approved by AAA's AREC. Where BBB's AREC declines to approve an amendment, it shall give reasons for not doing so, and may withdraw from the study if AAA proceeds with the study on the amended protocol
6. BBB agrees in writing that AAA's designated veterinarian will undertake the necessary veterinarian functions regarding
   a) any of BBB's project animals to be used in the study
   b) supervision as per SAVC requirements for SAVC-authorised personnel; and
   c) medicines used in the study

   and AAA's veterinarian agrees in writing to do so

   Note: Should it be necessary to move BBB's scheduled medicines to AAA's RAF, BBB's veterinarian must supervise the transport and certify that the (i) transport is compliant and (ii) that these fall under the control of AAA's veterinarian once they reach AAA's RAF.

7. AAA must
   a) provide BBB with its post-approval-monitoring schedule which must be acceptable to BBB
   b) submit post-approval monitoring reports to BBB; if such reports do not satisfy BBB, BBB may withdraw from the study
   c) agree with BBB that BBB's independent inspecting veterinarian, or a mutually agreed independent veterinarian may conduct inspections of the study at AAA's RAF, ensure that such reports as the inspecting veterinarian submits to BBB are provided to AAA, and
      - act on such recommendations as the inspecting veterinarian may make unless it can show good reason for not doing so; and
      - accept that BBB may withdraw from the study if in BBB's judgement the report of the inspecting veterinarian provides the basis for doing so
8. AAA must undertake to ensure, and must ensure that the study principle investigator (PI) submits
   a) annual reports on time to AAA and BBB
   b) a post study (final) report on time to AAA and BBB

   Provided that it is understood that should the PI
   i. Fail to submit a satisfactory report, AAA may cancel the study
   ii. Fail to submit a report that is satisfactory to BBB, BBB may withdraw from the study
9. AAA and BBB conclude an IP agreement before the study starts
10. AAA and BBB enter into an agreement, binding on all members of AAA and BBB, setting out disciplinary procedures for dealing with any misconduct during the study. Such an agreement should consider the applicable standard operating procedures (SOPs) of AAA and BBB

A3.3 AREC regulatory framework

A3.3.1. The SANS 10386:2021 2nd ed and SAMRC Guidelines on Responsible Conduct of Research Chapter 7 (2018) 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 and Responsibility. ARECs and researchers are expected to familiarise themselves with the content of both documents in addition to these Guidelines, as appropriate. International and foreign codes for animal research include the World Organisation for Animal Health (WOAH 2023)[106] Terrestrial Animal Health Code (Chapter 7.8, Use of Animals in Research and Education), also applies to South Africa as a WOAH Member State. 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 protection of animals used for scientific purposes, and the Australian Code for the Care and Use of Animals for Scientific Purposes (8th ed.) 2013.

A3.3.2. Various aspects relating to research with animals are regulated by different authorities besides the NHREC which sets norms and standards for the use of animals in health or health-related research. Although the NHREC does not regulate these aspects and is not authorised to enforce some of them, ARECs and researchers are reminded of the expectation that they are familiar with the latest requirements and to ensure compliance regarding good practice, including but not limited to:

a) Research animal facilities must be registered with the South African Veterinary Council (SAVC) as veterinary facilities, as required by the Regulations of the Veterinary and Para-Veterinary Professions Act (Act 19 of 1982) Such registration requires compliance with specified minimum standards that promote animal health and wellbeing and scientific quality. Institutional ARECs must thus ensure that institutional facilities are registered, to SANS 10386 requirements for ARECs to oversee animal facility standards.

b) Professional registration and competence of persons in performing animal procedures:

   i. The Veterinary and Para-Veterinary Professions Act requires that all persons who perform veterinary or para-veterinary procedures, functions or services, should be registered with the SAVC. Provision is made in terms of section 23(1)(c) of the Act for non-registered persons to be authorised by the SAVC to legally perform such procedures, functions, or services. Authorisation requires an SAVC-registered veterinarian to assess and confirm the competence of non-registered persons to perform the authorised procedures. The sustained competence of SAVC-authorised persons must be ensured by adequate supervision of registered veterinary or para-veterinary professionals (i.e., the SAVC-appointed supervisors), as defined in the SAVC supervision agreement signed by each authorised person, the SAVC-appointed supervisor and the institutional representative, which forms part of the formal SAVC authorisation process.

   ii. Practical competence in procedures is vital to animal welfare, the reproducibility of scientific findings and thus to animal ethics. The AREC should ensure that all persons who perform veterinary or para-veterinary procedures, functions, or services, are authorised by the SAVC, supervised appropriately and remain competent, in terms of meeting SANS

[106] Access online [hml].

10386 requirements for ARECs to oversee the competence of personnel.

iii. The Natural Scientific Professions Act (Act 27 of 2003) (sections 18 and 20(2)(a)) require all natural scientists who practise in a Field of Practice as defined in the Act, to register with the South African Council for Natural Scientific Professionals (SACNASP). Defined Fields of Practice include agricultural science, animal science, aquatic science (including marine science) biological science, conservation science, ecological science, environmental science, food science, zoological science and other defined natural sciences as relate to animals.

iv. Notwithstanding the above, ARECs must ensure that only persons who are practically competent perform procedures on animals, including capture, restraint, and euthanasia.

v. Regarding medicines and other scheduled substances, all uses of animals for scientific purposes must comply with the Medicines and Related Substances Control Act (Act 101 of 1965). The use of scheduled medicines for scientific purposes involving animals must occur under a veterinarian's control. The use of incorrect, inappropriate, expired, incorrectly stored or administered medicines can have negative consequences on animal health and wellbeing, scientific quality and animal ethics. ARECS must ensure appropriate use and control of scheduled medicines.

vi. Where research or testing involves animals that are or may be infected, or will be **infected, with pathogens**, or animals **or products of animal origin** that contain or may contain pathogens, including the transport of such animals or products, a section 20 permit in terms of the Animal Diseases Act (Act 35 of 1984) may be required. It should however be noted that all research / analysis / training using animals or biological materials should at least be cleared with DALRRD, and all laboratories storing / analysing such materials should clear biological safety level certification with DALRRD.

vii. Where research involves **genetically modified organisms**, such research must comply with the requirements of the Genetically Modified Organisms Act (Act 15 of 1997).

viii. Where animals or animal products are **transferred between collaborating institutions**, nationally or internationally, it is **good practice for a Materials Transfer Agreement** (MTA) to be in place, to prevent spread of disease, verify legality of materials, imports and exports, ensure protection of intellectual property, as well as the agreement regarding further housing of animals, storage of samples, use, sale, return, euthanasia of animals or destruction of samples, as well as waste disposal of the animals or products by the receiver.

ix. In cases where multi-institutional collaborative animal research is performed, it is good practice to draw up a Memorandum of Understanding before the research work is conducted, to define the extent and limits of responsibility of the various institutions and ARECs involved.

x. Researchers and ARECs should be familiar also with other relevant legislation and binding instruments as listed in A1.2 *List of statutes, regulations and other instruments* above.

recognition

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